

EPIC (Evaluation of Purified Poloxamer 188 in Children in Crisis): An Ongoing Pivotal Phase 3 Study in Patients with Sickle Cell Disease

Keefer, JR.¹, Benjamin, L.², Emanuele, M.³, Padgett, C.³, Vetticaden, S.³, Casella, JF.¹

¹The Johns Hopkins University School of Medicine, ²Albert Einstein College of Medicine (Emerita), ³Mast Therapeutics, Inc., San Diego, CA

Abstract

We have recently opened a Phase 3, randomized, double-blind, placebo-controlled clinical trial to determine definitively whether purified poloxamer 188 (MST-188) can be effective in treating acute painful vaso-occlusive crisis (VOC) of sickle cell disease (SCD) in children. Despite VOC being the hallmark of SCD, there are no currently approved disease modifying treatments for ongoing crises. MST-188 is a non-ionic surfactant that reduces blood viscosity by inhibition of cellular adhesion and improves microvascular blood flow, as measured by intravital microscopy, in patients with SCD. A prior phase 3 study of MST-188 for treatment of VOC in children and adults with SCD was suggestive of treatment effects; however, prospectively defined outcomes did not reach statistical significance, other than in subgroup and post-hoc analyses.¹ Specifically, for the primary outcome variable (length of crisis), an intention to treat analysis (249 participants) showed a shorter duration of crisis with MST-188 vs. placebo (PL) (132.34 + 41.42 hr vs. 140.35 + 42.39 hr, p = 0.072, T-test). The percentage of participants who achieved a resolution of crisis within 168 hours was higher for MST-188 than for PL (51.6% vs. 36.6% of patients, p = 0.022, Fisher's Exact Test). Two subgroups were assessed for efficacy, 1) participants receiving concurrent hydroxyurea (HU) (n=54) and; 2) participants 15 years of age or less (Ped) (n=73). HU participants who received MST-188 demonstrated a significant decrease in length of crisis vs. PL (141.36 + 37.04 hr vs. 157.19 + 27.58 hr, p = 0.024), as well as a significant increase in the percent of participants achieving crisis resolution within 168 hours (46.2% vs. 14.3%, p = 0.016). Ped participants treated with MST-188 also showed a significant decrease in the length of crisis vs. PL (127.07 + 42.47 hr vs. 148.58 + 36.71 hr, p = 0.01) and a significant increase in the percent of participants achieving crisis resolution within 168 hours (59.5% vs. 27.8%, p = 0.009).

Interpretation of the aforementioned study was potentially confounded by: 1) a study population heterogeneous for age, genotype and variation in pain management practices; 2) subjectivity of the definition for crisis resolution, which was complex, had multi-part definitions and relied on self-reported pain scales; 3) statistical imbalance in the numbers of participants in the placebo and treatment groups who did not achieve endpoints; and 4) a predefined observation period (168 hrs) that, in retrospect, was probably too short and eliminated the possibility of observing treatment benefit after 168 hours; and 5) missing or imputed data. Lessons learned and hypotheses generated from this study were used to inform the design of the EPIC trial, with the objective of replicating the results of the subset analyses suggesting favorable responses in children and those receiving hydroxyurea, avoiding the deficiencies of the previous trial and serving as the basis for registration with the US FDA.

"Evaluation of Purified Poloxamer 188 in Children in Crisis (EPIC): A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial of MST-188 (Purified Poloxamer 188) Injection in Children with Sickle Cell Disease Experiencing Vaso-occlusive Crisis," is now open at multiple sites in the U.S. and is actively enrolling participants presenting with acute VOC. This study will enroll 388 children ages ≥ 8 and <18 years with HbSS or S-Beta null thalassemia phenotypes, to achieve a more homogeneous population. Guidelines for control of pain were incorporated into the study to minimize variability in pain management practices across study centers. Data from recent trials in SCD were also used to derive statistical assumptions necessary for trial design. Duration of crisis, as measured by the time from randomization to the last dose of parenteral opioid, was chosen as the primary endpoint, as this is a clinically meaningful and objectively measurable outcome. Following subjects until discharge, rather than a pre-specified time-point, should reduce the potential for missing data. These changes incorporate insights from the prior MST-188 study into the EPIC trial and are expected to allow for the completion of a trial that will provide definitive data regarding the efficacy of MST-188 for the treatment of VOC in children with SCD.

MST-188 may represent a unique type of agent for treating VOC, exerting its effects through non-specific changes in cell adhesion. This could have theoretic and practical advantage over agents targeting one specific adhesion molecule; thus, MST-188 remains a promising drug, warranting further investigation.

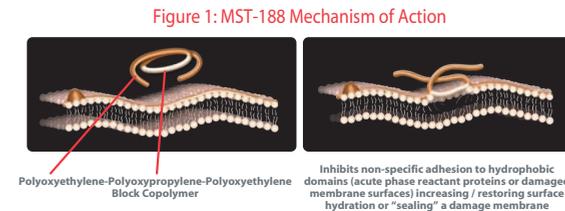
¹JAMA, 2001 Nov 7;286(17):2099-1106

Background

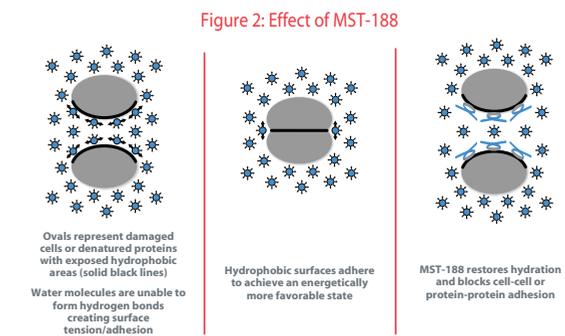
We have recently opened a Phase 3 trial titled "Evaluation of Purified Poloxamer 188 in Children in Crisis (EPIC): A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial of MST-188 (Purified Poloxamer 188) Injection in Children with Sickle Cell Disease Experiencing Vaso-occlusive Crisis." This trial¹ continues the investigation of an agent, MST-188, that has shown promise for the treatment of vaso-occlusive crisis (VOC) in subjects with sickle cell disease (SCD).

Painful crises in SCD result from vascular occlusion, which is probably a several-step process involving adherence of subsets of cells to the endothelium, log-jamming with high-density poorly deformable cells and endothelial dysfunction and vasculopathy. The redundancy of cellular adhesive mechanisms creates an argument for the potential utility of therapies that non-specifically disrupt cell-cell interactions for treating painful VOC.

The investigational agent, MST-188 (purified poloxamer 188 or PP-188), is a synthetic, nonionic, linear, block copolymer of polyoxyethylene and polyoxypropylene, with a mean peak molecular weight of 8500 ± 750 Da (Figure 1). It improves blood rheology by inhibiting red blood cell aggregation and limits cellular adhesion to the vascular endothelium, thus improving microvascular blood flow.



The underlying mechanism of action is hypothesized to involve binding of the polyoxypropylene core to hydrophobic portions of cells and molecules, leaving the hydrophilic polyoxyethylene chains free to interact with surrounding media forming a poorly compressible barrier that prevents hydrophobic adhesive interactions (Figure 2).



The idea that the improvement in microvascular blood flow induced by MST-188 may impact the duration or severity of a painful VOC led to the investigation of MST-188 as a potential therapeutic agent in SCD.

The results of a prior large, randomized, controlled study² of MST-188 for treatment of VOC in patients with SCD were reported over 10 years ago and were suggestive of treatment effects. Factors confounding the interpretation of the aforementioned study have been addressed in previous presentations and include a heterogeneous study population, subjectivity in the definition for crisis resolution, and a study observation period (168 hours) that was probably too short.

The study results and post hoc analyses from this prior trial provide insights regarding the potential for MST-188 in the treatment of VOC.

Specifically, for the primary outcome variable (length of crisis), an intention to treat analysis (n=249) showed a shorter duration of crisis with MST-188 vs. placebo (PL) and a higher percentage of participants who achieved a resolution of crisis within 168 hours, which was the end of the observation period (Table 1).

Table 1: All treated patients (n=249)

Group	MST-188	Placebo	P value
Length of crisis (hours)	132.34 ± 41.42	140.35 ± 42.39	0.072
Proportion with resolution of crisis (%)	51.6%	36.6%	0.022

Two subgroups were assessed for efficacy:

- 1) participants receiving concurrent hydroxyurea (HU) (n=54), and;
- 2) participants <16 years of age (pediatric) (n=73).

Hydroxyurea (HU) participants who received MST-188 demonstrated a significant decrease in length of crisis vs. PL, as well as a significant increase in the percent of participants achieving crisis resolution within 168 hours (Table 2).

Table 2: Patients concurrently receiving HU (n=54)

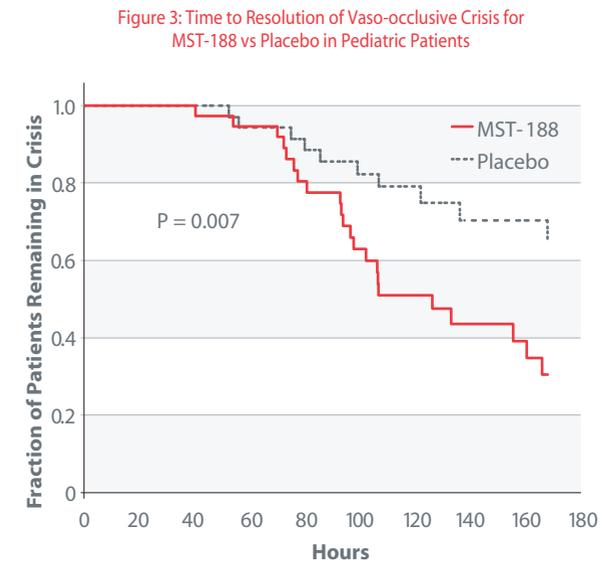
Group	MST-188	Placebo	P value
Length of crisis (hours)	141.36 ± 37.04	157.19 ± 27.58	0.024
Proportion with resolution of crisis (%)	46.2%	14.3%	0.016

Pediatric participants treated with MST-188 also showed a significant decrease in the length of crisis vs. PL and a significant increase in the percent of participants achieving crisis resolution within 168 hours (Table 3).

Table 3: Pediatric Patients (n=73)

Group	MST-188	Placebo	P value
Length of crisis (hours)	127.07 ± 42.47	148.58 ± 36.71	0.01
Proportion with resolution of crisis (%)	59.5%	27.8%	0.009

A Kaplan-Maier plot of the percentage of pediatric patients remaining in crisis over time for MST-188 vs. PL (Figure 3), graphically illustrates the degree of drug effect in this subgroup.



The subgroup analyses provide insights regarding the potential benefit of MST-188 for the treatment of VOC in patients with SCD and form the basis for the design and implementation of the definitive EPIC trial. The EPIC trial incorporates lessons learned from the previous MST-188 study and benefits from knowledge acquired from other clinical trials in SCD.

Objectives

Design and implement a pivotal Phase 3 study in SCD to:

- Determine definitively whether MST-188 can be effective in treating acute painful vaso-occlusive crisis (VOC) of SCD
- Serve as the basis for registration with the U.S. FDA

Methods

Protocol design based on:

- Analysis of data from prior trials of MST-188 and other agents in SCD
- Feedback and interactions with U.S. FDA, physician surveys, advisory panels of medical experts, and patient advocacy groups

Results & Discussion

The EPIC (Evaluation of Purified Poloxamer 188 In Children) Phase 3 study has been developed to address limitations of the prior MST-188 trial while incorporating successful elements to enhance the execution of this trial.

Key elements of the EPIC trial include:

- Randomized, double-blind, placebo-controlled, multi-center
 - Treatment arms:
 - » MST-188 administered as 100 mg/kg i.v. over 1 hour, followed by 30 mg/kg/hr i.v. for 48 hours
 - » Placebo: ½ normal saline i.v. over 49 hours
- Note: MST-188 and placebo are both administered in addition to standard of care. Volumes of MST-188 and placebo are matched to preserve blinding.

Key design changes include minimizing sources of potential variability and selecting population and endpoints to maximize trial success:

Population (key criteria)

- Pediatric population, and;
- Restricting phenotype to Hb SS and S-beta null thalassemia » provides a homogenous study population

Primary endpoint

- Duration of crisis resolution defined as the period from time of randomization to last dose of parenteral opioid » clinically meaningful outcome, objective, reduces complexity, limits the potential for missing data

Sample Size

- 90% power to detect a clinically meaningful reduction in time to crisis resolution » well powered trial to detect meaningful benefit

Other Considerations

- Guidelines for pain management and discontinuation of parenteral opioids » reduces variability of primary endpoint

Conclusions

MST-188 may represent a unique type of agent for treating VOC, exerting its effects through multiple rheologic mechanisms, including non-specific changes in red cell and leukocyte adhesion. MST-188 remains a promising drug that could have theoretic and practical advantage over agents targeting one specific adhesion molecule.

The EPIC trial is currently implemented in multiple sites in the U.S. and will be implemented in approximately 70 sites worldwide.

References

1. ClinicalTrials.gov (www.clinicaltrials.gov/ct2/show/NCT01737814)
2. Orringer EP et al. Purified Poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease. JAMA 2001;286(17):2099-2106.