Evaluation of Purified Poloxamer 188 In Children (EPIC) – Key Design Considerations

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Abstract

Background: There is no currently approved disease modifying treatment for ongoing vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD).
A prior phase 3 study investigating MST-188 (purified poloxamer 188) was suggestive of treatment effects; however, prospectively defined outcomes did not reach statistical significance, other than in subgroup analyses and post-hoc analyses[1]. Interpretation of that study was potentially confounded by a study population heterogeneous for age, genotype and variation in pain management practices, subjectivity of the primary endpoint, statistical imbalance in the numbers of patients in the placebo and treatment groups who did not achieve endpoints and missing or imputed data.

Objective: To achieve a phase 3 study design that could replicate the results of the subset analyses suggesting favorable responses in children and those receiving hydroxyurea, avoid the deficiencies of the previous trial, serve as the basis for registration with the US FDA and accomplish enrollment in a reasonable timeframe.

Methods: Discussion with medical experts in SCD, regulatory authorities, disease advocates and review of available studies of vaso-occlusive crisis.

Results:

1. The study should focus on children to achieve a more homogeneous population.
2. The study should enroll only patients with the SS or S-Beta null genotype.
3. The study should include guidelines for control of pain, minimizing variability in pain management practices among study centers.
4. Statistical assumptions (e.g., untreated duration of crisis) should reflect data from recent studies in SCD, including recently conducted NIH-funded studies.
5. The primary study endpoint should evaluate a clinically meaningful outcome that can be measured with as much objectivity as possible; for example, duration of crisis, as measured by the time from randomization to the last dose of parenteral opioid analgesia. An objective assessment of VOC resolution is preferable to complex, multi-part definitions and reliance on subjective pain scales.
6. The study should reduce "right censoring" and the potential for missing and imputed data by following subjects until discharge, rather than an artificial time-point (e.g., 168 hours after randomization, as in the previous study).

Conclusion: Incorporation of the above mentioned considerations should result in a study that overcomes the limitations of the prior study while maintaining rigor and feasibility of enrollment.

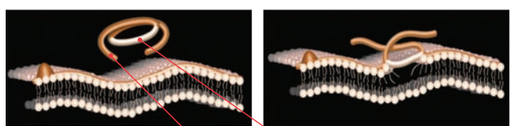
Background

The availability of effective treatments for vaso-occlusive crises (VOC) in patients with sickle cell disease (SCD) remains an area of significant unmet need, with no disease modifying therapies approved to treat an ongoing VOC. Hydroxyurea (HU) was granted FDA approval as a preventive treatment to reduce the frequency of VOC, but has not been shown to be effective in shortening the duration or decreasing the severity of an ongoing VOC. Clinical care remains supportive, consisting primarily of analgesia and anti-inflammatory agents, and does not adequately address the underlying cause of pain or the long-term cumulative effects of vaso-occlusion on end-organ damage. New treatment modalities are needed to address this significant unmet need.

A Potential New Treatment:

MST-188 (purified poloxamer 188) is a synthetic, nonionic, linear, block copolymer of polyoxyethylene and polyoxypropylene, with a mean peak molecular weight of 8500 ± 750 Da. It can reduce red blood cell aggregation, cellular adhesion to the vascular endothelium, and whole blood viscosity by inhibiting hydrophobic adhesive interactions. The underlying mechanism of action is not fully understood; however it is hypothesized that the polyoxypropylene core binds to hydrophobic portions of cells, leaving the hydrophilic polyoxyethylene chains free to interact with the surrounding media (Figure 1). When infused during VOC, these properties could play an important role in the restoration of compromised microvascular blood flow.[2] Rapid improvement in microcirculation after MST-188 infusion, as demonstrated in the conjunctival microvasculature of patients with SCD during VOC,[2] is expected to shorten the duration of VOC and associated pain.

Figure 1. MST-188 Mechanism of Action



Block Copolymer: Polyoxyethylene-Polyoxypropylene-Polyoxyethylene

Inhibits non-specific adhesion to hydrophobic domains
(acute phase reactant proteins or damaged membrane surfaces)
increasing/restoring surface hydration or "sealing" a damaged membrane.

MST-188 has been investigated in four clinical studies in subjects with SCD, including a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in patients with SCD experiencing VOC. In these prior clinical studies, MST-188 was generally well-tolerated.

In the prior Phase 3 study, treatment with MST-188 was associated with a shorter duration of VOC and a higher proportion of subjects achieving crisis resolution by a pre-specified time point (168 hours), although the decrease in duration of VOC in treated subjects did not reach statistical significance (p=0.07)[1]. (Table 1)

Table 1. Prior Phase 3 Study

Duration of Crisis (mean) (hours)

Group	MST-188	Control	Difference	*P* value	
All randomized subjects (n=255)	132.6	141.4	8.8	0.04	
All treated subjects (n=249)	132.3	140.3	8.0	0.07	Primary Endpoint
Subjects <16 years (n=73)	127.1	148.6	21.5	0.01	

Proportion Achieving Crisis Resolution within 168 Hours

Group	MST-188	Control	Difference	*P* value
All randomized subjects (n=255)	51.2%	35.2%	16%	0.01
All treated subjects (n=249)	51.6%	36.6%	15%	0.02
Subjects <16 years (n=73)	62.2%	27.8%	34.4%	0.01

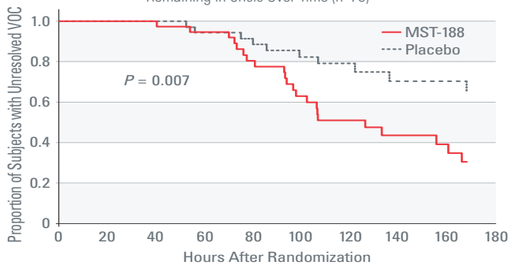
The results were likely impacted by the complexity of the primary endpoint, leading to protocol violations and right-censoring of the data, due to a pre-specified duration of 168 hours for endpoint assessment.

Post hoc analyses provided hypothesis-generating insight regarding the potential of MST-188 to shorten the duration of VOC[1]. (Table 1) (Figure 2)

Collectively, these data suggest that further study of MST-188 is warranted for patients with SCD and VOC.

Figure 2. Phase 3 Study: Post-hoc Analysis

Kaplan-Meier Analysis of Proportion of Patients <16 Years Old Remaining in Crisis Over Time (n=73)



Objectives

Determine the optimal design for a pivotal Phase 3 study in SCD that confirms the favorable responses previously observed in children, serves as the basis for registration with the US FDA, and accomplishes enrollment in a reasonable timeframe.

Methods

- Formal in-person meetings and written correspondence with US FDA
- Advice from SCD medical experts; physician surveys and interviews
- Input from SCD patient advocacy groups
- Analysis of data from recent, large studies in SCD

Results

Key Design Considerations Were As Follows:

- Regulatory authorities advised that:
  - Endpoints should incorporate as much objectivity as possible;
  - Missing data should be minimized;
  - Confounding variables (e.g., inter-site analgesic practices) should be identified and appropriately controlled.
- Medical experts agreed that crisis resolution was an appropriate and meaningful primary endpoint and that the point at which parenteral opioid analgesia was no longer needed was a reasonable surrogate for crisis resolution.

Discussion

These considerations and discussions led to the design of EPIC (Evaluation of Purified 188 In Children), a new Phase 3 study in SCD that is actively recruiting subjects.[3]

Notable Aspects of EPIC Include:

- Enrolling subjects age ≥8 and <18, and restricting phenotype to Hb SS and S-beta null thalassemia, which provides a homogenous study population, in which previous subgroup analyses suggest a statistically significant drug effect
- A primary endpoint based on time to crisis resolution, which medical experts agree is a clinically meaningful outcome
  - An assessment of crisis resolution based on last parenteral opioid administered, which reduces complexity, limits the potential for missing data and minimizes subjective assessments of crisis resolution
  - Following all subjects until discharge, which avoids "right censoring" and reduces the potential for missing data
- Assumptions regarding control-arm duration of crisis informed by recent, large studies in SCD
- A 90% probability to detect a clinically meaningful (16 hour) reduction in time to crisis resolution, which provides appropriate statistical power
- Guidelines for pain management and discontinuation of parenteral opioids, which reduces inter-site variability

Conclusion

The ongoing Phase 3 EPIC trial incorporates the above mentioned considerations, which should overcome the limitations of the prior phase 3 study while maintaining rigor and the ability to enroll patients efficiently. A successful trial is intended to support approval of a novel treatment to shorten the duration of ongoing VOC in SCD.

References

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2. Cheung AT, Chan MS, Ramanujam S et al. Effects of poloxamer 188 treatment on sickle cell vaso-occlusive crisis: computer-assisted intravital microscopy study. J Investig Med 2004;52(6):402-406.
3. www.clinicaltrials.gov/ct2/show/NCT01737814?term=anx-188&rank=2

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