biossil

14 February 2025

Re: Cover Letter for ClinicalTrials.gov NCT02187003

This Cover Letter accompanies the final Statistical Analysis Plan (Version 5; 10 July 2019) for the completed trial, NCT02187003.

Sincerely,

Signed by:
Debora Manning
7131A55FBB88471...

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

# Protocol B5201002

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

## Final Statistical Analysis Plan (SAP)

**Version**: 5 (Final)

**Authors**: [redacted]

**Date**: 10 July 2019





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## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

- Status of study when amendment made:

  Study protocol amendment 3 was made to use Cohort 1 and Cohort 2 as the primary analysis population. This change was formally endorsed by FDA through a Special Protocol Assessment Modification Agreement Letter (15 April 2019). Study enrollment has been completed on 25 April 2019. The study team has remained blinded. Per protocol, the external Data Monitoring Committee (E-DMC) has reviewed safety data approximately every 6 months since the start of the study. Accordingly, 7 interim safety E-DMC reviews have been completed at the time of this SAP amendment.

- A summary of SAP amendments made prior to the current amendment is provided in **Table 1** below.

**Table 1. SAP Version History**

| SAP Version | Primary Change(s) | Rationale for Primary Change(s) |
|---|---|---|
| V1 (dated 12 June 2015) | Not Applicable. | Not Applicable. |
| V2 (dated 08 March 2016) | [redacted] | [redacted] |
| V3 (dated 16 November 2017) | [redacted] | [redacted] |
| V4 (dated 7 September 2018) | [redacted] | [redacted] |



[redacted]

- Specifics on the changes in Version 5 of significance are provided in Table 2 below. These changes are related to the planned Primary Analysis Population and hence are considered significant. In addition, changes were made for editorial reasons (eg, to improve flow, to correct typographical errors, to remove redundancies or improve clarity). These do not represent changes in the statistical objectives or in the planned analyses from the previous version and therefore are not listed in the table below:

**Table 2. Summary of Changes in this Amendment from Previous Amendment**

| Location of Change | Details of Change(s) | Rationale for change(s) |
|---|---|---|
| **Primary analysis population** | Changed the primary analysis population from Cohort 1 to Cohort 1 and Cohort 2 combined. | Combining the two cohorts of subjects would allow for the powered primary efficacy analysis to be undertaken in the entire study population of subjects aged 6 years and above, rather than just in the subjects aged 12 years and above in Cohort 1. |
| **Imputation rules for missing stop date/time** | Replaced "withdrawal of consent" with "discontinuation from study". | For completeness, clarity and consistency. |
| **Section 7.1**<br><br>**TTRFD** | Added rules for handling missing data due to discontinuation from study in Table 6. | For completeness, clarity and consistency. |
| **Section 7.3**<br><br>**IV Opioids Use** | Addition of approach for handling missing start and/or stop times for intermittent IV opioid dosing assuming the corresponding start and stop date, route and dosage of IV opioids are present. | To allow for derivation of the endpoints related to IV opioid consumption in the rare situation when there are missing data of the nature described in this section. |
| **Section 8.1.1**<br><br>**Analysis for Time-to-Event Data** | Added mean, restricted mean (based on the RMST methodology), modified restricted mean and difference in treatment means with corresponding 95% CI of difference for reporting time-to-event data. | To provide a supplemental estimate of treatment difference which does not depend on the proportional hazards assumption. |
| [redacted] | [redacted] | [redacted] |



[redacted]

| Location of Change | Details of Change(s) | Rationale for change(s) |
|---|---|---|
| | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| **Appendix Sections 10.1, 10.2 and 10.3** | Added and updated details on reporting of exploratory endpoints and laboratory data. | For completeness, clarity and consistency. |
| **Appendix Section 10.5** | Added details for the estimated means and corresponding 95% confidence intervals. | For completeness and clarity. |





[redacted]

## 2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicized***.

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

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

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

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

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

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

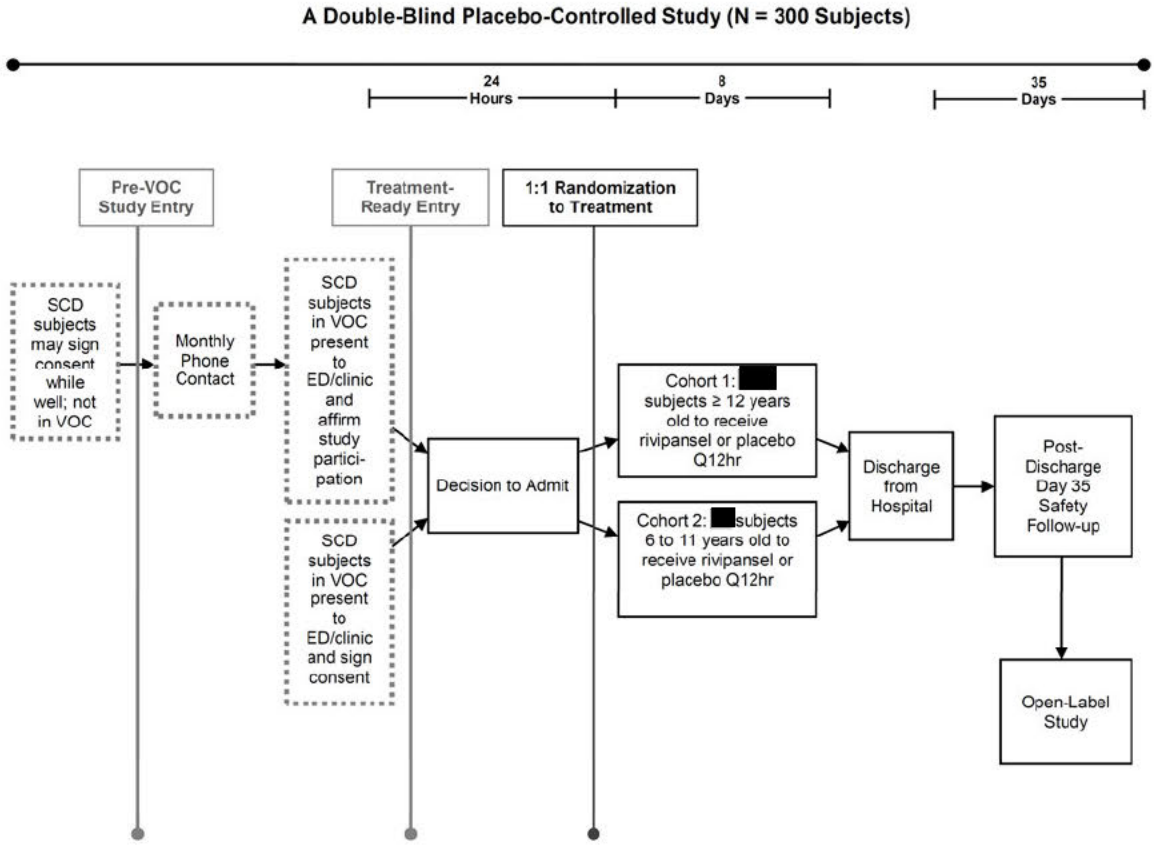




[redacted]

## 2.1. Study Design

**Figure 1. Study Design**




*This Phase 3 randomized, double-blind, placebo-controlled, parallel group, multicenter study is designed to demonstrate the efficacy of rivipansel in treating subjects with SCD who are ≥ 6 years of age experiencing an acute VOC event necessitating hospitalization.*

Cohorts:

This study has two cohorts:

**Cohort 1:** This cohort consists of
- a pediatric stratum (12-17 years old); and
- an adult stratum (≥18 years old).

**Cohort 2:** This cohort consists of:
- pediatric subjects only (6-11 years old).

Cohort 1 and Cohort 2 will be combined as the primary analysis population.



[redacted]

The two cohorts and the two age strata in Cohort 1 will be also analyzed separately.

Entry points

*There are two entry points into this study* (see Figure 1 above). *The first point of entry is referred to as "Pre-VOC/Study Entry Screening" and occurs while the subject is well. The second entry point is while the subject is experiencing a pain crisis and is termed "VOC/Treatment-Ready Screening".*

- Pre-VOC/Study Entry Screening

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

- VOC/Treatment-Ready Screening

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

Randomization

*Subjects with acute VOC who complete the VOC/Treatment-Ready screening assessments and meet all eligibility criteria are enrolled into the study and will be randomized in a 1:1 ratio to receive multiple IV doses of rivipansel or placebo for the treatment of VOC.*

Randomization will be stratified, forming a distinct stratum for each combination of age and genotype, using the categories shown below:

- Age
  - 6-11 years old;
  - 12-17 years old;
  - ≥18 years old.
- Genotype
  - Category 1: HbSS, HbSβ0 thalassemia and HbSD;

- Category 2: HbSC, HbSβ+ thalassemia and HbS-Variant (other than HbSD).

Dosing

*Dosing of eligible subjects with acute VOC will be initiated as early as possible but no later than 24 hours from the administration of the first dose of IV opioids for the current VOC. For subjects aged 12 and over who weigh >40 kg, study drug will be administered as a loading dose of 1680 mg followed by a maintenance dose of 840 mg every 12 ± 2 hours. Subjects aged 6 to 11 years, or any subject who weighs ≤40 kg, will receive a loading dose of 40 mg/kg (maximum of 1680 mg) followed by a maintenance dose of 20 mg/kg (maximum of 840 mg) every 12 ± 2 hours. Study drug will be administered until criterion 1 of the readiness-for-discharge criteria (see below) has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.*

Primary Endpoint Assessment

*The primary endpoint is **time to readiness-for-discharge (TTRFD)**. The event of **readiness-for-discharge (RFD)** occurs when all of the 6 protocol-specified criteria listed below have been met and appropriately documented. These six criteria are to be assessed in relation to treatment for the VOC event and acute complication(s) directly related to the VOC event.*

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

*The RFD criteria will be assessed by site-staff in all subjects at pre-defined intervals (and ad hoc as necessary) using an RFD questionnaire, from the start time of the loading dose of study drug until discharge* (see Section 6.1.1).

The RFD questionnaire is presented through the electronic Clinician Reported Outcome (eClinRO) system which is accessible via a web portal called TrialManager from a computer or mobile device. The appropriate electronic case report forms (eCRFs) are completed contemporaneously by site-staff to document the actual time and date at which criteria 3-6 are met.

Other assessments:

*Safety, including clinical and laboratory examinations, efficacy,* [redacted] *will be obtained throughout the study according to the Schedule of Activities* (see Appendix Section 10.6).

[redacted]

This study will use two independent Safety Endpoint Adjudication Committees:

- Acute Chest Syndrome Safety Endpoint Adjudication Committee (ACS-SEAC) for the evaluation of potential Acute Chest Syndrome (ACS) events
- Cutaneous Manifestations Safety Endpoint Adjudication Committee (CM-SEAC) for the evaluation of potential severe and/or generalized cutaneous events

In addition, an E-DMC will be responsible for ongoing safety monitoring.

Post-discharge

*Starting on Day 1 post-discharge from the hospital and continuing until the stopping rule (see Appendix Section 10.6) is met, or Day 10 post-discharge, whichever occurs first,* [redacted] *Additionally, subjects will be contacted by phone for safety follow-up 7 and 21 days after discharge from the hospital and will have a follow-up visit 35 days post-discharge (Note: If the subject or investigator prefer, the Day 7 Post-Discharge and Day 21 Post-Discharge contact may be a clinic visit).*

Approximate Duration of Subject Participation

*Subjects who enter the study in crisis will participate in the study for approximately 44 days. This includes 1 day for screening, up to 8 days for the double-blind treatment period, and a post-discharge follow-up period of approximately 35 days. Under certain situations, complications may occur during the subject's hospitalization and the subject's participation in the study may exceed 44 days.*

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



[redacted]

Approximate Duration of Study

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

### 2.2. Study Objectives

Primary Objective

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

Secondary Objective

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

[redacted]

## 3. INTERIM ANALYSES, FINAL ANALYSES AND REVIEW OF UNBLINDED DATA

### 3.1. Interim Analysis

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

[redacted]



[redacted]

### 3.2. Final Analysis

Cohort 1 and Cohort 2 combined will provide pivotal efficacy and safety data from subjects aged 6 years and older for the indication of treatment of VOC in SCD patients.

Analyses will also be performed separately for Cohort 1 (alone and/or by age group) and Cohort 2.

### 3.3. Review of Unblinded Data

Safety Data: The E-DMC will review safety data provided by treatment group but with treatment assignment masked, with reviews occurring approximately every 6 months. The treatment assignment decode will be provided to the E-DMC in a password-protected file, which they will review if considered necessary for accurate benefit/risk assessment.

Efficacy Data: Unblinded efficacy data will be available to the committee in the following scenarios:

a. If an interim analysis of Cohort 1 is performed, to assess futility (as described in Sections 3.1 and 4.2).

b. With every safety review. The efficacy data will be provided in a password-protected file, but this will only be reviewed by the E-DMC, if an unplanned review of efficacy is considered necessary for accurate risk-benefit assessment.

## 4. HYPOTHESES AND DECISION RULES

### 4.1. Statistical Hypotheses

- Hypothesis-testing will be performed only for Cohort 1 and Cohort 2 combined.
- The primary objective of separate Cohort 1 (alone and/or by age group) and Cohort 2 statistical analyses is estimation rather than hypothesis-testing.

This protocol is designed to establish the superiority of rivipansel to placebo in Cohort 1 and Cohort 2 combined for the following:

- Primary endpoint:
  - TTRFD in hours.
- Key secondary endpoints:
  - Time to discharge in hours (date and time of "discharge" is the date and time of the hospital discharge order by a qualified health care professional not the date and time of physical exit from the hospital).
  - Cumulative IV opioid consumption in MEU/kg (cumulative IV opioid consumption is standardized using morphine equivalents and normalized by body weight in kilograms) from the start time of the first infusion (loading dose) of

study drug to discharge (ie, all available IV opioid data that is post-loading dose while the subject is hospitalized).

- Time to discontinuation of IV opioids in hours.

A gatekeeping approach (see Section 4.2) will be used for Cohort 1 and Cohort 2 combined to control the overall Type I error rate for the statistical hypothesis-testing of the primary and key secondary endpoints (all using 2-sided tests) at 0.05.

Primary Efficacy Analysis

The statistical hypothesis to be tested in the primary analysis, in support of the primary objective of the study is

$$H_0: S_{Rivipansel}(t) = S_{Placebo}(t), \text{ for all } t > 0,$$

where

- $S_{Rivipansel}(t)$ is the survivor distribution of TTRFD in the rivipansel group; and
- $S_{Placebo}(t)$ is the corresponding survivor distribution in the placebo group.

The alternative hypothesis is:

$$H_A: S_{Rivipansel}(t) \neq S_{Placebo}(t), \text{ for some } t > 0.$$

Key Secondary Analysis

For each of the key secondary endpoints, the null hypothesis is that there is no difference between the rivipansel group and the placebo group with respect to the specific key secondary endpoint, and the alternative hypothesis is that there is a difference between the rivipansel group and the placebo group.

Sample Size Rationale

- Cohort 1 and Cohort 2 combined (all subjects ≥ 6 years old):

  For the Primary Analysis Population (Cohort 1 and Cohort 2 combined), the sample size calculation was based on the following assumptions:

  - Distribution of TTRFD is exponential.
  - Median times to readiness-for-discharge are 156 and 106 hours, for the placebo and rivipansel groups, respectively (based on observed data in the Phase 2 trial).





[redacted]

- The stratified log-rank test is used to test the statistical hypothesis in the primary efficacy analysis, in support of the primary objective of the study.

- Alpha=0.05 (two-sided test), power=0.90.

Based on above assumptions, a total of at least 300 subjects should be enrolled into Cohort 1 and Cohort 2 combined and at least 282 events observed, in order to have at least 90% power for the primary efficacy analysis conducted on data from Cohort 1 and Cohort 2 combined.

[redacted]





[redacted]

[redacted]

[redacted]

### 4.2. Statistical Decision Rules

For the Primary Analysis Population (Cohort 1 and Cohort 2 combined), a fixed-sequence testing (or gatekeeping) approach will be used to control the overall Type I error for multiple endpoints (ie, 1 primary and 3 key secondary endpoints). This implies that a given endpoint can only achieve significance if the prior endpoint is significant. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Primary Efficacy Analysis

The trial will meet the primary objective if the log-rank test (two-sided test) for the primary endpoint (TTRFD) in Cohort 1 and Cohort 2 combined is significant using an alpha of 0.05 (ie, 2-sided log-rank test p-value $\leq 0.05$).

Key Secondary Analysis

The hypothesis tests for the key secondary endpoints (described earlier in this section) are also conducted at the significance-level used for the primary analysis. In other words, significance for each key secondary endpoint will be assessed using 2-sided tests (alpha of 0.05), within the frame-work of the gatekeeping approach described in the protocol and earlier in this section.



[redacted]

Futility Interim Analysis

A futility interim analysis (IA) was initially planned to be conducted for Cohort 1 [redacted] if the E-DMC had become aware of a significant safety concern at a prior safety review. This IA was not required since no significant safety concern was raised in any E-DMC reviews. No futility IA is planned for Cohort 1 and Cohort 2 combined following the protocol amendment to make this the primary analysis population.

Details of the initial futility IA plan are provided in Appendix Section 10.4.

## 5. ANALYSIS SETS

### 5.1. Full Analysis Set

The primary analysis set for efficacy analyses is defined by the full analysis set (FAS) of subjects. The FAS will include all subjects who are randomized in the study.

### 5.2. 'PER PROTOCOL' Analysis Set

The primary endpoint will also be analyzed for the per-protocol analysis set (PPAS). The PPAS will be a subset of subjects from the FAS. Subjects who never received an infusion of study drug or had a protocol deviation or major violation that could affect efficacy will be excluded from the PPAS. The specific reasons for excluding subjects from the PPAS will be fully defined and documented before breaking the blind. The list of subjects along with the reasons for their exclusion from the PPAS will be stored in the Trial Master File (TMF).

### 5.3. Safety Analysis Set

The safety analysis set (SAS) is defined as those subjects who received at least one infusion of study drug. All safety analyses, including analyses of AEs, clinical laboratory results, vital signs, and physical examinations will be conducted on the safety analysis set.

[redacted]

### 5.5. Treatment Misallocations

If subjects were:

- Randomized but not treated: Subjects will be excluded from the safety analysis set. Subjects will appear in the subject evaluation table as randomized but not treated and will not be included in safety summaries. These subjects will be also excluded in the PPAS but will be included in the FAS.
- Treated but not randomized: Subjects will be excluded from the efficacy analyses but included in safety analyses.



[redacted]

- Randomized but took at least one dose of incorrect treatment: Subjects will be reported under their randomized treatment group for all efficacy analyses. For safety analyses, if any subjects received at least one dose of rivipansel, they will be reported under the rivipansel treatment group. These subjects will not be included in the PPAS. They will be also excluded from the biomarker analyses. If a subject was randomized to rivipansel but received incorrectly at least one dose of placebo, he/she will be still reported in the rivipansel group with appropriate adjustment for PK analyses. Otherwise the subject will be excluded from PK analyses.

### 5.6. Protocol Deviations

Protocol deviations will be reviewed and compiled based on reported deviations from inclusion/exclusion criteria, deviations in study drug administration, and other specifications as appropriate. These deviations will be reported in the CSR and will be compiled prior to database closure.

## 6. ENDPOINTS AND COVARIATES

### 6.1. Efficacy Endpoints

#### 6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is TTRFD from the hospital (in hours). The event of interest, RFD, is said to occur when all applicable criteria among C1-C6 below have been appropriately documented as being met:

C1. Only oral pain medication is required.
C2. Acute complications related to VOC (such as ACS, stroke, priapism) have resolved to the extent that management can be in an outpatient setting, if applicable.
C3. IV opioids have been discontinued.
C4. IV hydration has been discontinued, if applicable.
C5. IV antibiotics have been discontinued, if applicable.
C6. RBC transfusion is no longer required for the treatment of this VOC, if applicable.

To be specific, in order for RFD to be achieved, for a given subject, the response to C1 must be appropriately documented as "YES" in the eClinRO system, the response to C2 must be appropriately documented as "YES" or "NA" in the eClinRO system, and the final stop dates and times for IV opioids (C3), IV hydration (C4), IV antibiotics (C5) and RBC transfusion (C6) must be appropriately documented (as applicable) in the electronic Case Report Form.

**TTRFD is defined as the difference (in hours) between the date and time when RFD is achieved and the start date and time of the first infusion (loading dose) of study drug.**

Assessment of RFD for a subject

A brief description of the RFD evaluation is given below.

All criteria will be assessed by a member of the study site staff who will complete the RFD questionnaire. The corresponding eCRFs (related to IV opioids, IV hydration, IV antibiotics and RBC transfusion) will also need to be completed by a member of the study site staff. When C1 and/or C2 (as applicable) are documented as being met in the RFD questionnaire by a member of the study site staff other than the Investigator or qualified designee, they must be confirmed by the Investigator or qualified designee, prior to the time the next scheduled assessment is to be made, or the time the subject is discharged, whichever comes first. Confirmation will also be required if there is a change in subsequent assessments of criteria C1 or C2. The Investigator or qualified designee should be deemed, according to the institution's standard of care, appropriately qualified to determine discharge readiness.

*The readiness-for-discharge criteria will be assessed in all subjects at pre-defined intervals (and ad hoc as necessary) from the start time of the loading dose until discharge. Routine assessments are to be performed during "daytime hours" only (defined as 6:01am to 10:00pm). Assessments are not to be performed during "night-time hours" (defined as 10:01pm to 6am), unless it becomes apparent that the subject has become ready-for-discharge during the "night-time hours", in which case an ad hoc assessment should be undertaken.*

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

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

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

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

Evaluation of RFD for a subject

RFD criteria are to be assessed in relation to treatment for the VOC event and acute complication(s) directly related to the VOC event. For C1 and C2, the "YES" or "NO" response with appropriate confirmation from the investigator/designee on the RFD questionnaire is used to determine if these criteria are met. For C3 to C6, the final stop dates and times in the respective eCRFs are used to determine when these criteria are met. If a subject had no acute complications related to VOC, then the response for C2 will be recorded as "NOT APPLICABLE", and C2 will not be included in the determination of TTRFD. Similarly, if a subject never received any IV hydration, IV antibiotics or RBC transfusion for the VOC, then C4, C5 or C6 will not be included in the determination of TTRFD. See **Table 5** for details on determining the date and time when criteria C1-C6 are met.

**Table 5. Determination of Dates and Times When Criteria C1-C6 Are Met**

| Data Source | Criteria | Date and Time when Criterion is Met |
|---|---|---|
| **RFD questionnaire** | **C1** | C1 is considered met at the date and time of the first confirmation of a "YES" response to C1 after the last NO response to C1. |
| | **C2** | If all responses are "NA" then C2 will not be used in the derivation of TTRFD. Otherwise C2 is considered met at the date and time of the first confirmation of a "YES" response to C2 after the last response of "NO" or "NA" to C2. |
| **eCRFs** | **C3** | C3 is considered met at the latest stop date and time of IV Opioids.<br><br>For C3, if IV opioid use ended before the start of the first infusion (loading dose) of study drug, then C3 will be considered as having been met at the date and time of the start of first infusion (loading dose) of study drug. |
| | **C4** | If a subject never received any IV hydration, then C4 is not applicable and will not be used in the TTRFD derivation; otherwise C4 is considered met at the latest stop date and time of IV hydration.<br><br>For C4, if IV hydration use ended before the start of the first infusion (loading dose) of study drug, then C4 will be considered as having been met at the date and time of the start of first infusion (loading dose) of study drug. |
| | **C5** | If a subject never received any IV antibiotics, then C5 is not applicable and will not be used in the TTRFD derivation; otherwise C5 is considered met at |

| Data Source | Criteria | Date and Time when Criterion is Met |
|---|---|---|
| | | the latest stop date and time of IV antibiotics.<br><br>For C5, if IV antibiotics use ended before the first infusion (loading dose) of study drug, then C5 will be considered as having been met at the date and time of the start of first infusion (loading dose) of study drug. |
| | **C6** | If a subject never received a RBC transfusion, then C6 is not applicable and will not be used in the TTRFD derivation; otherwise C6 is considered met at the latest stop date and time of RBC transfusion.<br><br>For C6, if RBC transfusion ended before the first infusion (loading dose) of study drug, then C6 will be considered as having been met at the date and time of the start of first infusion (loading dose) of study drug. |

Derivation of TTRFD

**STEP 1**: For each subject, determine the date and time when each criterion is met, as shown in Table 5 above.

**STEP 2**: Determine the date and time when RFD is achieved, ie, **[RFD date and time]** for each subject.

**[RFD date and time]**

= Latest of the dates and times when the applicable criteria among C1-C6 are met (using Table 5)

**STEP 3:** Determine the TTRFD for each subject.

**TTRFD for a subject (in hours)**

= [RFD date and time] – [Date and time of start of 1st infusion (loading dose) of study drug]

Details on the handling of missing TTRFD data components or TTRFD censoring rules are provided in Section 7.1.





[redacted]

### 6.1.2. Secondary Efficacy Endpoints

**Key Secondary Endpoints:**

- **Time to discharge**, defined as the difference (in hours) between the date and time of the hospital discharge order issued by a qualified health care professional and the date and time of the start of the first infusion (loading dose) of study drug, ie,

  **Time to Discharge (in hours)**

  = [Date and time of hospital discharge order] ─ [Start date and time of 1st infusion (loading dose) of study drug]

- **Cumulative IV opioid consumption in MEU/kg** while the subject is in the hospital, beginning from the start date and time of the first infusion (loading dose) of study drug.

  - See Appendix Section 10.1.1 for derivation details.

- **Time to discontinuation of IV opioids**, defined as the difference (in hours) between the latest IV opioid stop date and time and the start date and time of the first infusion (loading dose) of study drug, ie,

  **Time to discontinuation of IV opioids (in hours)**

  = [Latest stop date and time for IV Opioids] ─ [Start date and time of 1st infusion (loading dose) of study drug]

Note: A bolus injection of an IV opioid and a continuous infusion of IV opioids can occur simultaneously. Therefore, care needs to be taken when identifying the latest stop date and time and/or in the imputation for missing start and/or stop time data for IV opioids.

**Other Secondary Endpoints:**

- *Cumulative IV opioid consumption in MEU/kg within the first 24 hours post the start of the first infusion (loading dose) of study drug.*

  - See Appendix Section 10.1.1 for derivation details.

- Percent of subjects re-hospitalized for VOC within 3 days of discharge.





[redacted]

### 6.2. Safety Endpoints

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

[redacted]





[redacted]

[redacted]

= [Date and time of the first of the 2 or more consecutive pain measurements that [redacted]





[redacted]

### 6.4. Covariates

Age Group (in the case of Cohort 1 and Cohort 2 combined or Cohort 1 alone) and Genotype will be used as covariates in the analysis of covariance (ANCOVA) models.

## 7. HANDLING OF MISSING VALUES

- Missing values for safety endpoints will not be imputed.
- For time to event and IV opioid use calculations, measurement begins from the start date and time of the first infusion (loading dose) of the study drug. If the start date and time of the first infusion of study drug (loading dose) are not available, including scenarios where the subject is randomized but not treated, the time of 12:00 (24-hr clock) on the randomization date, will be used (time of randomization is not collected as part of the study database).

- The time of discontinuation from study is not collected in the study database, therefore 23:59 (24-hr clock) on the date of discontinuation from study will be used, when the time of discontinuation from study is needed for the derivation of any endpoint.

- If the date of death is present, but the time of death is missing, 23:59 (24-hr clock) on the date of death will be used, when the time of death is needed in the derivation of any endpoint.

## 7.1. TTRFD

**Table 6. Handling of Missing TTRFD data components and Censoring Rules**

| Scenario | TTRFD Censored (Yes/No) | Computation of TTRFD (in hours) |
|---|---|---|
| **(i) C1 and/or C2 are never met**<br><br>For a treated subject, the date and time corresponding to C1 and/or C2 used in the computation of the censored TTRFD will be the date and time of the last RFD assessment when C1 and/or C2 are still unmet. | **Yes** | The dates and time for the unmet criteria from C1-C6, will be determined using Section the first column in this table. Dates and time for the met criteria from C1-C6, will be determined using Table 5.<br><br>**TTRFD** = STOP–START; where |
| **(ii) C3, C4, C5, and/or C6 are never met (subject did not discontinue from the study): Start date and time of the latest IV concomitant drug administration is recorded but the stop date and time is missing.**<br><br>For a treated subject, if any applicable criterion among C3-C6, has the latest start date and time for the last administration (of IV concomitant drug) present but the corresponding stop date and time is missing, then that criterion is considered not met. In this case, the time corresponding to the unmet criterion, to be used in the computation of the censored TTRFD, will be the start date and time for the last administration (of IV concomitant drug). | **Yes** | STOP = Latest date and time among the dates and times for the met or unmet criteria from C1- C6;<br><br>START = Start date and time of 1st infusion (loading dose) of study drug. |
| **(iii) Death before RFD criteria met**<br><br>If a treated subject dies in the hospital before RFD criteria are met, then TTRFD will be censored.<br><br>For C1and/or C2, that was not met prior to death, the time used in the computation of censored TTRFD, will be as described in (i) above.<br><br>For any of the criteria C3-C6 where death occurred prior to the recording of latest stop date and time of the corresponding IV concomitant drug, the date and time of death will be used as the date and time | **Yes** | |

| Scenario | TTRFD Censored (Yes/No) | Computation of TTRFD (in hours) |
|---|---|---|
| where the specific criterion was not met. | | |
| **(iv) C3, C4, C5, and/or C6 are never met due to discontinuation from the study: Start date and time of the latest IV concomitant drug administration is recorded but the stop date and time is missing.**<br><br>For a treated subject, if any applicable criterion among C3-C6, has the latest start date and time for the last administration (of IV concomitant drug) present but the corresponding stop date and time missing due to discontinuation from the study, then that criterion is considered not met. In this case, the time corresponding to the unmet criterion, to be used in the computation of the censored TTRFD, will be 23:59 on the date of discontinuation from study. | **Yes** | |
| **(v) Randomized and treated subjects with no data on C1-C6** | **Yes** | TTRFD = 0 hours. |
| **(vi) Randomized but not treated subjects [need to check if there is IV concomitant drug use based on eCRF data at or after 12:00 (24-hr clock) on the randomization date]**<br><br>In the case of missing stop date/time in any of C3-C6 due to discontinuation from the study, the criterion is considered not met. The date/time of the unmet criterion will be 23:59 on the date of discontinuation from study.<br><br>For subjects who have no IV concomitant drug use based on eCRF data at or after 12:00 (24-hr clock) on the date of randomization, the criterion C3 is considered met at 12:00 (24-hr clock) on the date of randomization. Criteria C4-C6 are considered NA. | **Yes** | **TTRFD** = STOP–START; where<br><br>STOP = Latest date and time among the dates and times for the met or unmet criteria from C3- C6 (data are not collected on C1 and C2 for untreated subjects);<br><br>**For subjects who have IV records at or after 12:00 (24-hr clock) on the date of randomization:**<br><br>START = 12:00 (24-hr. clock) on the date of randomization<br><br>**For subjects who have no IV records at or after 12:00 (24-hr clock) on the date of randomization:**<br><br>**TTRFD** = 0 hours. |
| **(vii) C3, C4. C5, C6: Latest stop date present, stop time missing**<br><br>If the stop time is missing, but the corresponding stop date (for any IV concomitant drug administration) is available, the missing stop time will be imputed at 23:59 (24-hr clock), and this criterion will be considered met. | **No** | **TTRFD** is computed as described in Section 6.1.1. |



[redacted]

## 7.2. Time to Discharge

### Table 7. Handling of Missing Data and Censoring Rules for Time to Discharge

| Scenarios | Censored? (Yes/No) | Computation of Time to Discharge (in hours) |
|---|---|---|
| **(i) Death prior to issue of discharge order**<br><br>Subject dies in the hospital prior to issue of the hospital discharge order. | Yes | Time to discharge<br><br>= (Date and time of subject's death) – (Date and time of start of the first infusion [loading dose] of study drug) |
| **(ii) Discharge order date present, discharge order time missing**<br><br>If the discharge order date is present but the discharge order time is missing, the missing time will be imputed as 23:59 on the date of the discharge order. | No | Time to discharge<br><br>= (23:59 [24-hr clock] on the date of the discharge order)<br>– (Date and time of start of the first infusion [loading dose] of study drug) |
| **(iii) Randomized, treated or untreated subjects who are not hospitalized** | Yes | Time to discharge = 0 hours |
| **(iv) Subject discontinuation from study resulting in missing discharge order date and time** | **Yes** | **For randomized and treated subjects:**<br><br>**Time to discharge**<br>= (23:59 on the date of discontinuation from study)<br>– (Date and time of start of the first infusion of study drug)<br><br>**For randomized subjects who are not treated:**<br><br>**Time to discharge**<br>= (23:59 on date of discontinuation from study)<br>– (12:00 [24 hr. clock] on the date of randomization) |





[redacted]

### 7.3. IV opioids use endpoints

This section describes the handling of missing data for the IV opioids (IVO) use endpoints of:

- Cumulative IV opioid consumption while hospitalized;
- Cumulative IV opioid in the first 24 hours;
- Hourly IV opioid in the first 48 hours;
- Daily IV opioid use.

The study site staff will monitor and record all IV opioids used during the study, based on directions provided in the protocol. We do not expect to have an entire missing record for any administration of IVO, but scenarios below describe the derivation of the IVO use endpoints when one or more fields in an individual record are missing:

- Missing final stop date and time (start date/time present) for the final IVO administration:

  If the start date with or without the corresponding start time for the final IV opioid dose is known but the corresponding stop date and/or time are missing, rules defined for handling of missing values/censoring (see Table 8) for the endpoint of time to discontinuation of IV opioids will be used to define the stop date and/or time for the final IV opioid dose.

- Missing start and/or stop time, but the start and stop date, route of administration, opioid dose amount and unit of IV opioid is recorded:

  Depending on the route of administration, the start and/or stop time will be imputed. Typically bolus injections have a total maximum duration of 15 minutes. Missing stop or start time for a bolus injection will be imputed accordingly from the available start or stop time, respectively. For continuous infusions with a missing stop time, the start time for the subsequent infusion will be imputed as the stop time for the previous infusion. For continuous infusions with a missing start time, the stop time of the preceding infusion will be used. When prior or subsequent continuous infusions are not present, then 0:00 will be used as the start time and 23:59 will be used as the stop time. If both start and stop times are missing for a bolus injection, then 12:00 (24-hr clock) noon will be used as the start time and 12:15 as the stop time.

- Dosage for any IV opioid dose missing:

  For any administration of IV opioid for which the opioid dose amount is missing, the primary analysis of IV opioid use endpoints (Cumulative use, daily use, and hourly use from 4-hour interval data for first 48 hours), will not use any imputation for the missing IV opioid dose amount, and the record will be excluded. Therefore the primary analysis of IV opioid used-related endpoints will be based only on the available IV opioid dosage

data with no imputation. The derivation of IV opioid use endpoints is provided in Appendix 10.1.

### 7.4. Time to discontinuation of IV opioids

Time to discontinuation of IV opioids is defined as the difference in hours between the time and date of completion of the last administration of IV opioid and the time and date of initiation of the first infusion (loading dose) of study drug. A bolus injection of an IV opioid and a continuous infusion of IV opioid can occur simultaneously. Therefore, care needs to be taken when identifying the date and time of completion of the last administration of IV opioid.

**Table 8. Handling of Missing Data and Censoring Rules for Time to Discontinuation of IV opioids**

| Scenarios | Censored? (Yes/No) | Computation of Time to Discontinuation of IV opioid (in hours) |
|---|---|---|
| **(i) Death**<br><br>Subject dies in the hospital prior to recording of the latest stop date and time of IV opioid. | **Yes** | **Time to discontinuation of IV opioids**<br><br>= STOP – START; where<br><br>STOP = Date and time of subject's death<br><br>START = Date and time of start of the first infusion (loading dose) of study drug |
| **(ii) Latest IV opioid start date and time are recorded. Stop date is recorded but stop time is missing** | **No** | **Time to discontinuation of IV opioids**<br><br>= STOP – START; where<br><br>STOP = 23:59 on the recorded date of the last IV opioid if the latest IV opioid is a continuous infusion OR STOP = 15 minutes after the start time if the latest IV opioid is a bolus injection.<br><br>START (for treated subjects) = Date and time of the start of the first infusion (loading dose) of study drug.<br><br>START (for randomized but not treated subjects) = 12:00 (24 hr. clock) on the date of randomization. |
| **(iii) Latest IV opioid has start date and time recorded but stop date and time are missing (subject did not discontinue from study)** | **Yes** | **Time to discontinuation of IV opioids**<br><br>=STOP – START; where<br><br>STOP = Start date and time of latest IV opioid.<br><br>START (for treated subjects) = start date and time of the first infusion (loading dose) of study drug.<br><br>START (for randomized but not treated subjects) = |

| Scenarios | Censored? (Yes/No) | Computation of Time to Discontinuation of IV opioid (in hours) |
|---|---|---|
| | | 12:00 (24 hr. clock) on the date of randomization. |
| **(iv) Subject does not have any IV opioid data recorded**. | **No** | **Time to discontinuation of IV opioids**<br><br>=STOP — START =0 hours; where<br><br>For treated subjects, STOP and START are both equal to the date and time of the start of the first infusion (loading dose) of study drug, resulting in a value of zero hours for the time to discontinuation of IV opioids.<br><br>For randomized but not treated subjects, STOP and START are both equal to 12:00 (24-hr clock) on the date of randomization, resulting a value of zero hours for the time to discontinuation of IV opioids. |
| **(v) Discontinuation from study**<br><br>Subject discontinuation from study resulting in incomplete information on IV opioids past the date of discontinuation from study | **Yes** | **Time to discontinuation of IV opioids**<br><br>= STOP — START; where<br><br>STOP = 23:59 (24-hr clock) on date of discontinuation from study.<br><br>START (for treated subjects) = start date and time of the first infusion (loading dose) of study drug.<br><br>START (for randomized but not treated subjects) = 12:00 (24 hr. clock) on date of randomization |
| **(vi) Randomized but not treated subjects** | **No** | **Time to discontinuation of IV opioids**<br><br>=STOP — START; where<br><br>STOP = Stop date and time of latest IV opioid<br><br>**For subjects who have IV opioid records at or after 12:00 (24-hr clock) on the date of randomization:**<br><br>START = 12:00 (24 hr. clock) on the date of randomization<br><br>**For subjects who have no IV opioid records at or after 12:00 (24-hr clock) on the date of randomization:**<br><br>Time to discontinuation of IV opioids = 0 hours. |





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[redacted]

## 8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

### 8.1. Statistical Methods

All analyses will be conducted for Cohort 1 and Cohort 2 combined, Cohort 1 by age group and Cohort 2 separately. Analyses of TTRFD will also be conducted for Cohort 1 alone. In general, counts and percentages will be presented for categorical variables. The number of non-missing observations, mean, standard deviation (standard error of the mean), median, minimum, and maximum will be presented for continuous variables. In addition, graphical displays will be used when appropriate.

#### 8.1.1. Analysis for Time-to-Event Data

Kaplan-Meier product limit method will be used to estimate median with 95% confidence interval and mean time for time-to-event endpoints and to produce a graphical representation of the distribution of time-to response. Difference between treatment median times, estimated mean times with standard error (SE) and the 95% confidence interval (CI) of difference between treatment means will be reported. This difference between the treatment mean times will be considered as the primary estimate for treatment difference in mean times to event.

In addition, the following two supportive mean estimates that are restricted to a cut-off time will be reported with SE, difference between treatment means and the corresponding 95% CI (See Appendix 10.5 for more details):

- **Restricted mean** with cut-off time equal to the minimum of the maximum observed times in the two treatment groups (based on the restricted mean survival time [RMST] methodology)
- **Modified restricted mean** with cut-off time equal to the maximum of the maximum observed times in the two treatment groups

A stratified log-rank test where the stratification variables are Age Group (3 age groups: two in Cohort 1 and one in Cohort 2) and Genotype will be performed for the primary analysis population (Cohort 1 and Cohort 2 combined) to test for differences between the rivipansel and placebo treatment groups.

For each analysis, a Cox regression model with Age Group (for analyses of Cohort 1 and Cohort 2 combined and of Cohort 1 alone) and Genotype (for all analysis groups) as stratification variables will be used to estimate the hazard ratio (HR, placebo rate divided by rivipansel rate) and the corresponding two-sided 95% CI. Note that the HR will be placebo/rivipansel since for data in exponential distributions the HR is equivalent to the reversed ratio of treatment median times to event.



[redacted]

Counts and percentages of subjects who experienced the event as well as counts and percentages of subjects who were censored and the type of censoring (eg, death or missing data) will be reported for each of the treatment groups.

### 8.1.2. Analysis of Binary Data

Descriptive statistics of binary data will include the number of non-missing observations and frequencies of the observed endpoint as well as the observed proportions. A two-sided 95% CI for the difference in proportions and the corresponding p-value will be provided (when appropriate) using the exact method proposed by Chan and Zhang (1999).

### 8.1.3. Analysis of Continuous Data

For continuous variables that have skewed data (eg, cumulative IV opioid use, hourly and daily opioid use), the data will be rank-transformed and ANCOVA, with the covariates of Age Group (for analyses of Cohort 1 and Cohort 2 combined) and Genotype (for all analysis groups), will be used to obtain p-values for the hypothesis of interest. The difference between medians of the untransformed data will be used to estimate the treatment effect. A bootstrap (with stratification by Age Group and Genotype) 95% confidence interval for this difference in medians will be reported.

## 8.2. STATISTICAL ANALYSES

### 8.2.1. Primary Endpoint Analysis

Analysis of the primary endpoint TTRFD will be performed using the FAS and the methods described in Section 8.1.1 with specific details provided below. The primary endpoint will be analyzed in Cohort 1 and Cohort 2 combined (as the primary analysis population), as well as Cohort 1 (alone and by age group) and Cohort 2 separately.

**Cohort 1 and Cohort 2 Combined:**

Primary Efficacy Analysis: The primary analysis will consist of a stratified log-rank test to compare the survival distributions of the primary endpoint TTRFD between the rivipansel and placebo groups, where the stratifications are age group and genotype. The trial will meet the primary objective if this stratified log-rank test is statistically significant using an alpha of 5% (ie, 2-sided log-rank test p-value $\leq 0.05$).





[redacted]

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### 8.2.2. Key Secondary Endpoint Analysis

A fixed-sequence approach will be used to control overall Type I error for the primary and key secondary endpoints at 0.05 for Cohort 1 and Cohort 2 combined. Please see Section 4.2 for details. Analyses of all key secondary endpoints are based on the FAS.

1. Time to discharge (in hours) will be analyzed in the same manner as the primary endpoint using the methods described in Section 8.1.1 except that analyses will not be performed for Cohort 1 alone.

2. Cumulative IV opioid consumption (in MEU/kg) will be analyzed using an ANCOVA model as described in Section 8.1.3, using rank-transformed cumulative IV opioid consumption data. This endpoint will not be analyzed for Cohort 1 alone.

3. Time to discontinuation of IV opioid (in hours) will be analyzed in the same manner as the primary endpoint using the methods described in 8.1.1 except that analyses will not be performed for Cohort 1 alone.

### 8.2.3. Sensitivity Analyses

To support the interpretation of the analyses of the primary and key secondary endpoints (described in 8.2.1. and 8.2.2), robustness or sensitivity analyses will be performed. [redacted]

[redacted]





[redacted]

The alternative definition of date and time when C1/C2 are met would result in





[redacted]

### 8.2.4. Other Secondary Endpoints Analysis

Analyses of all of the secondary endpoints for Cohort 1 and Cohort 2 combined and for Cohort 1 by Age Group and Cohort 2 separately are based on the FAS.

- Cumulative IV opioid consumption in MEU/kg within the first 24 hours post-loading dose of study drug (See Appendix Section 10.1.1 for details).

  This endpoint will be analyzed using an ANCOVA model as described in Section 8.1.3. using rank-transformed endpoint data.

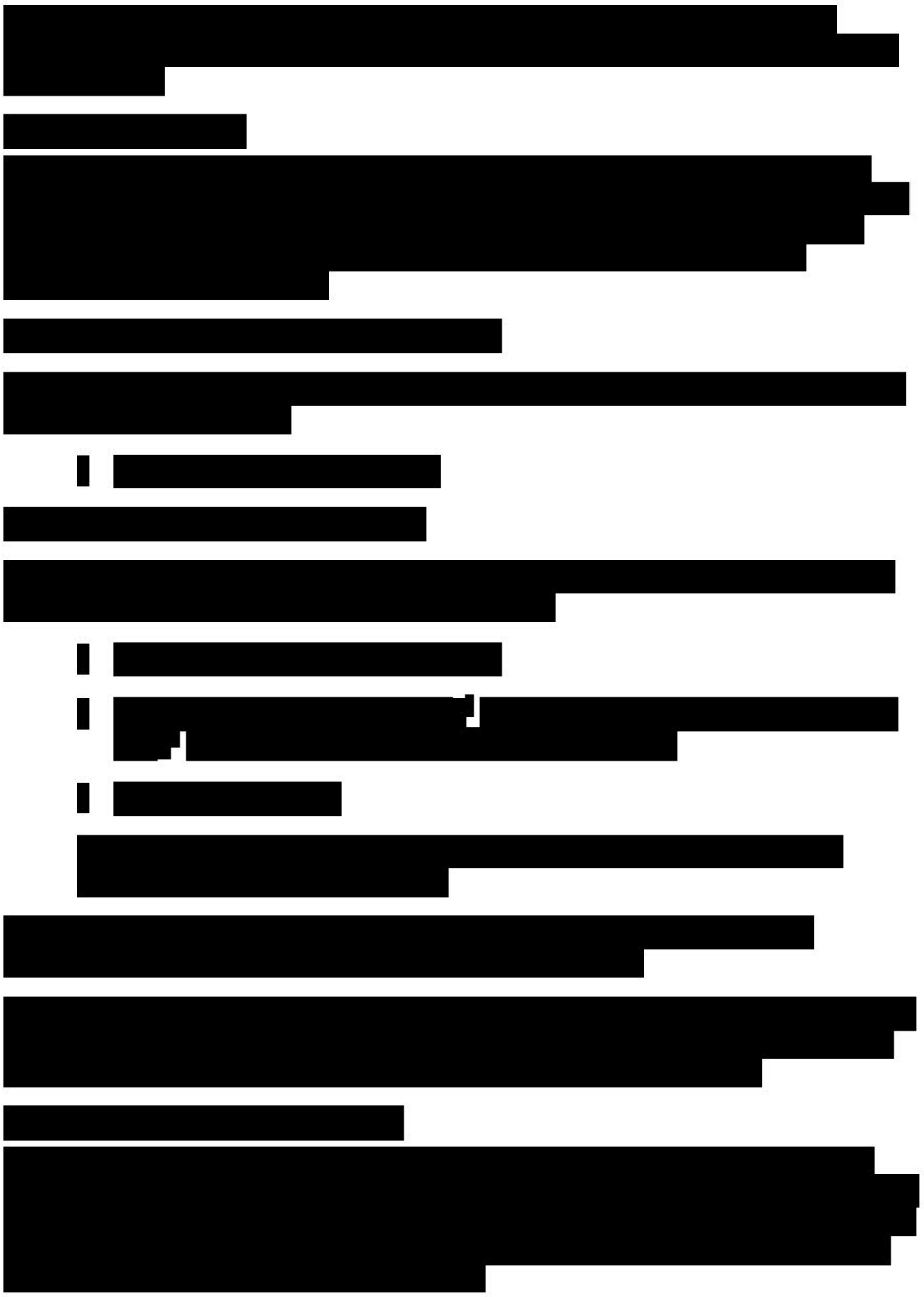
- Percent of subjects re-hospitalized for VOC within 3 days of discharge

  This endpoint will be analyzed using the statistical methods for binary endpoints described in Section 8.1.2.

[redacted]



[redacted]



## 8.5. Analysis of Safety Data

For Cohort 1 and Cohort 2 combined, Cohort 1 by age group and Cohort 2 alone based on the Safety Analysis Set, the safety data (eg, AEs, SAEs, vital signs, physical examinations, laboratory tests) will be summarized in accordance with CDISC and Pfizer Standards (CaPS). In addition, for Cohort 1 and Cohort 2 combined ONLY, a 3-tier approach described below will be used for summarizing AE data. Safety data that will be specifically summarized include:

- Adverse events:

  The analyses of adverse events will make use of the 3-tiered approach described below for Cohort 1 and Cohort 2 combined ONLY. These analyses will be considered exploratory. Under the 3-tier approach, AEs are classified into one of three tiers with different analyses performed for different tiers.

  - Tier-1 events: These are events that are pre-specified events of clinical importance and are maintained in the custom AE term list system (CAETeLiSt).

  - Tier-2 events: These are events that are not ier-1 but are "common". A MedDRA Preferred Term (PT) is defined as a Tier-2 event ("common" event) if there are at least 4 in any treatment group.

  - Tier-3 events: These are events that are neither tier-1 nor tier-2 events. Tier-3 events will be reported with observed proportions by treatment group without comparative statistics.

  For Tier-1 events, the unconditional exact method for 95% CI for risk difference and p-value proposed by Chan and Zhang (1999) will be used to compare rivipansel with placebo. For Tier-2 events, the normal approximation will be used for calculating the 95% CI for risk difference. There will be no adjustment for multiple comparisons or stratification factors in the analyses.

- Safety laboratory tests reported according to CDISC and Pfizer standards (CaPS). Shift tables summarizing the changes in laboratory test results from baseline will be presented (see Appendix Section 10.3 for details on shift tables).

- Incidence of clinically significant changes in physical examination will be summarized using descriptive statistics.

- Change from baseline at End of Treatment and at the Day 35 Post-discharge Visit in vital signs (eg, blood pressure, heart rate, temperature, respiratory rate, and pulse oximetry) will be reported using descriptive statistics.

- Incidence of adjudicated AEs will be analyzed using the same approach as for Tier-1 events.

- Percentage of subjects re-hospitalized for VOC within 7, 14 and 30 days of discharge will be summarized using descriptive statistics.

- AE data (Summary of TEAE-all causality, TEAE-all causality, TE-SAE-all causality) will be also reported for the following 3 non-age subgroups: Genotype, Hydroxyurea use at baseline and Gender based on the safety analysis set in Cohort 1 and Cohort 2 Combined.

[redacted]





[redacted]





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## 9. REFERENCES


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# 10. APPENDICES

## 10.1. Derivation for Endpoints

### 10.1.1. Cumulative IV Opioid Consumption

The cumulative amount of IV opioid use will be standardized using morphine equivalent units (MEU). The conversion to MEU will be performed using the formula below:

$$\text{Cumulative MEU} = \sum_{i=1}^{n} (\text{Total dose of the } i^{th} \text{ IV medication in mg})/(E_i)\text{x}10 \qquad (1)$$

where $E_i$ is the equianalgesic dose for the $i^{th}$ IV medication.

Alternatively the cumulative MEU could be calculated using the following formula:

$$\text{Cumulative MEU} = \sum_{i=1}^{n} (\text{Total dose of the } i^{th} \text{ IV medication in mg}) \text{ x } CF_i \qquad (2)$$

where $CF_i$ is the conversion factor for the $i^{th}$ IV medication.

Equianalgesic doses for opioids, shown in below table, were obtained from the VHA/DoD Guideline for the Management of Postoperative Pain (https://www.healthquality.va.gov/guidelines/Pain/pop/pop_fulltext.pdf).

**Equianalgesic Doses for IV Opioids**

| Medication | Route | Equianalgesic Dose (mg) | Conversion Factor (CF) to Give Morphine Equivalent* |
|---|---|---|---|
| Buprenorphine | IV | 0.3 | 33.33 |
| Butorphanol | IV | 2 | 5 |
| Codeine | IV | 120 | 0.083 |
| Dezocine | IV | 10 | 1 |
| Fentanyl | IV | 0.1** | 100 |
| Hydromorphone | IV | 1.4 | 7.14 |
| Levorphanol | IV | 2 | 5 |
| Meperdine | IV | 87.5** | 0.114 |
| Methadone | IV | 10 | 1 |
| Morphine | IV | 10 | 1 |
| Nalbuphine | IV | 10 | 1 |
| Oxymorphone | IV | 1 | 10 |
| Pentazocine | IV | 30 | 0.333 |

*Conversion Factor = 10 / (Equianalgesic Dose) which is based on 10mg morphine.

** The morphine conversions for doses administered via IM or IV are equivalent. Reference: https://cha.com/wp-content/uploads/2018/04/Colorado-Opioid-Safety-Pilot-Conversion-Table-1.pdf.

Once the cumulative opioid usage is expressed in MEU, this dosage will be normalized by dividing by the subject's body weight (ie, MEU/kg).

- For cumulative IV opioid consumption for the treated VOC all administered IV opioid doses after the start of the first infusion (loading dose) of study drug while the subject is hospitalized, will be counted using formula (1).

- For cumulative IV opioid consumption within the first 24 hours post-loading dose of study drug, the total computed in formula (1) will be from the start of the first infusion (loading dose) of study drug to 24 hours after the start of the first infusion (loading dose) of study drug.

### 10.1.2. Hourly IV Opioid Use in MEU/kg/hour (every 4 hours, for the first 48 hours post-loading dose of study drug)

Hourly IV opioid use (based on data collected every 4 hours) will be calculated by first totaling the amount of IV opioids administered in increments of 4 hours for the first 48 hours after the start of the first infusion (loading dose) of study drug. The amount of IV opioid use will be standardized using morphine equivalent units (MEU) (see Section 10.1.1). Hourly IV opioid use will then be calculated by dividing the total amount of opioids used within each 4-hour period by 4. This quantity will then be normalized by dividing by the subject's body weight. Consequently, hourly IV opioid use will be expressed in units of MEU /kg/hour. A subject will be assigned an IV opioid use of 0 for any 4-hour period in which the subject did not receive any IV opioids. For subjects who are discharged less than 48 hours after the first infusion (loading dose) of study drug, the subject's hourly IV opioid use will be assigned a value of 0 for any 4-hour interval within the 48-hour period that occurs after the subject has been discharged from hospital.

### 10.1.3. Daily IV Opioid Use

In this study, subjects may receive study drug for up to 8 days (up to 15 doses of study drug: 1 loading dose and a maximum of 14 maintenance doses). In the Phase 2 study, 79% of subjects were discharged from hospital within 8 days. Therefore, daily IV opioid use will be analyzed from Day 1 through Day 8. The subject's daily opioid use will be the total amount of opioid used in increments of 24 hours starting at the start of the first infusion (loading dose) of study drug and continuing for the entire duration of the subject's hospitalization or through the Day 8 / Hour 24 time point. The amount of IV opioid received will be standardized using morphine equivalent units (MEU) and normalized by the subject's body weight (see Section 10.1.1). A subject will be assigned an IV opioid use of 0 for any day in which the subject did not receive any IV opioids. For subjects who are discharged before Day 8, the subject's daily IV opioid use will be assigned a value of 0 for any 24-hour interval within the 8-day period that occurs after the subject has been discharged from hospital.

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## 10.2. Definition and Use of Visit Windows in Reporting

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[redacted]

[redacted]

[redacted]

Other Endpoints:

For other endpoints, such as physical examination and vital signs, the data will be analyzed and presented based on the CRF recorded study visit time point. If there is more than one record for the same subject at the same time point, the most clinically extreme value will be



[redacted]

used as the observation for that time point. All observations will, however, be included in the listings.

### 10.3. Shift Tables for Reporting of Laboratory Test Results

For the lab variables included in the table below, shift tables will be generated showing the shift at End of treatment and at the Day 35 post-discharge follow-up visit, from the grade category at Baseline.

| Lab parameters | Grade | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Hemoglobin | >11g/dl | >9 to 11 g/dl | >7 to 9 g/dl | 5 to 7 g/dl | <5g/dl |
| Reticulocyte Count | <1% | 1 to 5% | >5 to 10% | >10 to 20% | >20% |
| Leukocyte (WBC) | ≤ ULN | >ULN to 15,000/mm3 | >15,000 to 20,000/mm3 | >20,000 to 50,000/mm3 | >50,000/mm3 |
| Absolute Neutrophil Count (ANC) | ≥ LLN | <LLN to 1,500/mm3 | <1,500 to 1,000 /mm3 | <1,000 to 500/mm3 | <500/mm3 |
| Blood urea nitrogen (BUN) | ≤ ULN | >ULN to 1.5 x ULN | >1.5 to 3.0 x ULN | >3.0 x ULN | >6.0xULN |
| Creatinine | ≤ ULN | >ULN to 1.5 x ULN | >1.5 to 3.0 x ULN | >3.0 x ULN | >6.0 x ULN |
| Lactate dehydrogenase (LDH) | ≤ ULN | >ULN to 3.0 x ULN | >3.0 to 5.0 x ULN | >5.0 to 20.0 x ULN | >20.0 x ULN |
| Alanine transaminase (ALT/SGPT) | ≤ ULN | >ULN to 3.0 x ULN | >3.0 to 5.0 x ULN | >5.0 to 20.0 x ULN | >20.0 x ULN |
| Aspartate aminotransferase (AST/SGOT) | ≤ ULN | >ULN to 3.0 x ULN | >3.0 to 5.0 x ULN | >5.0 to 20.0 x ULN | >20.0 x ULN |
| Fractionated bilirubin | ≤ ULN | >ULN to 1.5 x ULN | >1.5 to 3.0 x ULN | >3.0 to 10.0 x ULN | >10.0 x ULN |
| Urine Protein | Negative (0-15 mg/dL) | Trace (>15-30 mg/dL) | 1+ (>30-100 mg/dL) | 2+ (>100-300 mg/dL) | 3+ or 4+ (>300 mg/dL) |
| Platelet | ≥ 150K | ≥ 100K to <150K | ≥ 50K to <100K | <50K | |
| eGFR | ≥ 90 mL/min/1.73 m^2 | ≥ 60 to < 90 mL/min/1.73 m^2 | ≥ 30 to < 60 mL/min/1.73 m^2 | ≥ 15 to < 30 mL/min/1.73 m^2 | <15 mL/min/1.73 m^2 |

### 10.4. Futility Interim Analysis

Conditional power would have been used to aid decision-making around an interim futility assessment. Conditional power is the probability that the final study result will be statistically significant, given the data observed up to the data cutoff for the interim, and a specific assumption about the pattern of the data to be observed in the remainder of the study (such as the original assumed treatment effect, or the observed effect at the interim, or under the null hypothesis). The conditional power for this study would have been calculated based on the protocol-assumed treatment effect occurring for the remainder of the study.





[redacted]

If conditional power were low (≤ 20%) this would have been considered to indicate futility and hence a lack of identifiable efficacy benefit from the addition of rivipansel to standard of care for the treatment of sickle cell VOC. However, as this futility IA was only to be conducted in the presence of a significant safety concern, the safety profile would also need to have been carefully assessed to determine overall risk/benefit. Consequently, the E-DMC could potentially have recommended stopping the study for futility with conditional power >20%.

Detailed calculation for conditional power is provided below:

Conditional power ( $P(\theta)$ , 1-sided) at look $k$ $(0,...,k,...,K)$ is calculated as shown below (Chang, 2008):

$$P(\theta) = \Phi\left( \frac{-Z_k\sqrt{I_k} - z_{0.975}\sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}} \right)$$

where $\theta = \log(HR) = \log(\lambda_p / \lambda_r)$ , $\lambda_p$ , $\lambda_r$ are the hazard rates for placebo group and rivipansel group respectively. From the protocol assumption, $\theta = \log(HR) = -0.386417$. $\Phi$ is the cumulative distribution function of the standard normal distribution, $Z_k = S_k / \sqrt{I_k}$ is the test statistic, $S_k$ is the log-rank score statistic at look $k$ , $I_k = E_k P_1(1-P_1)$ is the information level, $E_k$ is the number of events and $P_1$ is the proportion of the subjects assigned to the placebo group.

**10.5. Estimated mean for time to event endpoints**

Three methods will be used to calculate the mean time to event.

The first method calculates the mean survival time using all of the available data (TIMELIM=observed option in SAS PROC LIFETEST).

The second method provides the restricted mean survival time (RMST). The RMST methodology is applicable independently of the proportional hazards (PH) assumption and can be used, at a minimum, as a supplemental analysis to explore the robustness of the primary analysis results. A restricted mean time is calculated up to a cut-off point in time, which is defined as the minimum between the largest observed times in rivipansel and placebo groups. The PROC LIFETEST procedure is applied with a data step (Qi and Wang, 2018) to overcome the limitation of the procedure.

The third method provides the modified restricted mean, which is calculated up to the cut-off point in time of the maximum of the maximum observed times in rivipansel and placebo groups. If the smaller maximum observed time is censored, the smaller maximum observation is imputed with the maximum of maximum observed times in the two treatment groups prior to calculation.

For each method, SAS procedure PROC LIFETEST is used to estimate the mean ($x_1$ and $x_2$) and standard error ($s_1$ and $s_2$) for each treatment group.

The difference between the means in the two treatment groups is estimated by $x_1 - x_2$.

The standard error (SE) of the difference is estimated by

$$SE_{x_1 - x_2} = \sqrt{s_1^2 + s_2^2}$$

The associated 95% CI for the difference between means is

$$(x_1 - x_2) \pm Z_{0.975} * SE_{x_1 - x_2}$$

### 10.6. SCHEDULE OF ACTIVITIES

The Schedule of Activities table below provides an overview of the protocol visits and procedures. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.





[redacted]

## Schedule of Activities

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



[redacted]

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



[redacted]

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



[redacted]

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

a. Temperature, respiratory rate, pulse, blood pressure, pulse oximetry.
b. Hematology and serum chemistry. See Table 3 in Section 7.2.3.
c. See Table 3 in Section 7.2.3.
d. Serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, is required to be performed on all female subjects of childbearing potential. A negative pregnancy test result is required before study drug may be administered; study drug may not be administered when the pregnancy test result is indeterminate or positive. Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations.

[redacted]

g. Sample will only be collected if subject's diagnosis of SCD (ie, laboratory result by hemoglobin electrophoresis, High Performance Liquid Chromatography [HPLC], or genotype analysis) cannot be source documented.

[redacted]

i. For subjects ≥12 years of age.
j. All eligible subjects should be dosed with study drug as early as possible, but the start of study drug dosing should be no later than 24 hours from the administration of the first dose of IV opioids. Dosing to continue every 12 (±2) hours until criterion 1 of the readiness-for-discharge criteria has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.
k. Study site staff will complete readiness-for-discharge criteria using an electronic device (eg, smart phone, tablet, or computer) to access an electronic data capture system. The criteria will be assessed in all subjects at pre-defined intervals (and ad hoc as necessary) from the start time of the loading dose until discharge. Routine assessments are to be performed during "daytime hours" only (defined as 6am to 10pm). Assessments are not to be performed during "night-time hours" (defined as 10pm to 6am), unless it becomes apparent that the subject has become ready-for-discharge during the "night-time hours", in which case an ad hoc assessment should be undertaken. In addition, an assessment should always be made at the time the decision is made to discharge the subject, regardless of the hour. See Section 7.1.1.
l. All parenteral opioid administration will be collected daily (eg, subcutaneous, intravenous, etc), but specifically intravenous opioid administration will be recorded approximately every 4 hours for the first 48 hours from the start time of the loading dose, then daily until discharge.
m. Informed consent/assent for the Open Label Extension Study may be obtained from the time of the Day 35 Post-Discharge Follow Up visit up to 180 days after the Day 35 Post-Discharge Follow-Up visit.
n. Investigators are asked to identify, through chart review, those subjects who may be appropriate for the study before they develop VOC. These subjects may be educated about the study while they are well, for example in the office setting, and approached for consent/assent (Pre-VOC/Study Entry Screening). Serious adverse events must be reported to Pfizer from the time of signing Pre-VOC/Study Entry informed consent. Formal assessment for eligibility into the study or enrollment/randomization will not be performed at this time. At the time of VOC, the subject will be asked if they want to continue participating in the VOC/Treatment-Ready Screening and if eligible, be randomly assigned to blinded study drug. The subject's affirmation must be documented. Other subjects may be initially approached for consent when presenting to the emergency room/clinic in VOC.
o. Contacts are to be conducted every 4 weeks (±7 days) from the time of signing the consent/assent to the VOC/Treatment-Ready Screening visit (may be a clinic visit instead of a phone call, if preferred).
p. During the first 24 hours from the start time of the loading dose.
q. Every 4 (±1) hours (while awake).
r. Assessment to be collected at 8 (±4) hours after start of loading dose, while subject is awake.
s. Performed daily through 24 hours after the last dose of study drug (if not discharged first).
t. Performed daily until time of discharge.



[redacted]