JAMA | Original Investigation

Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease
A Randomized Clinical Trial

James F. Casella, MD; Bruce A. Barton, PhD; Julie Kanter, MD; L. Vandy Black, MD, MSc; Suvankar Majumdar, MD; Adlette Inati, MD; Yasser Wali, MD; Richard A. Drachtman, MD; Miguel R. Abboud, MD; Yurdanur Kilinc, MD; Beng R. Fuh, MD; Murtadha K. Al-Khabori, MD; Clifford M. Takemoto, MD; Emad Salman, MD; Sharada A. Sarnaik, MD; Nirmish Shah, MD; Claudia R. Morris, MD; Jennifer Keates-Baleeiro, MD; Ashok Raj, MD; Ofelia A. Alvarez, MD; Lewis L. Hsu, MD, PhD; Alexis A. Thompson, MD, MPH; India Y. Sisler, MD; Betty S. Pace, MD; Suzie A. Noronha, MD; Joseph L. Lasky III, MD; Elena Cela de Julian, MD, MSc, PhD; Kamar Godder, MD; Courtney Dawn Thornburg, MD, MS; Natalie L. Kamberos, DO; Rachelle Nuss, MD; Anne M. Marsh, MD; William C. Owen, MD; Anne Schaefer, MD; Cameron K. Tebbi, MD; Christophe F. Chantrain, MD, PhD; Debra E. Cohen, MD; Zeynep Karakas, MD; Connie M. Piccone, MD; Alex George, MD; Jason M. Fixler, MD; Tammuella C. Singleton, MD; Thomas Moulton, MD; Charles T. Quinn, MD, MS; Clarisse Lopes de Castro Lobo, MD, PhD; Abdulkareem M. Almomen, MD; Meenakshi Goyal-Khemka, MD; Philip Maes, MD; Marty Emanuele, PhD, MBA; Rebecca T. Gorney, MS; Claire S. Padgett, PhD; Ed Parsley, DO; Shari S. Kronsberg, MS; Gregory J. Kato, MD; Mark T. Gladwin, MD

IMPORTANCE Although effective agents are available to prevent painful vaso-occlusive episodes of sickle cell disease (SCD), there are no disease-modifying therapies for ongoing painful vaso-occlusive episodes; treatment remains supportive. A previous phase 3 trial of poloxamer 188 reported shortened duration of painful vaso-occlusive episodes in SCD, particularly in children and participants treated with hydroxyurea.

OBJECTIVE To reassess the efficacy of poloxamer 188 for vaso-occlusive episodes.

DESIGN, SETTING, AND PARTICIPANTS Phase 3, randomized, double-blind, placebo-controlled, multicenter, international trial conducted from May 2013 to February 2016 that included 66 hospitals in 12 countries and 60 cities; 388 individuals with SCD (hemoglobin SS, SC, S-β^0 thalassemia, or S-β^+ thalassemia disease) aged 4 to 65 years with acute moderate to severe pain typical of painful vaso-occlusive episodes requiring hospitalization were included.

INTERVENTIONS A 1-hour 100-mg/kg loading dose of poloxamer 188 intravenously followed by a 12-hour to 48-hour 30-mg/kg/h continuous infusion (n = 194) or placebo (n = 194).

MAIN OUTCOMES AND MEASURES Time in hours from randomization to the last dose of parenteral opioids among all participants and among those younger than 16 years as a separate subgroup.

RESULTS Of 437 participants assessed for eligibility, 388 were randomized (mean age, 15.2 years; 176 [45.4%] female), the primary outcome was available for 384 (99.0%), 15-day follow-up contacts were available for 357 (92.0%), and 30-day follow-up contacts were available for 368 (94.8%). There was no significant difference between the groups for the mean time to last dose of parenteral opioids (81.8 h for the poloxamer 188 group vs 77.8 h for the placebo group; difference, 4.0 h [95% CI, −7.8 to 15.7]; geometric mean ratio, 1.2 [95% CI, 1.0-1.5]; $P = .09$). Based on a significant interaction of age and treatment ($P = .01$), there was a treatment difference in time from randomization to last administration of parenteral opioids for participants younger than 16 years (88.7 h in the poloxamer 188 group vs 71.9 h in the placebo group; difference, 16.8 h [95% CI, 1.7-32.0]; geometric mean ratio, 1.4 [95% CI, 1.1-1.8]; $P = .008$). Adverse events that were more common in the poloxamer 188 group than the placebo group included hyperbilirubinemia (12.7% vs 5.2%); those more common in the placebo group included hypoxia (12.0% vs 5.3%).

CONCLUSIONS AND RELEVANCE Among children and adults with SCD, poloxamer 188 did not significantly shorten time to last dose of parenteral opioids during vaso-occlusive episodes. These findings do not support the use of poloxamer 188 for vaso-occlusive episodes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01737814

JAMA. 2021;325(15):1513-1523. doi:10.1001/jama.2021.3414

Visual Abstract

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Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: James F. Casella, MD, Pediatric Hematology, The Johns Hopkins University School of Medicine, 720 Rutland Ave, Baltimore, MD 21205 (jcasella@jhmi.edu).

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Sickle cell disease (SCD) is a group of inherited hemoglobinopathies for which the hallmark feature is the acute painful vaso-occlusive episode. There are 3 agents approved by the US Food and Drug Administration for the prevention of painful vaso-occlusive episodes (hydroxyurea, L-glutamine, and crizanlizumab-tmca). No available agent effectively manages vaso-occlusive episodes once they have begun.[1] Current treatment remains supportive, with analgesia and hydration. Frequent vaso-occlusive episodes are also associated with higher mortality in individuals with SCD.[2] Acute pain is estimated to account for 95% of hospital admissions for those with SCD, creating a burden for individuals with SCD, their families, and health care systems.[3] The ability to reduce the severity and duration of vaso-occlusive episodes would be a significant advance.

The pathophysiology of vaso-occlusive episodes involves inflammation, hemolysis, hemostasis, cell adhesion, vaso-occlusion, and reperfusion injury. Vaso-occlusion results from complex interactions of sickle red blood cells, leukocytes, and platelets with the endothelium, mediated by adhesive molecules and receptors, including P-selectins, E-selectins, vascular cellular adhesion molecule 1, von Willebrand factor, glycoprotein Ib, thrombospondin, CD36 receptors, fibronectin, and vitronectin.[4-7] Inhibition of these interactions remains an attractive therapeutic target. Poloxamer 188 (vepoloxamer, MST-188, RheothRx) is a nonionic block polymer surfactant for which numerous activities have been reported, including improved microvascular blood flow by blocking cell-to-cell interactions, reduced blood viscosity and adhesion of sickle cells to endothelium, and antithrombotic and anti-inflammatory properties.[8]

Poloxamer 188 has been evaluated in 3 clinical trials of SCD demonstrating safety and possible efficacy for painful vaso-occlusive episodes and acute chest syndrome, which involves intrapulmonary vascular occlusion and/or infection.[9-12] These studies included a previous phase 3 trial that suggested efficacy for painful vaso-occlusive episodes, particularly in children and participants receiving hydroxyurea.[10]

Because intravenous poloxamer 188 is neither approved by the US Food and Drug Administration nor available for clinical use and because other drugs for managing ongoing vaso-occlusive episodes are absent, the present trial was designed to determine whether poloxamer 188 is efficacious for painful vaso-occlusive episodes in SCD.

Key Points

Question Can poloxamer 188, an agent that is reported to reduce blood viscosity and cell-cell interactions, effectively reduce the duration of vaso-occlusive episodes (painful crises) in hospitalized patients with sickle cell disease?

Findings In this randomized clinical trial that included 388 children and adults with sickle cell disease, treatment with poloxamer 188 vs placebo resulted in mean time to last dose of parenteral opioids during vaso-occlusive episodes of 81.8 vs 77.8 hours, a difference that was not statistically significant.

Meaning Among patients with sickle cell disease, poloxamer 188 did not significantly shorten the duration of painful vaso-occlusive episodes.

Methods

Study Design

Overview

The Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease (EPIC) study was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial designed to assess the effectiveness of poloxamer 188 in reducing the duration of painful vaso-occlusive episodes in SCD. The protocol and statistical analysis plan are included in Supplement 1 and Supplement 2. Institutional review board or ethics committee approval was obtained at each site as well as written informed consent for each participant, including assent from children, following institutional guidelines. A data and safety monitoring board met at least annually and actively monitored study conduct and participant safety throughout the study.

Patients

Participants were enrolled between May 2013 and February 2016 at 46 sites in the US and 20 non-US sites in 11 countries (Belgium, Brazil, Dominican Republic, Jamaica, Jordan, Lebanon, Oman, Panama, Saudi Arabia, Spain, and Turkey) (eTable 1 in Supplement 3). The final date of follow-up was April 7, 2016. The study included patients hospitalized for acute pain typical of vaso-occlusive episodes requiring treatment with parenteral opioid analgesia. Moderate to severe pain lasting at least 4 hours before randomization was required. Outpatient screening for eligibility and baseline studies was allowed, but hospital admission was required for randomization. Full inclusion/exclusion criteria are included in eTable 2 in Supplement 3. Race and ethnicity were self-reported because SCD disproportionately affects some populations and disease severity can vary by ethnic group and race. Categories were presented by the investigator, with the option for participants to self-define under "other." The initial study design included participants aged 8 to 18 years with hemoglobin SS or S-β^0 thalassemia phenotype, but was later amended to allow inclusion of individuals aged 4 to 65 years as well as other SCD phenotypes (hemoglobin SC and S-β^+ thalassemia).

Randomization

Participants who met all eligibility requirements were centrally registered and randomly assigned in a 1:1 ratio to receive poloxamer 188 or placebo using permuted blocks with sizes of 4 to 8. Randomization was stratified by age (<16 or ≥16 years), use of hydroxyurea (yes or no), and pain score (<8 or ≥8) using the Wong-Baker FACES Pain Rating Scale[13,14] at randomization.

Intervention

After randomization (target of <2 hours and not >24 hours after presentation), poloxamer 188 or placebo was administered intravenously as a 1-hour loading dose of 100 mg/kg,

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followed by a continuous infusion at 30 mg/kg/h for at least 13 hours (1-hour loading; 12-48 hours of maintenance infusion). The maximum infusion time was 49 hours of actual infusion, which could be given over a period of 53 hours to allow for up to 4 cumulative hours of interrupted infusion. The bag or bottle of infusate, infusion lines, and drip chambers were covered with opaque sheaths and foil to maintain blinding. Concurrent use of hydroxyurea was allowed if a stable dose was expected throughout the study. Use of parenteral opioids was initially restricted to morphine, hydromorphone, nalbuphine, and tramadol. Transdermal opioid patches were prohibited. Allowable oral opioids included codeine, hydrocodone, hydromorphone, morphine, and oxycodone. Ketorolac was the only allowable parenteral, nonsteroidal anti-inflammatory agent. Allowable nonopioid analgesics included acetaminophen, aspirin, diclofenac sodium, ibuprofen, and naproxen. Long-acting variants of oral analgesics were allowed. The protocol was later amended to include parenteral preparations of allowed oral opioids. Sites were encouraged to adhere to standardized pain treatment guidelines. All opioid and nonopioid analgesic use was recorded. Systemic corticosteroids for painful vaso-occlusive episodes, L-glutamine after randomization, and other investigational treatments for painful vaso-occlusive episodes were prohibited. Participants were followed up for 30 days after discharge. Screening procedures included chest radiograph, platelet count, creatinine, alanine transaminase, and pregnancy testing, if applicable.

Outcomes

The primary outcome was hours from randomization until the last administration of parenteral opioid analgesic for painful vaso-occlusive episodes prior to hospital discharge.

Secondary outcomes included hospitalization for recurrence of painful vaso-occlusive episodes within 14 days of initial hospital discharge and occurrence of acute chest syndrome within 120 hours of randomization. Acute chest syndrome was defined per the National Acute Chest Syndrome Study Group.[15]

Prespecified subgroups included age at randomization (<16, ≥16 years); sex; use of hydroxyurea (yes, no), with "yes" defined as receiving hydroxyurea at least 14 days before randomization and continuing to receive hydroxyurea until at least the day before randomization; Wong-Baker FACES Pain Rating Scale score (range, 0 [no pain] to 10 [worst pain]) at randomization (<8, ≥8); duration of pain at presentation (≤12, >12 hours); region/country (US, non-US); hemoglobin phenotypes; and younger than 16 years with hydroxyurea use at a US study site. Because of a shorter duration of crisis for children younger than 16 years and those receiving hydroxyurea in the previous phase 3 study, age and hydroxyurea use were prespecified for comparison.

Other prespecified analyses included length of study drug infusion, total opioid use (morphine equivalents/kg) from time of randomization to discharge, time from randomization to discharge, re-hospitalization at 30 days, and pharmacokinetics and pharmacodynamics (not analyzed in the current study).

Statistical Analyses

Sample Size

Using data from the previous phase 3 study, the sample size was calculated based on a mean time to last dose of parenteral opioids of 96 hours for the placebo group vs 80 hours for the poloxamer 188 group (presumed 20% improvement) (Marty Emanuel, PhD, Visgenx, email, February 15, 2021), a 2-sided α of .05, and a coefficient of variation of 54% (accounting for log-normal distribution). Under these assumptions, a sample size of 376 (188 per group) achieved 90% power to detect a significant difference between treatment groups using a 2-sample *t* test. To account for dropout of 3%, the sample size was adjusted to 388 participants (194 per group). Sample size calculations were performed using SAS, version 9.3, PROC POWER for a 2-sample mean comparison. The same statistical software was used for all other statistical analyses.

Primary Outcome Analysis

Primary outcomes were analyzed by randomization group, including all randomized patients (primary analysis population; **Figure 1**). For participants who received no parenteral opioids after randomization, 1 hour (zero on log scale) was imputed as their time to last dose of parenteral opioids. For participants who were receiving parenteral opioids for reasons other than vaso-occlusive episodes, if the time of the last vaso-occlusive episode–related parenteral opioid dose was not documented, 3 blinded observers adjudicated the primary outcome. No other imputations were performed.

The primary outcome was compared between treatment groups using analysis of covariance (ANCOVA) modeling with natural logarithm time as the outcome,[16] adjusting for the prespecified stratification groups.

Least squares means and differences from ANCOVA modeling were calculated to obtain geometric means and mean ratios due to the log-normally distributed primary outcome. The reported *P* values were from the 2-sided *t* test. For prespecified sensitivity analyses of primary outcomes and subgroups, nonparametric stratified van Elteren tests were used, as well as time-to-event Kaplan-Meier analyses with log-rank test statistics.

Interaction terms were added to the main ANCOVA model, in the form of treatment × covariate, to test for differential treatment effects in subgroups. Two-sided *P* values <.05 were considered significant, without multiplicity adjustment.

To detect heterogeneity of treatment effect across sites, an ANCOVA model for the primary outcome was fit with treatment as a fixed effect.[17] Random effects were site and treatment × site interaction, using type III tests to determine overall significance of the random effects. To maintain stability of treatment effect within site, only sites with at least 5 participants were included in the analysis.

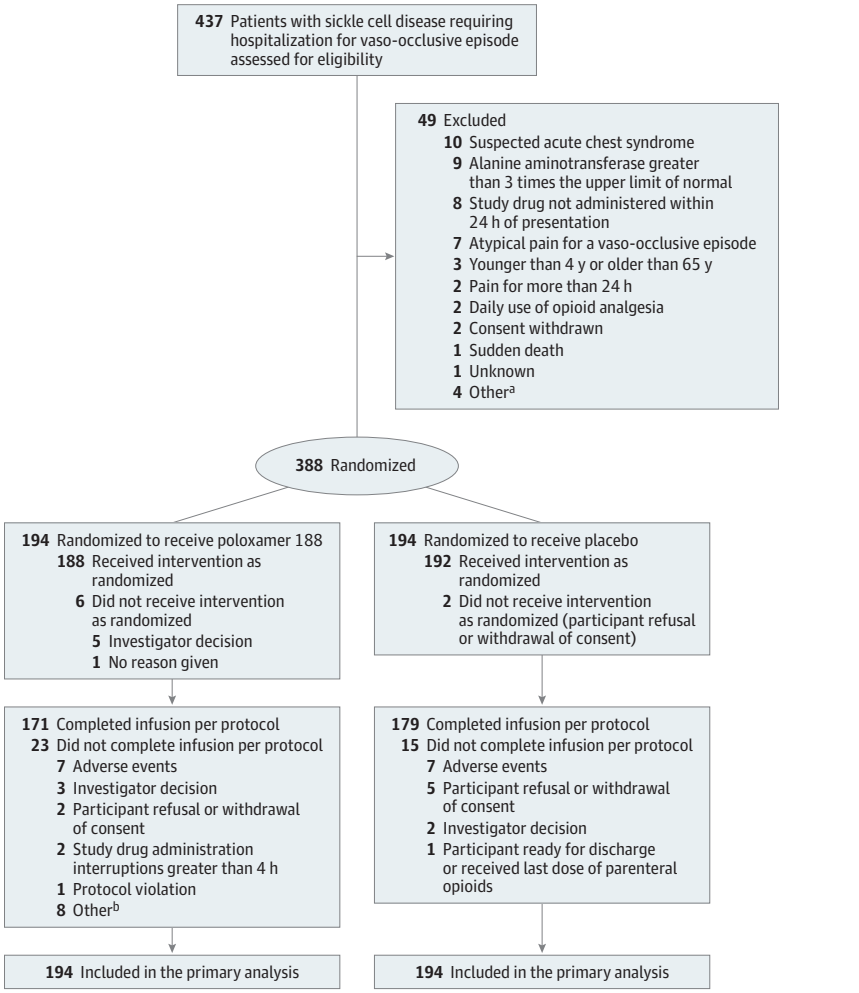
Secondary Outcome Analyses

The number of participants hospitalized for painful vaso-occlusive episode recurrences within 14 days of initial discharge was tabulated by treatment group. The denominator was the number of participants with at least 1 follow-up visit or contact at least 14 days after initial hospital discharge.

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Figure 1. Participant Flow in a Study of the Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease



[a] Including 1 participant with known or suspected bleeding disorder, 1 with pain crisis requiring hospitalization in the preceding 14 days, 1 for whom it was the investigator's belief that the participant was suffering from chronic pain and not acute pain associated with an ongoing vaso-occlusive episode, and 1 who was not an appropriate study candidate (investigator decision).

[b] Including 3 participants who did not receive the investigational drug, 3 whose total duration of infusion exceeded 53 hours, 1 for whom infusion could not be started within 24 hours of presentation to site, and 1 who withdrew immediately after the start of the loading dose.

A likelihood ratio test was used to compare the percentage of re-hospitalized participants in each treatment group. A logistic model was constructed to adjust for stratification factors. In a prespecified sensitivity analysis, a time-to-event analysis was conducted for time from hospital discharge to re-hospitalization. The statistical analysis was hierarchical; significance for the secondary outcomes was not declared unless the *P* value for the primary analysis was less than .05.

The number and percentage of participants with acute chest syndrome occurring within 120 hours of randomization were tabulated by treatment group. The primary and survival sensitivity analyses were performed in the same way as they were for re-hospitalization; for analyses of percentages by treatment group, adjustment was made for the same predictive factors.

Other Prespecified Analyses

For the length of study drug infusion, total opioid use, and time from randomization to discharge, the approach was analogous to the primary outcome. Thirty-day re-hospitalization was analyzed as a binary outcome, analogous to 14-day re-hospitalization. Predictors were modeled as binary variables with a chosen reference level.

Significance of each variable was based on the ANCOVA model parameter Z test. Geographic region (based on similarities and differences in standard treatment protocols for patients with SCD) was tested as a center-pooled variable, with smaller sites combined into a single prespecified region (eg, the 3 Saudi Arabian sites were included as "Saudi Arabia"). Because non-US regions were not significantly different among themselves, region was condensed to a dichotomous variable (US, non-US).

Adverse Event Analyses

The safety population included participants who received a study infusion, with groups defined by treatment received. Summaries of treatment-emergent adverse events (TEAEs), coded using the Medical Dictionary for Regulatory Activities, were screened to identify TEAEs for which 95% CIs of the difference between treatment groups did not include 0. Multiple adverse event records for an individual were counted as a single adverse event if preferred terms were the same and

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the dates were contiguous. TEAEs were analyzed by incidence in each treatment group, as well as severity, seriousness, and potential relationship to study medication.

Results

Patient Population

A total of 388 participants were enrolled in the trial (194 randomized to receive poloxamer 188 and 194 randomized to receive placebo). Key demographic variables and baseline characteristics are shown in **Table 1**. A total of 227 participants (58.5%) were younger than 16 years, with an overall mean age of participants of 15.2 years. The groups were well-balanced for other demographic characteristics, laboratory parameters, and baseline study characteristics, including duration of pain at presentation and randomization, baseline pain scores, and time from randomization to study drug administration.

Eight participants received no study treatment after randomization (6 in the poloxamer 188 group and 2 in the placebo group; Figure 1). Five participants received their last dose of parenteral opioids before randomization (1 in the poloxamer 188 group and 4 in the placebo group) and were assigned a time of 1 hour (natural logarithm time to last dose of parenteral opioids = 0). Time and date of the last dose of parenteral opioids were unavailable for 4 participants (1 in the poloxamer 188 group and 3 in the placebo group). They were assigned a time to last dose of parenteral opioids of 1 hour; thus, the primary outcome was available for 384 of 388 (99.0%) participants and imputed for 4 (1.0%). Fifteen-day follow-up contacts occurred for 357 participants (92.0%) and 30-day follow-up contacts occurred for 368 (94.8%). Fourteen-day re-hospitalization data were available for 192 participants (99.0%) in the poloxamer 188 group and 190 (97.9%) in the placebo group and 30-day re-hospitalization data were available for 132 participants (68.0%) in the poloxamer 188 group and 142 (73.2%) in the placebo group.

Primary Outcome

For the primary analysis population, there was no significant difference between treatment groups in the mean time from randomization to last administration of parenteral opioids by ANCOVA (81.8 hours in the poloxamer 188 group vs 77.8 hours in the placebo group; difference, 4.0 hours [95% CI, −7.8 to 15.7]; geometric mean ratio, 1.2 [95% CI, 1.0-1.5]; P = .09; **Table 2**). Box and Kaplan-Meier plots are shown in **Figure 2**.

Secondary Outcomes

For the primary analysis population, there were 32 participants with acute chest syndrome in the poloxamer 188 group (16.5%) and 22 (11.3%) in the placebo group (difference, 5.2% [95% CI, −1.7% to 12.0%]). Sixteen of 192 participants (8.3%) in the poloxamer group and 13 of 190 (6.8%) in the placebo group with 15-day follow-up visits were re-hospitalized for recurrence of painful vaso-occlusive episodes within 14 days (difference, 1.5% [95% CI, −3.8% to 6.8%]) (Table 2). Because of the hierarchical statistical testing, significance was not declared for the secondary outcomes.

Prespecified Subgroup Analyses

Based on a significant interaction of age and treatment (P = .01), there was a treatment difference in the mean time from randomization to last administration of parenteral opioids by ANCOVA for participants younger than 16 years, favoring the placebo group (88.7 hours in the poloxamer 188 group vs 71.9 hours in the placebo group; difference, 16.8 hours [95% CI, 1.7-32.0]; geometric mean ratio, 1.4 [95% CI, 1.1-1.8]; P = .008; Van Elteren test P < .05). For participants aged 16 years and older, the mean time from randomization to last administration of parenteral opioids was 71.7 hours in the poloxamer 188 group vs 86.0 hours in the placebo group (difference −14.3 hours [95% CI, −32.8 to 4.3]; geometric mean ratio, 0.9 [95% CI, 0.7-1.4]; P = .76; Van Elteren test P = .82) (Table 2). For participants who received hydroxyurea (n = 236), the results of the interaction test between hydroxyurea (yes, no) and treatment were not significant. Among the subgroup of participants younger than 16 years, there were 24 acute chest syndrome events (20.9%) in the poloxamer 188 group vs 12 (10.7%) in the placebo group (difference, 10.2% [95% CI, 0.8%-19.5%]); among participants aged 16 years or older, 8 acute chest syndrome events (10.1%) occurred in the poloxamer 188 group and 10 (12.2%) occurred in the placebo group (difference, −2.1% [95% CI, −11.8% to 7.7%]). Because acute chest syndrome was a secondary outcome, significance was not declared for either subgroup. Results of all other subgroup analyses, including duration of pain at presentation, pain score at randomization, and region, were nonsignificant (eTable 4 in Supplement 3).

Site Effects

A post hoc test for site × treatment interaction indicated no significant heterogeneity of treatment effect across the 25 sites with at least 5 participants (F_{23} = 0.91; P = .58).

Other Prespecified Analyses

No significant differences were seen for length of study drug infusion, total opioid use in morphine equivalents, time from randomization to discharge, or re-hospitalization for painful vaso-occlusive episode within 30 days (eTable 5 in Supplement 3).

Adverse Events

The 189 participants in the poloxamer 188 group and 191 participants in the placebo group safety population were compared for adverse events across all system organ classes and specific adverse events. Adverse events that were more common in the poloxamer 188 group than the placebo group included abdominal distension, hepatobiliary disorders, hyperbilirubinemia, and upper respiratory infections; hypoxia and infusion site swelling and pain were more common in the placebo group than in the poloxamer 188 group (**Table 3**). The majority of hepatobiliary disorders (77.3%) were elevated direct or total bilirubin, known adverse effects of poloxamer 188,[10] which resolved in all participants in the poloxamer 188 group who were tested at the 30-day follow-up visit. Serious adverse events were similar between the poloxamer 188 and placebo groups, but anemia was more common in the placebo group (4 vs 0 participants) (Table 3).

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Table 1. Demographic and Baseline Characteristics of Participants in a Study of the Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease

Characteristic	Mean (SD)		Normal values[a]
	Poloxamer 188 (n = 194)	Placebo (n = 194)	
Demographic characteristics			
Age at randomization, y	15.2 (6.2)	15.1 (7.3)	
Age <16 y, No. (%)[b]	115 (59.3)	112 (57.7)	
Sex, No. (%)			
Male	105 (54.1)	107 (55.2)	
Female	89 (45.9)	87 (44.8)	
Ethnicity, No. (%)			
Hispanic or Latino	31 (16.0)	20 (10.3)	
Race, No. (%)[c]			
Black/African descent	109 (57.4)	118 (61.5)	
White	63 (33.2)	62 (32.3)	
Other	18 (9.5)	12 (6.3)	
Weight at screening, kg	47.8 (18.9)	48.7 (22.3)	
Hemoglobin phenotype, No. (%)[d]			
SS disease	134 (69.1)	129 (66.5)	
S-β^+ thalassemia disease	21 (10.8)	28 (14.4)	
S-β^0 thalassemia disease	20 (10.3)	19 (9.8)	
SC disease	19 (9.8)	18 (9.3)	
Participants receiving hydroxyurea, No. (%)	117 (60.3)	119 (61.3)	
US hospital, No. (%)	107 (55.2)	121 (62.4)	
Baseline laboratory characteristics[e]			
White blood cell count, $\times 10^{-3}/\mu L$	15.2 (5.9) [n = 188]	13.7 (5.6) [n = 190]	4.5-15.5
Hemoglobin, g/dL	9.1 (1.5) [n = 188]	9.2 (1.6) [n = 190]	11.7-16.3
Mean corpuscular volume, fL	85.9 (14.4) [n = 188]	84.0 (13.2) [n = 190]	75.0-100.0
Mean corpuscular hemoglobin concentration, g/dL	34.4 (1.8) [n = 186]	34.1 (1.8) [n = 190]	31.0-37.0
Platelet count, $\times 10^{-3}/\mu L$	373.7 (171.2) [n = 188]	351.0 (162.3) [n = 190]	150.0-350.0
Reticulocyte count, %	8.8 (5.8) [n = 167]	8.2 (5.6) [n = 163]	0.5-1.8
Creatinine, mg/dL	0.5 (0.2) [n = 189]	0.5 (0.2) [n = 188]	0.3-1.3
Lactate dehydrogenase, median (IQR), U/L[e]	594.0 (482.0) [n = 171]	532.0 (464.0) [n = 169]	110.0-295.0
Bilirubin, mg/dL			
Total	2.8 (2.0) [n = 185]	2.5 (1.7) [n = 182]	0.0-1.2
Direct	0.5 (0.4) [n = 175]	0.4 (0.3) [n = 165]	0.0-0.4
Aspartate aminotransferase, U/L	52.5 (30.4) [n = 185]	47.9 (23.5) [n = 182]	≤37.0
Alanine transaminase, U/L	28.4 (22.4) [n = 188]	25.0 (17.5) [n = 185]	≤40.0
Key baseline study characteristics			
Duration of pain at presentation, h[f]	6.5 (5.4) [n = 193]	7.2 (6.0) [n = 192]	
Time from presentation to randomization, h	13.7 (6.6)	13.6 (6.4)	
Duration of pain prior to randomization, h	20.2 (7.8)	20.6 (8.4)	
Wong-Baker FACES Pain Rating Scale score at randomization, No. (%)[g]			
<8	94 (48.5)	95 (49.0)	
≥8	100 (51.5)	99 (51.0)	
Time from randomization to study drug start, h	2.2 (1.7) [n = 188]	2.0 (1.5) [n = 192]	

Abbreviation: IQR, interquartile range.

SI conversion factors: To convert white blood cell count and platelet count to 10^9/L, multiply values by 0.001; hemoglobin and mean corpuscular hemoglobin concentration to g/L, multiply by 10.0; creatinine to μmol/L, multiply by 88.4; bilirubin to μmol/L, multiply by 17.104; and lactate dehydrogenase, aspartate aminotransferase, and alanine transaminase to μkat/L, multiply by 0.0167.

[a] For laboratory values for which normal values vary significantly for children and adults, the values represented are the lowest and highest values for either children or adults.[18]

[b] The age of 16 years was chosen as the cutoff to mirror that used in the previous phase 3 trial so that comparisons of results could be made between the trials.

[c] Race was not reported for 2 participants in the poloxamer 188 group and 2 participants in the placebo group. Race was reported as unknown for 2 participants in the poloxamer 188 group. "Other" race was designated on the demographic form and further detail was not available.

[d] Hemoglobin SS (HbSS) is homozygous HbS (sickle cell anemia). HbS-β^+ thalassemia is double heterozygosity for HbS and β plus thalassemia trait. Some normal adult hemoglobin (HbA) is present. HbS-β^0 thalassemia is double heterozygosity for HbS and beta null thalassemia. No HbA is present. HbSC is double heterozygosity for HbS and HbC.

[e] Mean (SD) is shown when normally distributed and median (IQR) is shown otherwise.

[f] Duration of pain at presentation was self-reported and measured as time of onset of moderate/severe vaso-occlusive episode to time of hospitalization.

[g] The Wong-Baker FACES Pain Rating Scale (range, 0-10) is a 6-item ordinal scale depicting painful and nonpainful faces that are each assigned an ordinal value, with 0 representing no pain and 10 representing the worst pain.[13]

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Table 2. Outcomes in a Study of the Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease[a,b]

Outcome	Poloxamer 188	Placebo	Difference (95% CI)	Least squares geometric mean ratio (95% CI)[c]	*P* value[d]
Primary outcome					
Time from randomization to last administration of parenteral opioids for treatment of vaso-occlusive episodes, mean, h					
Primary analysis population	81.8 (n = 194)	77.8 (n = 194)	4.0 (−7.8 to 15.7)	1.2 (1.0 to 1.5)	.09
Participants aged <16 y	88.7 (n = 115)	71.9 (n = 112)	16.8 (1.7 to 32.0)	1.4 (1.1 to 1.8)	.008
Participants aged ≥16 y	71.7 (n = 79)	86.0 (n = 82)	−14.3 (−32.8 to 4.3)	0.9 (0.7 to 1.4)	.76
Secondary outcomes, No./total No. (%)					
Acute chest syndrome	32/194 (16.5)	22/194 (11.3)	5.2 (−1.7 to 12.0)		
Re-hospitalization for recurrence of vaso-occlusive episodes within 14 d of initial hospital discharge	16/192 (8.3)	13/190 (6.8)	1.5 (−3.8 to 6.8)		

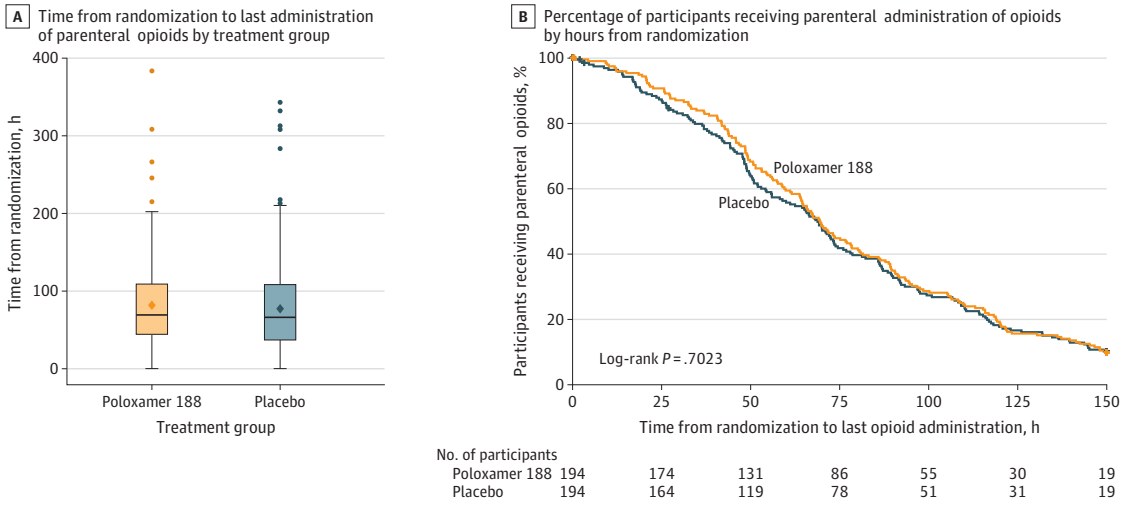
[a] All primary analysis population results are shown. Only prespecified subgroups for which interaction testing was significant are shown. The interaction between treatment and age was significant (*P* = .01). Interactions between treatment and other subgroups of interest, including hydroxyurea usage and region, were tested and found to be not significant (*P* = .51 and *P* = .87). All other nonsignificant prespecified analyses are shown in eTables 3, 4, and 5 in Supplement 3.

[b] Comparisons between treatment groups in the primary efficacy analysis were adjusted for age (<16, ≥16), hydroxyurea use (yes, no), Wong-Baker FACES Pain Rating Scale score at randomization (<8, ≥8), and region (US, non-US) in an analysis of covariance model. Secondary outcome comparisons between treatment arms were adjusted for the same variables, using logistic regression.

[c] For the primary outcome, the natural log transformation was applied to individual values prior to conducting each analysis. The least squares means and least squares mean differences were calculated on a log scale and transformed back to the original scale using the exponential function to obtain geometric means and geometric mean ratios. The least squares geometric mean ratio is an indication of the difference between the log mean time for poloxamer 188 and placebo adjusted for other factors in the model. A CI that does not include 1.0 indicates a significant difference.

[d] Computed using a geometric analysis of covariance test.

Figure 2. Time From Randomization to Last Administration of Parenteral Opioids in a Study of the Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease



A, The mean values are represented as diamonds. Outliers are represented as circles beyond the whiskers. Error bars indicate the highest and lowest values within 1.5 × the interquartile range. The median (interquartile range) time from randomization to last administration of parenteral opioids was 69.2 (44.7-108.7) hours in the poloxamer 188 group and 66.4 (37.8-107.3) hours in the placebo group. B, No significant difference in time from randomization to last administration of parenteral opioids was observed between treatment groups in the primary analysis population.

Discussion

In the current study, there was no evidence of favorable effects of poloxamer 188 on time to last dose of parental opioids. In contrast to the apparent benefit to participants younger than 16 years in the previous phase 3 study, apparent harm with poloxamer 188 was found in this age group in the current study.

Prior to the current study, more than 300 participants with SCD and painful vaso-occlusive episodes or acute chest syndrome were treated with poloxamer 188 in phase 1 to phase 3 studies. A placebo-controlled, randomized, phase 2 study of 28 participants treated with poloxamer 188 and 22 who were given placebo showed statistically significant differences in use of parenteral opioids, with non-statistically significant reductions in pain intensity and durations of crisis

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Table 3. Adverse Events in a Study of the Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease

Adverse event	No. (%)	
	Poloxamer 188 (n=189)	Placebo (n=191)
Treatment-emergent adverse events[a]		
≥1 Adverse event	184 (97.4)	186 (97.4)
Abdominal distension	4 (2.1)	0
Hepatobiliary disorders	30 (15.9)	14 (7.3)
Hyperbilirubinemia	24 (12.7)	10 (5.2)
Hypoxia	10 (5.3)	23 (12.0)
Infusion site pain	0	4 (2.1)
Infusion site swelling	0	4 (2.1)
Upper respiratory tract infection	15 (7.9)	5 (2.6)
Treatment-emergent serious adverse events[b]		
≥1 Serious adverse event	64 (33.9)	57 (29.8)
Anemia	0	4 (2.1)

[a] Treatment-emergent adverse events (TEAEs) were defined as AEs occurring after the start of infusion; existing AEs that worsened during the study; or AEs that began prior to the start of infusion but were reported as possibly, probably, or definitely related to treatment. The safety group and all subgroups were screened by the Medical Dictionary for Regulatory Activities system organ class and preferred terms for TEAEs for which the 95% CIs of the difference between treatment groups did not include 0. Multiple AE records for an individual participant were counted as a single AE occurrence if preferred terms were the same and the stop date of the first AE matched the start date of the subsequent AE. TEAEs were analyzed with respect to incidence in each randomized treatment group, as well as by severity, seriousness, and potential relationship of the AE to the study medication.

[b] TEAEs that were fatal, were life-threatening, required hospitalization, or prolonged hospitalization.

and hospitalization, all favoring the poloxamer 188 group.[9] These results led to a multicenter, double-blind, randomized, placebo-controlled, phase 3 study of 255 children and adults with painful vaso-occlusive episodes that reported a reduction in mean duration of crisis (the primary outcome) of 8.8 hours (P = .04).[10] The reduction was greater (approximately 21 hours) in participants younger than 16 years (127.1 hours in the poloxamer 188 group and 148.6 hours in the placebo group; P = .01) and in those receiving hydroxyurea (approximately 16 hours) (141.4 hours in the poloxamer 188 group vs 157.2 hours in the placebo group; P = .02). The study did not reach its enrollment goal (350 participants), raising the question of whether a larger study might have shown more significant results. The authors concluded that these results needed to be confirmed in subsequent clinical trials.

In evaluating such discrepant results in 2 phase 3 studies, several factors were considered. The findings may have occurred by chance; however, assuming the null hypothesis is correct (no difference between poloxamer 188 and placebo), the odds that 2 studies would produce such differing results in participants younger than 16 years by chance would be less than 1 in 10 000 (0.008 × 0.01). Thus, it seems likely that additional factors affected the results. The current study enrolled a younger population (mean age of 15.2 years vs 21.1 years), but was otherwise similar in design. The most significant difference was the primary outcome.

The choice of outcome measure has been critical to studies of SCD, especially for painful vaso-occlusive episodes. Assessment of pain is subjective and difficult to quantify. There are no precise biomarkers for painful vaso-occlusive episodes. In the first phase 3 study, stringent crisis termination criteria were used as an outcome. It proved difficult for study personnel and participants to adhere to these criteria, with a high rate of incomplete documentation of crisis resolution criteria (61 of 255 participants [23.9%]). In addition, these occurrences were unevenly distributed; more participants in the placebo group (38 of 128 [29.7%]) fell into this category than participants in the poloxamer 188 group (23 of 127 [18.1%]). This resulted in imputation for more participants in the placebo group than in the poloxamer 188 group, with assignment of the worst possible outcome of 168 hours, the imbalance favoring the poloxamer 188 group. Participants whose crises did not resolve in 168 hours were also assigned the worst possible outcome. Overall, 145 participants (56.9%) did not meet crisis resolution criteria within 168 hours, including 62 of 127 (48.8%) in the poloxamer 188 group and 83 of 128 (64.8%) in the placebo group, and were assigned the worst possible outcome. This included 6 randomized participants who did not receive the study drug (5 in the placebo group and 1 in the poloxamer 188 group) who were assigned the worst possible outcome, contributing to the imbalance in results for duration of crisis. Without these 6 participants, the P value increased from .04 to .07.[10]

In the current study, the study team attempted to develop an easily verified, quantifiable outcome measure more likely to be attained for each participant. Thus, time to last dose of parenteral opioids was selected as the primary outcome measure. This primary outcome was available for 99% of study participants, limiting imputations to 1%, which avoided imbalances in participants reaching verifiable outcomes seen in the prior study.

In the first phase 3 study, a small, nonsignificant difference was seen in the incidence of acute chest syndrome for children (3 of 37 in the poloxamer 188 group vs 6 of 36 in the placebo group). No beneficial effect on acute chest syndrome was seen in the current study. Rather, although not statistically significant, there were more participants younger than 16 years who developed acute chest syndrome in the poloxamer 188 group than in the placebo group, paralleling the direction of effects on the primary outcome for participants younger than 16 years.

In the current study, there were no apparent effects on acute chest syndrome or readmission for painful vaso-occlusive episodes in participants receiving hydroxyurea, despite the known effect of hydroxyurea in reducing rates of painful vaso-occlusive episodes and acute chest syndrome. Also, significant reductions in duration of crisis for participants receiving hydroxyurea in either treatment group were not seen. Cautious interpretation is warranted because the study was not designed to address these questions, more severely affected patients may be prescribed hydroxyurea, and hydroxyurea adherence for participants in the trial is unknown.

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Limitations

This study has several limitations. First, the primary outcome measure, although it is quantitative and relatively easy to determine, still has subjective aspects. A variety of factors contribute to decisions to discontinue parenteral opioids, including patient, family, and clinician preferences and timing of assessments, which can vary widely among sites and individuals. Second, poloxamer 188 is difficult to blind effectively. As a detergent, agitation can cause foaming that might unblind participants or staff to treatment assignment. Although appropriate blinding procedures were in place, assessment of their success was not performed in this study or previous studies of poloxamer 188.

Conclusions

Among children and adults with SCD, poloxamer 188 did not significantly shorten time to last dose of parenteral opioids during vaso-occlusive episodes. These findings do not support the use of poloxamer 188 for vaso-occlusive episodes.

ARTICLE INFORMATION

Accepted for Publication: February 23, 2021.

Author Affiliations: Johns Hopkins University School of Medicine, Baltimore, Maryland (Casella, Takemoto, Gorney); University of Massachusetts Medical School, Worcester (Barton, Kronsberg); Medical University of South Carolina, Charleston (Kanter); University of Alabama at Birmingham, Birmingham (Kanter); Our Lady of the Lake Regional Medical Center, Baton Rouge, Louisiana (Black); University of Florida College of Medicine, Gainesville (Black); University of Mississippi Medical Center, Jackson (Majumdar); Children's National Hospital, Washington, DC (Majumdar); Lebanese American University, Byblos and Beirut, Lebanon (Inati); Nini Hospital, Tripoli, Lebanon (Inati); Sultan Qaboos University, Muscat, Oman (Wali, Al-Khabori); Rutgers University, New Brunswick, New Jersey (Drachtman); American University of Beirut Medical Center, Beirut, Lebanon (Abboud); Çukurova University Medical Faculty Balcali Hospital, University of Çukurova, Adana, Turkey (Kilinc); East Carolina University, Greenville, North Carolina (Fuh); St Jude Children's Research Hospital, Memphis, Tennessee (Takemoto); Golisano Children's Hospital of Southwest Florida, Ft Myers (Salman); Wayne State University School of Medicine, Detroit, Michigan (Sarnaik); Children's Hospital of Michigan, Detroit (Sarnaik); Duke University School of Medicine, Durham, North Carolina (Shah); Emory University School of Medicine, Atlanta, Georgia (Morris); Children's Healthcare of Atlanta, Atlanta, Georgia (Morris); T.C. Thompson Children's Hospital at Erlanger, University of Tennessee, Chattanooga (Keates-Baleeiro); University of Louisville/Norton Children's Hospital, Louisville, Kentucky (Raj); University of Miami, Miami, Florida (Alvarez); University of Illinois at Chicago, Chicago (Hsu); Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, Evanston, Illinois (Thompson); Children's Hospital of Richmond at Virginia Commonwealth University, Richmond (Sisler); Augusta University, Augusta, Georgia (Pace); University of Rochester School of Medicine and Dentistry, Golisano Children's Hospital at University of Rochester Medical Center, Rochester, New York (Noronha); Harbor-UCLA Medical Center, Torrance, California (Lasky); Cure 4 The Kids Foundation, Las Vegas, Nevada (Lasky); Hospital General Universitario Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain (de Julian); Nicklaus Children's Hospital, Miami, Florida (Godder); Rady Children's Hospital - San Diego, San Diego, California (Thornburg); UC San Diego School of Medicine, La Jolla, California (Thornburg); University of Iowa Children's Hospital, Iowa City (Kamberos); Loyola University Medical Center, Maywood, Illinois (Kamberos); Children's Hospital Colorado, University of Colorado, Aurora (Nuss); UCSF Benioff Children's Hospital Oakland (UBCHO), Oakland, California (Marsh); University of Wisconsin–Madison, Madison (Marsh); Children's Hospital of the King's Daughters, Norfolk, Virginia (Owen); Joe DiMaggio Children's Hospital, Hollywood, Florida (Schaefer); Tampa General Hospital, Tampa, Florida (Tebbi); Clinique MontLegia, CHC, Liège, Belgium (Chantrain); UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania (Cohen); Studer Family Children's Hospital Ascension Sacred Heart, University of Florida, Pensacola (Cohen); Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey (Karakas); Rainbow Babies and Children's Hospital, Cleveland, Ohio (Piccone); Carle Foundation Hospital, Urbana, Illinois (Piccone); Baylor College of Medicine, Houston, Texas (George); Wake Forest School of Medicine, Winston-Salem, North Carolina (George); The Herman and Walter Samuelson Children's Hospital at Sinai, Baltimore, Maryland (Fixler); Tulane University, New Orleans, Louisiana (Singleton); Mississippi Center for Advanced Medicine, Slidell, Louisiana (Singleton); Bronx-Lebanon Hospital, Bronx, New York City, New York (Moulton); Bayer Pharmaceuticals, Whippany, New Jersey (Moulton); Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Quinn); Instituto estadual de Hematologia Arthur de Siqueira Cavalcanti – HEMORIO, Rio de Janeiro, Brasil (de Castro Lobo); Blood and Cancer Center, King Khalid University Hospital (KKUH), King Saud University Medical City, Riyadh, Saudi Arabia (Almomen); Phoenix Children's Hospital, Phoenix, Arizona (Goyal-Khemka); Rutgers Cancer Institute of New Jersey, New Brunswick (Goyal-Khemka); University Hospital of Antwerp (UZA), Edegem, Belgium (Maes); Visgenx, San Diego, California (Emanuele); Mast Therapeutics Inc, San Diego, California (Emanuele, Padgett, Parsley); Sanifit Therapeutics, San Diego, California (Padgett); Biotechnology, San Diego, California (Parsley); CSL Behring, King of Prussia, Pennsylvania (Kato); University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Kato, Gladwin).

Author Contributions: Drs Casella and Barton had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Casella, Barton, Kanter-Washko, Black, Kilinc, Thompson, Quinn, Lopes de Castro Lobo, Almomen, Emanuele, Padgett, Parsley, Kato, Gladwin.
Acquisition, analysis, or interpretation of data: Casella, Barton, Kanter-Washko, Black, Majumdar, Inati, Wali, Drachtman, Abboud, Kilinc, Fuh, Al-Khabori, Takemoto, Salman, Sarnaik, Shah, Morris, Keates-Baleeiro, Raj, Alvarez, Hsu, Thompson, Sisler, Pace, Noronha, Lasky, Cela de Julian, Godder, Thornburg, Kamberos, Nuss, Marsh, Owen, Schaefer, Tebbi, Chantrain, Cohen, Karakas, Piccone, George, Fixler, Singleton, Moulton, Quinn, Goyal-Khemka, Maes, Emanuele, Gorney, Padgett, Parsley, Kronsberg, Kato.
Drafting of the manuscript: Casella, Barton, Kanter-Washko, Black, Majumdar, Drachtman, Sarnaik, Karakas, Parsley, Kronsberg.
Critical revision of the manuscript for important intellectual content: Casella, Barton, Kanter-Washko, Black, Majumdar, Inati, Wali, Abboud, Kilinc, Fuh, Al-Khabori, Takemoto, Salman, Sarnaik, Shah, Morris, Keates-Baleeiro, Raj, Alvarez, Hsu, Thompson, Sisler, Pace, Noronha, Lasky, Cela de Julian, Godder, Thornburg, Kamberos, Nuss, Marsh, Owen, Schaefer, Tebbi, Chantrain, Cohen, Piccone, George, Fixler, Singleton, Moulton, Quinn, Lopes de Castro Lobo, Almomen, Goyal-Khemka, Maes, Emanuele, Gorney, Padgett, Parsley, Kato, Gladwin.
Statistical analysis: Barton, Black, Kronsberg.
Obtained funding: Emanuele, Gladwin.
Administrative, technical, or material support: Casella, Kanter-Washko, Black, Inati, Kilinc, Fuh, Al-Khabori, Sarnaik, Keates-Baleeiro, Hsu, Thompson, Lasky, Nuss, Chantrain, Karakas, George, Lopes de Castro Lobo, Goyal-Khemka, Emanuele, Gorney, Padgett, Parsley, Kato, Gladwin.
Supervision: Casella, Barton, Inati, Drachtman, Morris, Pace, Lasky, Godder, Owen, Chantrain, Fixler, Singleton, Almomen, Maes, Emanuele, Parsley, Kato.
Other - drafting protocol, membership in steering committee, involvement in manuscript drafting: Kato.
Other - Conduct of the clinical trial and data collection for analysis: Padgett.
Other - site PI for study; recruitment and management of study participants; participation in investigator meetings: Takemoto.
Other - Responsible for recruitment of patients at my institution, administration of study drug, collection of data on every enrolled patient: Keates-Baleeiro.
Other - patient enrollment and supervision of study interventions: Owen.
Other - center investigator for this trial: Alvarez.
Other - Care of patients on trial, local PI: Drachtman.
Other - interpretation of children VOC episodes: Cela de Julian.

Conflict of Interest Disclosures: Dr Casella reported receiving grants from Mast Therapeutics Inc (previously Adventrx Pharmaceuticals Inc) and receiving an honorarium, travel expenses, and salary support through Johns Hopkins for providing consultative advice to Mast Pharmaceuticals Inc

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during development of the clinical trial and for serving as the principal investigator for the clinical trial; being an inventor and a named party on a patent and licensing agreement to ImmunArray through Johns Hopkins for a panel of brain biomarkers for the detection of brain injury; and holding a patent for aptamers as a potential treatment for sickle cell disease. Dr Barton reported receiving grants from Mast Therapeutics Inc during the conduct of the study. Dr Kanter-Washko reported receiving institutional research support to conduct the study from Mast Therapeutics Inc during the conduct of the study; receiving personal fees for serving on a steering committee from Novartis and AstraZeneca; receiving personal fees from Guidepoint Global and GLG; and serving on a data and safety monitoring board for NovoNordisc outside the submitted work. Dr Black reported receiving grants from Mast Therapeutics Inc during the conduct of the study and grants from the National Hearth, Lung, and Blood Institute, the Health Resources Service Administration, Pfizer, Novartis, and Sancilio and Company and personal fees from Prolong Pharmaceuticals and Sanofi outside the submitted work. Dr Wali reported receiving a research grant from Mast Therapeutics Inc during the conduct of the study. Dr Drachtman reported receiving personal fees from Global Therapeutics and Novartis outside the submitted work. Dr Abboud reported receiving grants from Novartis; serving on a data and safety monitoring board for CRISPR Therapeutics; receiving grants from AstraZeneca; serving on an advisory board for Emmaus and Novartis; and receiving personal fees from Amgen outside the submitted work. Dr Fuh reported receiving personal fees for consultancy from Bayer, Novartis, and Pfizer and grants from Global Blood Therapeutics outside the submitted work. Dr Al-Khabori reported receiving investigator fees from Mast Therapeutics Inc during the conduct of the study and honoraria from Novartis outside the submitted work. Dr Takemoto reported receiving grants from Johns Hopkins University during the conduct of the study and personal fees from Novartis for serving on a data and safety monitoring board for an aplastic anemia trial, personal fees from Genentech for serving on an advisory board for hemophilia, and grants from Daiichi Sankyo for serving as a site primary investigator for an anticoagulant medication trial outside the submitted work. Dr Shah reported receiving grants from Novartis and Global Blood Therapeutics; being a speaker for Alexion; and consulting for CSL Behring and bluebird bio outside the submitted work. Dr Morris reported receiving grants from Mast Therapeutics Inc to support the EPIC study at Emory-Grady during the conduct of the study and personal fees from Pfizer outside the submitted work and having a patent for diagnostics and therapies for conditions of decreased arginine bioavailability issued; multiple patents issues to Children's Hospital Oakland Research Institute and a patent for methods of treating autism/apraxia with royalties paid from Lifetrients; and multiple patents issues to Children's Hospital Oakland Research Institute. Dr Keates-Baleeiro reported receiving grants from Mast Therapeutics Inc for EPIC to enroll patients (data entry by clinical research associates), but personally did not receive any payments for institutional participation in the trial, during the conduct of the study and grants from TN Sickle Cell for data collection outside the submitted work. Dr Raj reported receiving grants from the University of Louisville during the conduct of the study and personal fees from Forma Therapeutics and Global Blood Therapeutics outside the submitted work. Dr Alvarez reported being an advisory board member for Novartis and Forma Therapeutics outside the submitted work. Dr Hsu reported receiving grants from Mast Therapeutics Inc to participate in this multicenter clinical trial during the conduct of the study and serving on an advisory board for AstraZeneca, Cyclerion, Hoffman LaRoche, Novartis, Emmaus, Pfizer, and Forma Therapeutics; receiving grants from Forma Therapeutics, Imara, Global Blood Therapeutics, Pfizer, AstraZeneca, and Novartis for clinical research and on a data and safety monitoring board for Aruvant outside the submitted work. Dr Thompson reported receiving personal fees from Agios, Beam, and Celgene and grants from Baxalta, Biomarin, bluebird bio, and Novartis outside the submitted work. Dr Pace reported receiving funding from Mast Therapeutics Inc during the conduct of the study. Dr Cela de Julian reported receiving funding from Mast Therapeutics Inc during the conduct of the study and contribution to Novartis advisory boards. Dr Thornburg reported receiving grants from Mast Therapeutics Inc during the conduct of the study and personal fees from Ironwood Pharmaceuticals, now Cyclerion, outside the submitted work. Dr Nuss reported receiving grants from the University of Colorado during the conduct of the study. Dr Cohen reported receiving the drug and research-associated tests from Mast Therapeutics Inc during the conduct of the study. Dr Karakas reported receiving grants from Mast Therapeutics Inc during the conduct of the study. Dr Piccone reported being a speaker for Novartis and Global Blood Therapeutics outside the submitted work. Dr Singleton reported being in a speakers bureau for and receiving advisory board fees from Novo Nordisk, Takeda, Bayer, Biomarin, CSL Behring, Grifols, Hema Biologics, Spark, Sanofi-Genzyme, and Genetech outside the submitted work. Dr Moulton reported receiving funding from Mast Therapeutics Inc to cover costs of participating in the current study and being an employee of Bayer US LLC Pharmaceuticals (not when participating in the study, but when reviewing the manuscript). Dr Quinn reported receiving clinical trial funding from Mast Therapeutics Inc during the conduct of the study and clinical trial funding from Emmaus Medical Inc and Aruvant and grants from the National Heart, Lung, and Blood Institute outside the submitted work. Dr Goyal-Khemka reported receiving grants and nonfinancial support from Phoenix Children's Hospital for the administrative support for opening and running the study and study drug and travel expenses to the annual study meeting during the conduct of the study. Dr Emanuele reported being employed by Mast Therapeutics Inc during the conduct of the study. Ms Gorney reported receiving grants from Mast Therapeutics Inc for conduct of the trial. Dr Parsley reported receiving personal fees from and being employed by Mast Therapeutics Inc during the conduct of the study. Ms Kronsberg reported receiving grants from Mast Therapeutics Inc during the conduct of the study. Dr Kato reported receiving support to the University of Pittsburgh for salary support as a steering committee member from Mast Therapeutics Inc during the conduct of the study and grants from Bayer; receiving personal fees from Global Blood Therapeutics and Novartis; receiving personal fees from and full-time employment with CSL Behring; and having a patent for topical sodium nitrite issued, held by the National Institutes of Health, outside the submitted work. Dr Gladwin reported receiving grants from Bayer and personal fees from Actelion, Pfizer, Fulcrum, and Novartis outside the submitted work; being a co-inventor of patents and patent applications directed to the use of recombinant neuroglobin and heme-based molecules as antidotes for carbon monoxide poisoning, which have been licensed by Globin Solutions Inc; being a shareholder, advisor, and director in Globin Solutions Inc; being a co-inventor on patents directed to the use of nitrite salts in cardiovascular diseases, which were previously licensed to United Therapeutics, and are now licensed to Globin Solutions and Hope Pharmaceuticals; being a principal investigator in a research collaboration with Bayer Pharmaceuticals to evaluate riociguate as a treatment for patients with sickle cell disease; actively serving as a scientific consultant for Actelion, Pfizer, Bayer Healthcare, Fulcrum, and Novartis; previously serving as a consultant for Acceleron Pharma Inc, Sujana Biotech, Epizyme Inc, Catalyst Biosciences, Complexa, United Therapeutics, and Modus Therapeutics; and serving on a research advisory board for Bayer HealthCare LLC's Heart and Vascular Disease. No other disclosures were reported.

Funding/Support: This clinical trial was funded by Mast Therapeutics Inc (previously Adventrx Therapeutics Inc).

Role of the Funder/Sponsor: Mast Therapeutics Inc provided funding and selected the clinical coordinating center (Theradex), statistical center (Department of Quantitative Health Sciences, University of Massachusetts Medical School, Dr Barton), primary investigator (Dr Casella), and steering committee for the study. All data collection and management was performed by the clinical coordinating center. Statistical analysis and interpretation of data were performed by the statistical center. Neither Mast Therapeutics Inc nor its successor by merger, Savara Inc, had control over or participated in the decision to submit this manuscript for publication, preparation, review of the manuscript or analysis of data, nor had any control of the journal selected. Drs Emanuele, Parsley and Padgett were previously employed by Mast Therapeutics Inc and participated in manuscript preparation after severance from the company.

Data Sharing Statement: See Supplement 4.

Members of the Steering Committee: James Casella, MD (chair); Gregory Kato, MD; Mark Gladwin, MD; Marty Emanuele, PhD; Ed Parsley, DO; and Claire Padgett, PhD (Santosh Vetticaden, MD, PhD, and Jeffrey Keefer, MD, PhD, did not complete their terms). Drs Parsley, Vetticaden (chief medical officers), Padgett (vice president of development operations), and Emanuele (scientific officer) were employees of Mast Therapeutics Inc.

Site Investigators: Adlette Inati, MD (Nini Hospitol, Tripoli, Lebanon); Yasser Wali, MD (Sultan Qaboos University Hospital – Child Health, Muscat, Oman); Julie Kanter, MD (Medical University of South Carolina, Charleston, South Carolina); Richard A. Drachtman, MD (Rutgers University, New Brunswick, New Jersey); Miguel R. Abboud (American University of Beirut Medical Center, Beirut, Lebanon); Yurdanur Kilinc, MD (University

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of Çukurova and Çukurova University Medical Faculty Balcali Hospital, Adana, Turkey); Beng R. Fuh, MD (East Carolina University, Greenville, North Carolina); Lucien Vandy Black, MD, MSc (Our Lady of the Lake Regional Medical Center, Baton Rouge, Louisiana); Jeffrey E. Deyo, MD (Our Lady of the Lake Regional Medical Center, Baton Rouge, Louisiana); Murtadha K. Al-Khabori, MD (Sultan Qaboos University, Muscat, Oman); Krismely Annalissa Moya Mejia, MD (Robert Reid Cabral Children's Hospital, Santo Domingo, Dominican Republic); Emad Salman, MD (Golisano Children's Hospital of Southwest Florida, Fort Myers, Florida); Clifford M. Takemoto, MD (Johns Hopkins University School of Medicine, Baltimore, Maryland); Suvankar Majumdar, MD (University of Mississippi Medical Center, Jackson, Mississippi); Sharada A. Sarnaik, MD (Children's Hospital of Michigan, Detroit, Michigan); Gladys Maria Paulino, MD (General Hospital Plaza de la Salud, Santo Domingo, Dominican Republic); Jean Williams-Johnson, MBBS, MSc, DM (Caribbean Institute of Medical Research, Mona, Jamaica); Hilze Maria Rodriguez de Ramirez, MD, DCSs, MCS (Hospital Del Nino, San Juan, Puerto Rico); Nirmish Shah, MD (Duke University, School of Medicine, Durham, North Carolina); Claudia R. Morris, MD (Grady Memorial Hospital, Atlanta, Georgia); Jennifer Keates-Baleeiro, MD (T.C. Thompson Children's Hospital at Erlanger affiliated with the University of Tennessee, Chattanooga, Tennessee); Ashok Raj, MD (University of Louisville/Norton Children's Hospital, Louisville, Kentucky); Ofelia A. Alvarez, MD (University of Miami, Miami, Florida); Clarissa Johnson, MD (Cook Children's Hospital, Fort Worth, Texas); Monica Khurana, MD (Riley Hospital for Children, Indianapolis, Indiana); Lewis L. Hsu, MD (University of Illinois at Chicago, Chicago, Illinois); Alexis A. Thompson, MD, MPH (Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, Evanston, Illinois); India Y. Sisler, MD (Children's Hospital of Richmond at Virginia Commonwealth University, Richmond, Virginia); Betty S. Pace, MD (Augusta University, Augusta, Georgia); Suzie A. Noronha, MD (University of Rochester School of Medicine and Dentistry, Golisano Children's Hospital at University of Rochester Medical Center, Rochester, New York); Joseph L. Lasky III, MD (Harbor-UCLA Medical Center, Torrance, California); Elena Cela de Julian, MD, MSc, PhD (Hospital General Universitario Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain); Hala Saleh Alremawi (King Abdullah University Hospital, Ar Ramtha, Jordan); Selma Unal (Mersin University Medical Faculty Hospital, Mersin, Turkey); Kamar Godder, MD (Miami Children's Hospital, Miami, Flordia); Courtney Dawn Thornburg, MD, MS (Rady Children's Hospital - San Diego, San Diego, California); Natalie L. Kamberos, DO (University of Iowa Children's Hospital, Iowa City, Iowa); Rachelle Nuss, MD (Children's Hospital Colorado, University of Colorado, Aurora, Colorado); Anne M. Marsh, MD (UCSF Benioff Children's Hospital Oakland [UBCHO], Oakland, California); William C. Owen, MD (Children's Hospital of the King's Daughters, Norfolk, Virginia); Sandra Regina Calegare (Hospital Santa Marcelina, São Paulo, Brazil); Anne Schaefer, MD (Joe DiMaggio Children's Hospital, Hollywood, Florida); Dimas Ariel Quiel Rodriguez, MD (Metropolitan Hospital Complex Dr Arnulfo Arias Madrid, Panama City, Panama); Cameron K. Tebbi, MD (Tampa General Hospital, Tampa, Florida); Abdul Hafeez Siddiqui, MD (University of South Alabama, Mobile, Alabama); Gregory Hale, MD (All Children's Hospital, St Petersburg, Florida); Christophe F. Chantrain, MD, PhD (Clinique MontLegia, CHC, Liège, Belgium); Debra E. Cohen, MD (UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania); Edna Kakitani Carbone, MD (Hospital Pequeno Principe, Curitiba, Parana, Brazil); Zeynep Karakas, MD (Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey); Renee Gardner, MD (LSUHC – Children's Hospital of New Orleans, New Orleans, Louisiana); Connie M. Piccone, MD (Rainbow Babies and Children's Hospital, Cleveland, Ohio); Jason M. Glover, MD (Randall Children's Hospital, Portland, Oregon); Alex George, MD (Texas Children's Hospital, Houston, Texas); Jason M. Fixler, MD (The Herman and Walter Samuelson Children's Hospital at Sinai, Baltimore, MD); Tammuella C. Singleton, MD (Tulane University, New Orleans, Louisiana); Timothy L. McCavit, MD (University of Texas Southwestern Medical Center, Dallas, Texas); Shilpa Jain, MD (Women and Children's Hospital of Buffalo, Buffalo, New York); Thomas Moulton, MD (Bronx-Lebanon Hospital, Bronx, New York City, New York); Charles T. Quinn, MD, MS (Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio); Clarisse Lopes de Castro Lobo, MD, PhD (Instituto estadual de Hematologia Arthur de Siqueira Cavalcanti – HEMORIO, Rio de Janeiro, Brazil); Alaaeldin Mohamed Abbas Morsi, MD (King Fahad Medical City, Riyadh, Saudi Arabia); Abdulkareem M. Almomen, MD (King Khalid University Hospital, King Saud University Medical City and Blood and Cancer Center, Riyadh, Saudi Arabia); Meenakshi Goyal-Khemka, MD (Phoenix Children's Hospital, Phoenix, Arizona); Ashraf Abdelmonem Mohamed, MD (The Children's Hospital at St Francis, Tulsa, Oklahoma); Philip Maes, MD (University Hospital of Antwerp, Edegem, Belgium); Rupa C. Redding-Lallinger, MD (University of North Carolina – Chapel Hill, Chapel Hill, North Carolina).

Additional Contributions: Clarissa Johnson, MD (Cook Children's Hospital, Fort Worth, Texas), and Rupa C. Redding-Lallinger, MD (University of North Carolina – Chapel Hill, Chapel Hill, North Carolina), are acknowledged for their work as site principal investigators for the trial. Dr Johnson reported no compensation for her role in the study. Dr Redding-Lallinger reported that her site received only the per-patient compensation and that she did not receive other compensation. The authors wish to thank Theradex, the clinical coordinating center for the study; all of the study coordinators, pharmacists, and collaborating site investigators who participated in the trial; and, especially, the individuals with sickle cell disease who enrolled in the trial.

REFERENCES

1. Cooper TE, Hambleton IR, Ballas SK, Johnston BA, Wiffen PJ. Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults. *Cochrane Database Syst Rev*. 2019;2019(11):CD012187. doi:10.1002/14651858.CD012187.pub2

2. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639-1644. doi:10.1056/NEJM199406093302303

3. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. *Am J Hematol*. 2005;79(1):17-25. doi:10.1002/ajh.20336

4. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. *Annu Rev Pathol*. 2019;14(1):263-292. doi:10.1146/annurev-pathmechdis-012418-012838

5. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573. doi:10.1056/NEJMra1510865

6. Hebbel RP, Belcher JD, Vercellotti GM. The multifaceted role of ischemia/reperfusion in sickle cell anemia. *J Clin Invest*. 2020;130(3):1062-1072. doi:10.1172/JCI133639

7. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers*. 2018;4:18010. doi:10.1038/nrdp.2018.10

8. Hunter RL, Luo AZ, Zhang R, Kozar RA, Moore FA. Poloxamer 188 inhibition of ischemia/reperfusion injury: evidence for a novel anti-adhesive mechanism. *Ann Clin Lab Sci*. 2010;40(2):115-125.

9. Adams-Graves P, Kedar A, Koshy M, et al. RheothRx (poloxamer 188) injection for the acute painful episode of sickle cell disease: a pilot study. *Blood*. 1997;90(5):2041-2046. doi:10.1182/blood.V90.5.2041

10. Orringer EP, Casella JF, Ataga KI, et al. Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA*. 2001;286(17):2099-2106. doi:10.1001/jama.286.17.2099

11. Gibbs WJ, Hagemann TM. Purified poloxamer 188 for sickle cell vaso-occlusive crisis. *Ann Pharmacother*. 2004;38(2):320-324. doi:10.1345/aph.1D223

12. Ballas SK, Files B, Luchtman-Jones L, et al. Safety of purified poloxamer 188 in sickle cell disease: phase I study of a non-ionic surfactant in the management of acute chest syndrome. *Hemoglobin*. 2004;28(2):85-102. doi:10.1081/HEM-120035919

13. Garra G, Singer AJ, Taira BR, et al. Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. *Acad Emerg Med*. 2010;17(1):50-54. doi:10.1111/j.1553-2712.2009.00620.x

14. Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults. *Pain Manag Nurs*. 2006;7(3):117-125. doi:10.1016/j.pmn.2006.06.005

15. Vichinsky EP, Neumayr LD, Earles AN, et al; National Acute Chest Syndrome Study Group. Causes and outcomes of the acute chest syndrome in sickle cell disease. *N Engl J Med*. 2000;342(25):1855-1865. doi:10.1056/NEJM200006223422502

16. Wagenmakers E-J, Brown S. On the linear relation between the mean and the standard deviation of a response time distribution. *Psychol Rev*. 2007;114(3):830-841. doi:10.1037/0033-295X.114.3.830

17. Feaster DJ, Mikulich-Gilbertson S, Brincks AM. Modeling site effects in the design and analysis of multi-site trials. *Am J Drug Alcohol Abuse*. 2011;37(5):383-391. doi:10.3109/00952990.2011.600386

18. Test directory for The Johns Hopkins Hospital. Johns Hopkins Medical Laboratories Services. Accessed January 12, 2021. http://pathology.jhu.edu/jhml-services/test-directory/

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