Supplemental Online Content

Casella JF, Barton BA, Kanter J, et al. Effect of Poloxamer 188 vs Placebo on Painful Vaso-Occlusive Episodes in Children and Adults With Sickle Cell Disease. *JAMA.* Published online April 20, 2021. doi:10.1001/jama.2021.3414

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1: Investigational Site Information.

Country	Site	Number of Patients Enrolled Per Site	Number of Patients Enrolled Per Country
U.S.	Medical University of South Carolina	19	228
	Rutgers University	19	
	East Carolina University	15	
	Our Lady of the Lake Regional Medical Center	13	
	Children's Hospital of Southwest Florida	11	
	Johns Hopkins University	11	
	University of Mississippi	11	
	Children's Hospital of Michigan	8	
	Duke University Medical Center	6	
	Grady Memorial Hospital	6	
	T.C. Thompson Children's Hospital at Erlanger	6	
	University of Louisville/Norton Children's Hospital	6	
	University of Miami	6	
	Cook Children's Hospital	5	
	Riley Hospital for Children	5	
	University of Illinois	5	
	Ann and Robert H. Lurie Children's Hospital of Chicago	4	
	Children's Hospital of Richmond	4	
	Georgia Regents University	4	
	Golisano Children's Hospital of Southwest Florida	4	
	Harbor-UCLA Medical Center	4	
	Miami Children's Hospital	4	
	Rady Children's Hospital San Diego	4	
	University of Iowa Children's Hospital	4	
	Children's Hospital Colorado	3	
	UCSF Benioff Children's Hospital Oakland	3	
	Children's Hospital of the King's Daughters	3	
	Joe DiMaggio Children's Hospital	3	
	Tampa General Hospital	3	
	University of South Alabama	3	
	All Children's Hospital	2	
	Children's Hospital of Pittsburgh	2	
	LSUHC – Children's Hospital of New Orleans	2	
	Rainbow Babies and Children's Hospital	2	
	Randall Children's Hospital	2	
	Texas Children's Hospital	2	
	The Herman and Walter Samuelson Children's Hospital at Sinai	2	
	Tulane University	2	
	University of Texas Southwestern Medical Center	2	
	Women and Children's Hospital of Buffalo	2	
	Bronx-Lebanon Hospital	1	
	Cincinnati Children's Hospital Medical Center	1	
	Phoenix Children's Hospital	1	
	The Children's Hospital at Saint Francis	1	
	University of Florida College of Medicine	1	
	University of North Carolina-Chapel Hill	1	

Lebanon	Nini Hospital	29	45
	American University of Beirut Medical Center	16	
Oman	Sultan Qaboos University Hospital – Child Health and Hematology	38	38
Turkey	Cukurova Univresity Medical Faculty Balcali Hospital	16	22
	Mersin University Medical Faculty Hospital	4	
	Istanbul University Medical Faculty Hospital	2	
Dominican Republic	Robert Reid Cabral Children's Hospital	11	19
	General Hospital Plaza de la Salud	8	
Jamaica	Caribbean Institute of Medical Research	7	7
Brazil	Hospital Santa Marcelina	3	6
	Hospital Pequeno Principe	2	
	Instituto estadual de Hematologia Arthur de Siqueira Cavalcanti – HEMORIO	1	
Jordan	King Abdullah University Hospital	4	4
Spain	Hospital General Universitario Gregorio Maranon	4	4
Belgium	Clinique MontLegia, CHC	2	3
	University Hospital Antwerp (UZA)	1	
Panama	Metropolitan Hospital Complex Dr. Arnulfo Arias Madrid	3	10
	Hospital Del Nino	7	
Saudi Arabia	King Fahad Medical City	1	2
	King Khalid University Hospital (KKUH)	1	

eTable 2: Inclusion/Exclusion Criteria.

Inclusion/Exclusion Criteria
Inclusion Criteria
1) Written documentation of informed consent and assent as applicable. Note: Minors must provide assent to participate in this study at an age-appropriate level determined and approved by the Institutional Review Board/International Ethics Committee (IEC) for the study center.
2) Participant is ≥ 4 and ≤ 65 years of age.
3) Participant has confirmed diagnosis of HbSS, HbSC, HbSβ^+thal, or HbSβ^0thal.
4) Participant is experiencing acute pain typical of a vaso-occlusive episode and requires treatment with parenteral opioid analgesia.
5) Participant has been in moderate to severe pain as a result of the current vaso-occlusive episode for no more than 24 hours at the time of presentation to the study center and for at least 4 hours prior to randomization.
6) Participant is hospitalized or in the process of admission for a vaso-occlusive episode at time of randomization.
7) If the participant is taking hydroxyurea, the dose is expected to remain stable through discharge.
8) If sexually active, the participant agrees to use reliable contraception while participating in this study and for at least 30 days after discontinuation of blinded study drug infusion.
9) If the participant is female and of child-bearing potential, must have negative pregnancy test (urine or serum).
Exclusion Criteria
1) Participant has suspected acute-chest syndrome (ACS), including either: a) baseline chest X-ray indicating a new pulmonary infiltrate or b) acute respiratory symptoms consistent with ACS or acute asthma attack.
2) Participant has platelet count <80,000/mm^3.
3) Participant has a known or suspected bleeding disorder.
4) Participant has inadequate liver function defined as ALT >3X the institution's upper limit of normal.
5) Participant has the following serum creatinine value: • Age ≥ 4-7 years: > 0.8 mg/dL (>70.7 µmol/L) • Age ≥ 8-13 years: >0.9 mg/dL (>79.6 µmol/L) • Age ≥ 14 years: >1.0 mg/dL (>88.4 µmol/L) • Participants with a confirmed diagnosis of HbSC: o Age ≥ 18 years: >1.2 mg/dL (>106.1 µmol/L)
6) Participant is pregnant or nursing.
7) Participant has had an episode of painful crisis requiring hospitalization within the preceding 14 days.
8) Participant has been transfused within the past 14 days.
9) Participant is already hospitalized for any condition other than the current vaso-occlusive episode.
10) Participant uses opioid analgesia on a daily basis for any reason.
11) Participant is currently receiving another investigational drug or has received any investigational drug within 30 days prior to randomization.
12) Participant presents with complications related to SCD, such as: aplastic crisis, priapism, sepsis, stroke, hepatic or splenic sequestration, or any complication expected to require surgical intervention.
13) Participant has experienced >5 hospitalizations for vaso-occlusive episodes in the prior 6 months.
14) Investigator believes participant is suffering from chronic pain (e.g., necrotic tissues resulting from repeated prior VOCs) and not acute pain associated with an ongoing vaso-occlusive episode.
15) Participant is otherwise not an appropriate study candidate, in the Investigator's judgement.
16) Participant has been previously enrolled in the present trial or any prior MST-188 clinical trial.

eTable 3: Summary of Secondary Outcome Subgroup Analyses.

Summary of Secondary Outcome Subgroup Analyses[a]					
		Poloxamer 188, No, (%)	Placebo, No. (%)	Difference (95% CI)	P-Value[b]
Occurrence of Acute Chest Syndrome					
	Age, yrs				
	< 16	24/115 (20.9%)	12/112 (10.7%)	10.2 (0.8, 19.5)	0.05[c]
	≥ 16	8/79 (10.1%)	10/82 (12.2%)	-2.1 (-11.8, 7.7)	0.80
	Hydroxyurea Usage				
	Yes	18/117 (15.4%)	15/119 (12.6%)	2.8 (-6.1, 11.6)	0.58
	No	14/77 (18.2%)	7/75 (9.3%)	8.8 (-2.0, 19.7)	0.16
	Region				
	U.S.	18/107 (16.8%)	11/121 (9.1%)	7.7 (-1.0, 16.5)	0.11
	Non-U.S.	14/87 (16.1%)	11/73 (15.1%)	1.0 (-10.2, 12.3)	1.00
Re-hospitalization for Recurrence of Vaso-occlusive Episodes within 14 days of Initial Hospital Discharge					
	Age, yrs				
	< 16	6/114 (5.3%)	5/109 (4.6%)	0.7 (-5.0, 6.4)	1.00
	≥ 16	10/78 (12.8%)	8/81 (9.9%)	2.9 (-6.9, 12.8)	0.62
	Hydroxyurea Usage				
	Yes	8/117 (6.8%)	8/116 (6.9%)	-0.1 (-6.6, 6.4)	1.00
	No	8/75 (10.7%)	5/74 (6.8%)	3.9 (-5.1, 12.9)	0.56
	Region				
	U.S.	11/106 (10.4%)	11/117 (9.4%)	1.0 (-6.9, 8.8)	0.83
	Non-U.S.	5/86 (5.8%)	2/73 (2.7%)	3.1 (-3.1, 9.3)	0.45

Abbreviations: CI, confidence interval; SD, standard deviation.

[a] Secondary outcome comparisons between treatment arms were adjusted for age (<16, ≥16), hydroxyurea usage (yes, no), pain score at randomization (<8, ≥8), and region (US, non-US), using logistic regression.

[b] P-value computed using Fisher's exact test (two-tailed)

[c] $p = 0.045$

eTable 4: Primary Outcome – Additional Subgroup Analyses: Time (hrs) from Randomization to Last Administration of Parenteral Opioids for Treatment of Vaso-occlusive Episodes.

Primary Outcome – Additional Subgroup Analyses: Time (hrs) from Randomization to Last Administration of Parenteral Opioids for Treatment of Vaso-occlusive Episodes[a,b]					
	Poloxamer 188, mean (SD)	Placebo, mean (SD)	Difference (95% CI)	Least Squares Geometric Mean Ratio (95% CI)[c]	P-Value[d]
Sex					
Male	77.14 (47.58) (n = 105)	81.14 (68.92) (n = 107)	-4.0 (-20.1, 12.1)	1.2 (0.9, 1.5)	0.33
Female	87.26 (65.16) (n = 89)	73.76 (50.93) (n = 87)	13.5 (-3.9, 30.9)	1.2 (0.9, 1.7)	0.19
Hydroxyurea Usage					
Yes	83.4 (61.2) (n = 117)	76.3 (63.0) (n = 119)	7.1 (-8.8, 23.0)	1.3 (1.0, 1.8)	0.04
No	79.3 (48.6) (n = 77)	80.3 (59.3) (n = 75)	-1.0 (-18.3, 16.4)	1.0 (0.7, 1.4)	0.99
FACES Pain Score at Randomization (0-10)[e]					
< 8	71.09 (50.33) (n = 94)	74.33 (62.76) (n = 95)	-3.2 (-19.6, 13.1)	1.2 (0.9, 1.6)	0.30
≥ 8	91.83 (59.94) (n = 100)	81.18 (60.33) (n = 99)	10.6 (-6.2, 27.5)	1.2 (0.9, 1.7)	0.14
Duration of Pain at Presentation, yrs[f]					
≤ 12	81.15 (55.01) (n = 161)	78.95 (64.60) (n = 155)	2.2 (-11.1, 15.5)	1.2 (1.0, 1.6)	0.11
> 12	84.84 (63.63) (n = 33)	73.35 (47.45) (n = 39)	11.5 (-14.7, 37.6)	1.2 (0.8, 1.8)	0.46
Region					
U.S.	79.6 (54.5) (n = 107)	76.8 (64.8) (n = 121)	2.8 (-12.9, 18.6)	1.4 (1.0, 1.9)	0.04
Non-U.S.	84.5 (58.9) (n = 87)	79.6 (55.9) (n = 73)	4.9 (-13.2, 22.9)	1.0 (0.8, 1.3)	0.98
Hemoglobin Phenotype[g]					
HbSS	86.25 (59.52) (n = 134)	77.77(63.39) (n = 129)	8.5 (-6.4, 23.4)	1.4 (1.1, 1.9)	0.02
HbS-β^+ thal	73.04 (43.13) (n = 21)	84.92 (68.12) (n = 28)	-11.8 (-46.0, 22.3)	0.8 (0.4, 1.3)	0.35
HbS-β^0 thal	70.43 (38.52) (n = 20)	86.22 (57.96) (n = 19)	-15.8 (-47.6, 16.0)	0.8 (0.5, 1.1)	0.18
HbSC	71.83 (61.79) (n = 19)	58.34 (33.88) (n = 18)	13.5 (-20.0, 47.0)	0.9 (0.4, 1.8)	0.66
<16 yrs old, taking Hydroxyurea, and in the U.S.	94.02 (63.15) (n = 41)	77.02 (63.98) (n = 36)	17.0 (-11.9, 45.9)	1.9 (1.1, 3.2)	0.02

Abbreviations: CI, confidence interval; SD, standard deviation; thal, thalassemia.

[a] All groups listed are subgroups of the primary analysis population. The primary analysis population and the subgroup of children <16 years of age are reported in the main manuscript.

[b] Comparisons between treatment arms in the primary efficacy analysis were adjusted for age (<16, ≥16), hydroxyurea usage (yes, no), pain score at randomization (<8, ≥8), and region (US, non-US) in an ANCOVA model.

[c] 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 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 confidence interval not including 1.0 indicates a significant difference.

[d] Computed using geometric ANCOVA test

[e] The Wong-Baker FACES Pain Rating Scale (0-10) is a six item ordinal scale depicting painful and non-painful faces, with the low and high endpoints representing no pain and worst pain, respectively, and with each face assigned a numerical value.[13]

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

[g] HbSS is homozygous HbS (Sickle cell anemia). HbS-β^+ thalassemia is double heterozygosity for HbS and beta 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.

eTable 5: Pre-specified Analyses Not Otherwise Reported.

Pre-specified Analyses Not Otherwise Reported[a]					
	Poloxamer 188	**Placebo**	**Difference (95% CI)**	**Least Squares Geometric Mean Ratio (95% CI)[b]**	**P-Value**
Length of Study Drug Infusion (hrs), mean (SD)[c]					
Primary Analysis Population	45.6 (9.3) (n = 188)	44.9 (10.1) (n = 192)		1.0 (0.93, 1.11	0.80
Total Opioid Usage (Morphine Equivalent Units) from Randomization to Last Administration of Parenteral Opioids, mean (SD)[d,e]					
Safety Population	3.2 (5.3) (n = 186)	3.0 (3.8) (n = 185)	-0.1 (-1.1, 0.8)	1.1 (0.8, 1.4)	0.61
Age, yrs					
< 16	3.5 (6.5) (n = 110)	2.8 (3.3) (n = 105)	-0.7 (-2.1, 0.7)	1.2 (0.9, 1.6)	0.24
≥ 16	2.7 (2.6) (n = 76)	3.4 (4.4) (n = 80)	0.7 (-0.5, 1.8)	0.9 (0.6, 1.3)	0.54
Hydroxyurea Usage					
Yes	3.8 (6.6) (n = 113)	3.1 (4.0) (n = 113)	-0.7 (-2.1, 0.7)	1.3 (0.9, 1.7)	0.14
No	2.2 (1.9) (n = 73)	3.0 (3.5) (n = 72)	0.8 (-0.2, 1.7)	0.8 (0.6, 1.1)	0.20
Region					
U.S.	3.0 (3.2) (n = 104)	3.6 (4.4) (n = 112)	0.6 (-0.4, 1.6)	1.0 (0.7, 1.3)	0.80
Non-U.S.	3.4 (7.2) (n = 82)	2.2 (2.5) (n = 73)	-1.2 (-3.0, 0.5)	1.3 (0.9, 1.8)	0.17
Time (hrs) from Randomization to Hospital Discharge, mean (SD)[d]					
Primary Analysis Population	113.1 (66.4) (n = 194)	110.7 (80.2) (n = 192)	2.4 (-12.4, 17.1)	1.0 (0.9,1.2)	0.62
Age					
< 16	124.1 (74.6) (n = 115)	110.2 (87.1) (n = 111)	13.9 (-7.3, 35.1)	1.2 (1.0, 1.4)	0.04
≥ 16	96.9 (48.4) (n = 79)	111.3 (70.2) (n = 81)	-14.4 (-33.2, 4.5)	0.9 (0.7, 1.0)	0.09
Hydroxyurea Usage					
Yes	112.6 (67.1) (n = 117)	110.9 (87.3) (n = 117)	1.7 (-18.4, 21.8)	1.0 (0.9, 1.2)	0.60
No	113.8 (65.8) (n = 77)	110.4 (68.2) (n = 75)	3.4 (-18.1, 24.9)	1.0 (0.8, 1.2)	0.94
Region					
U.S.	102.9 (63.0) (n = 107)	107.2 (87.7) (n = 119)	-4.3 (-24.5, 16.0)	1.0 (0.8, 1.2)	0.95
Non-U.S.	125.5 (68.8) (n = 87)	116.4 (66.3) (n = 73)	9.1 (-12.1, 30.3)	1.1 (0.9, 1.3)	0.29
Re-hospitalization for Recurrence of Vaso-occlusive Episode within 30 Days of Initial Hospital Discharge, No. (%)[f]					
Primary Analysis Population	21/132 (15.9)	27/142 (19.0)	-3.1 (-12.0, 5.9)		0.53
Age					
< 16	9/77 (11.7)	10/77 (13.0)	-1.3 (-12.0, 9.1)		1.00
≥ 16	12/55 (21.8)	17/65 (26.2)	-4.3 (-20.0, 10.9)		0.67
Hydroxyurea Usage					
Yes	13/82 (15.9)	17/87 (19.5)	-3.7 (-15.0, 7.8)		0.55
No	8/50 (16.0)	10/55 (18.2)	-2.2 (-17.0, 12.2)		0.80
Region					
U.S.	14/72 (19.4)	18/89 (20.2)	-0.8 (-13.0, 11.6)		1.00
Non-U.S.	7/60 (11.7)	9/53 (17.0)	-5.3 (-18.0, 7.7)		0.43

Abbreviations: CI, confidence interval; SD, standard deviation.

[a] Comparisons between treatment arms in the primary efficacy analysis were adjusted for age (<16, ≥16), hydroxyurea usage (yes, no), pain score at randomization (<8, ≥8), and region (US, non-US) in an ANCOVA model.

[b] The least squares means and least squares mean differences were calculated on 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 (or usage) for poloxamer 188 and placebo adjusted for other factors in the model. A confidence interval not including 1.0 indicates a significant difference.

[c] P-value computed using two-sample t-test (two-tailed)

[d] P-value computed using geometric ANCOVA test

[e] Each opioid dose (mg/kg) was converted to morphine equivalent units and the sum total from randomization to LPO was calculated for each subject. The calculation of morphine equivalent units per kg body weight is as follows: MEU/kg = [Dose in mg] x [MEU factor] ÷ [Wt in kg]. The conversion factors utilized to calculate morphine equivalent units were based upon the following conversion factors:

Medication	Route	MEU Factor
Buprenorphine	TD	0.1
Codeine	IM	0.1
Codeine (including Codafalgan and Solpadeine)	PO	0.05
Codeine	SC	0.1
Hydrocodone	PO	0.4
Hydromorphone	PO	2
Hydromorphone	IM	5
Hydromorphone	IV	5
Meperidine (Pethidine)	IM	0.1
Meperidine (Pethidine)	IV	0.1
Meperidine	PO	0.05
Morphine	IM	1
Morphine	IV	1
Morphine	SC	1
Morphine	PO	0.4
Nalbuphine	IV	1
Nalbuphine	IM	1
Nalbuphine	SC	1
Oxycodone	PO	0.63
Oxycodone	SC	1.5
Oxycodone	IV	1.5
Tramadol	PO	0.05
Tramadol	SC	0.1
Tramadol	IV	0.1
Tramadol	IM	0.1
Fentanyl	PO	0.05
Fentanyl	IV/IM	0.1
Fentanyl	SC	0.1
Fentanyl	TD	0.1
Fentanyl	IN	0.1
Butorphanol	IV	0.2
Methadone	PO	0.5
Oxymorphone	PO	1.0

Abbreviations: IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous; TD, transdermal; IN, intranasal

[f] P-value computed using Fisher's exact test (two-tailed)

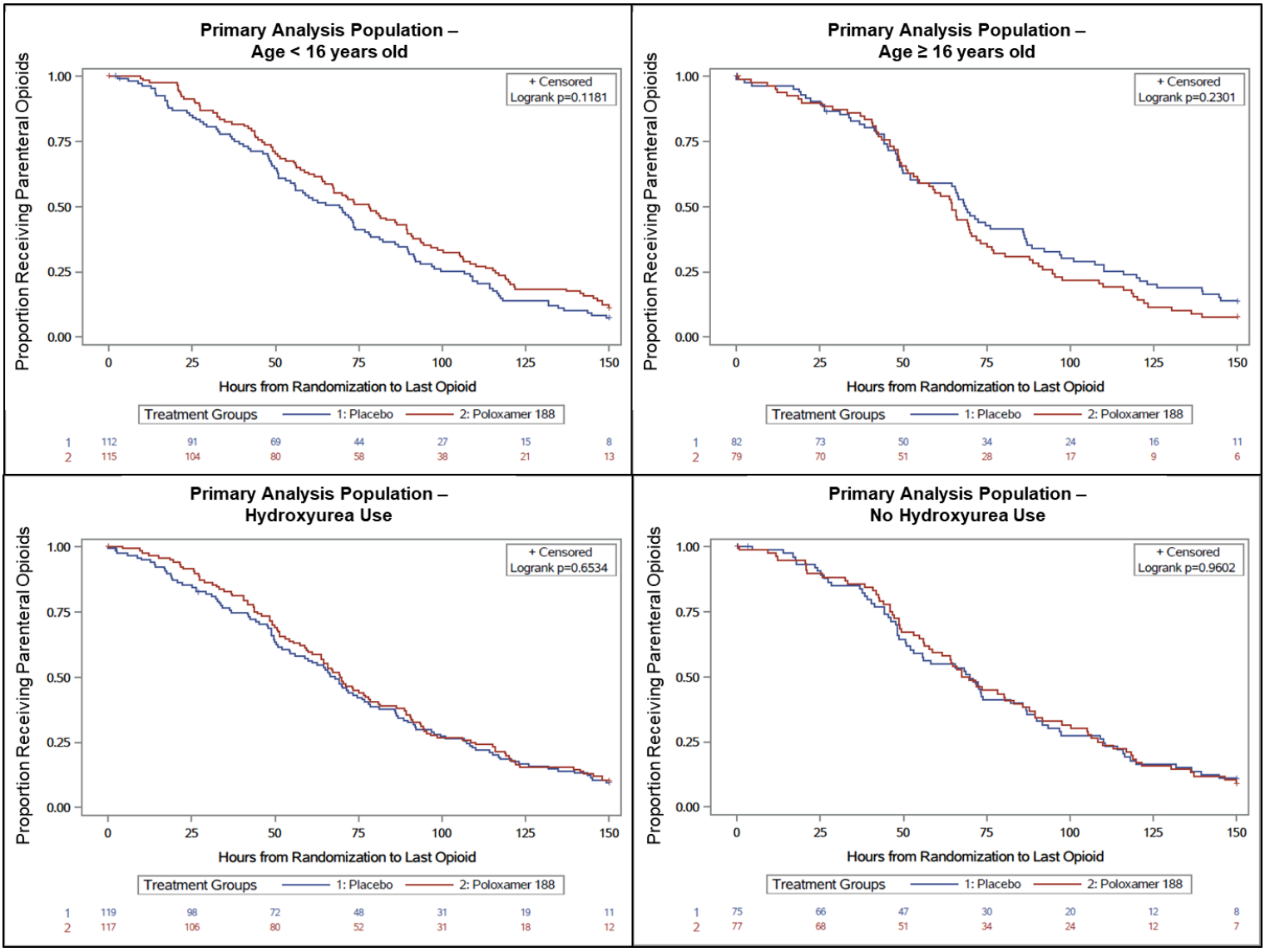
eTable 6: Adverse Events – Subgroup Analyses.

Adverse Events – Subgroup Analyses				
		Subgroup	**Poloxamer 188, No. (%)**	**Placebo, No. (%)**
Treatment-Emergent Adverse Events				
	Abdominal Distension	< 16	4/113 (3.5%)	0/109 (0.0%)
	Decreased appetite	Hydroxyurea use	1/116 (0.9%)	9/118 (7.6%)
	Diarrhea	≥ 16	4/76 (5.3%)	0/82 (0.0%)
	Dyspnea	≥ 16	1/76 (1.3%)	7/82 (8.5%)
	Edema	< 16	5/113 (4.4%)	0/109 (0.0%)
	Hepatobiliary disorders	< 16	15/113 (13.3%)	6/109 (5.5%)
		Hydroxyurea use	19/116 (16.4%)	8/118 (6.8%)
	Hyperbilirubinemia	≥ 16	15/76 (19.7%)	5/82 (6.1%)
		Hydroxyurea use	16/116 (13.8%)	6/118 (5.1%)
	Hypoxia	No hydroxyurea use	2/73 (2.7%)	8/73 (11.0%)
	Upper Respiratory Tract Infection	≥ 16	6/76 (7.9%)	1/82 (1.2%)
Treatment-Emergent Serious Adverse Events[a]				
	Pyrexia	No hydroxyurea use	7/73 (9.6%)	1/73 (1.4%)

Treatment-emergent adverse events (TEAE) are defined as adverse events (AE) 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 (MedDRA) system organ class and preferred terms for TEAEs for which the 95% confidence intervals of the difference between treatment groups did not include 0. Multiple AE records for an individual subject were counted as a single AE occurrence if preferred terms were the same and the stop date of one AE matched the start date of the subsequent AE. TEAEs were analyzed with respect to incidence within each randomized treatment group, as well as by severity, seriousness, and potential relationship of the AE to study medication. AEs are listed in alphabetical order.

[a] Treatment-Emergent Serious Adverse Events comprises subjects who experienced a treatment-emergent adverse event that was fatal, life-threatening, required hospitalization, or prolonged hospitalization.

eFigure 1: Analysis of time, in hours, from randomization to last administration of parenteral opioids by age and hydroxyurea use.



Kaplan-Meier analyses of time (hrs) from randomization to last administration of parenteral opioids for the primary analysis population are shown by the subgroups age < 16, age ≥ 16, hydroxyurea use, and no hydroxyurea use. No significant differences in time (hrs) from randomization to last administration of parenteral opioids were observed between treatment groups in the primary analysis population subgroups of age < 16, age ≥ 16, hydroxyurea use, or no hydroxyurea use.