SANGUINATE™ for the Treatment of Sickle Cell Disease

ABST-1097

Hemant Misra, Peter Buontempo, Ronald Jubin, Prayag Shah, Abraham Abuchowski- Prolong Pharmaceuticals, South Plainfield, NJ USA

Introduction: Oxygen carriers have been proposed as an approach to treat SCD complications (i.e., vaso-occlusive crisis [VOC]). SANGUINATE is a dual oxygen and carbon monoxide transfer agent that has received orphan drug status from the US-FDA for the treatment of SCD comorbidities. Clinical studies have been undertaken to assess its safety and efficacy in SCD indications.

Methodology: Five different clinical studies have been designed to assess the safety and efficacy profile of SANGUINATE. These include patients with stable SCD, leg ulcer, VOC (hospitalized and ambulatory), as well as an open label safety study enrolling other patients with life-threatening anemia who are unable to receive blood transfusions.

Observations: Preclinical Studies: SANGUINATE has been shown to return sickled red blood cells (RBC) to a more normal morphology and reduce inflammatory markers in whole blood samples collected from SCD patients (Figure 1 & 2).

Figure 1. SANGUINATE transfers oxygen and restores morphology to Sickle Cells *in vitro*

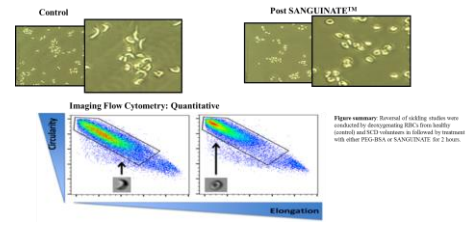


Figure 2. SANGUINATE transfers oxygen and restores morphology to Sickle Cells *in vitro*

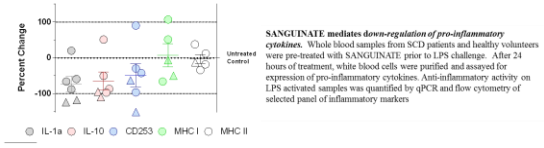
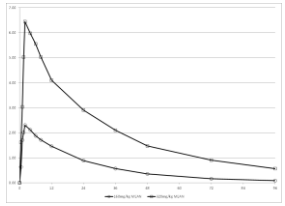


Figure 3. Mean SANGUINATE Blood Levels (mg/mL) by Dose



Phase Ib safety study in stable SCD patients:

- Assessed 2 dose levels of SANGUINATE as compared to hydroxyurea in 24 patients with stable SCD (low dose of 160 mg/kg of SANGUINATE or HU 15 mg/kg or high dose of 320 mg/kg of SANGUINATE or HU 15 mg/kg).
- Adverse Effects: Musculoskeletal and connective tissue disorder-related AEs were the most commonly reported. Transient troponin I levels increased in 3 patients, and one of whom had an increase in tricuspid regurgitant jet velocity (TRV); however, no clinical signs or symptoms of concern were noted.
- This trial established the pharmacokinetics and safety of SANGUINATE at both dose levels and permitted its advance into phase II trials. (Figure 3)

Phase II Leg Ulcers:

- The study was conducted in Panama and the Dominican Republic. This was an escalating, repeated-dose, open-label, Phase 2 study to test SANGUINATE at 320 mg/kg (8 mL) in subjects suffering from leg ulceration associated with SCD. All enrolled subjects underwent a 3-week Run-In Period; Cohort 1 received once-weekly, 2-hr IV infusions of SANGUINATE 320 mg/kg for 4 weeks and Cohort 2 received once-weekly infusions for 6 weeks.
- The administration of once-weekly infusions of SANGUINATE was well tolerated. 2/10 patients report treatment emergent adverse events considered related to study drug.. Changes in ECG intervals were seen in a few subjects, but those changes were not considered clinically meaningful. There were no clinically meaningful changes in laboratory values, physical examinations, or concomitant medications.
- The administration of 4 or 6 once-weekly infusions of SANGUINATE at a dose of 320 mg/kg was generally well tolerated. Slight improvements in total and individual VCSS are promising and may warrant further study.

Phase II Vaso-Occlusive Crisis:

- The study was conducted in Panama and the Dominican Republic. This was an escalating, repeated-dose, open-label, Phase 2 study to test SANGUINATE at 320 mg/kg (8 mL) in subjects suffering from leg ulceration associated with SCD. All enrolled subjects underwent a 3-week Run-In Period; Cohort 1 received once-weekly, 2-hr IV infusions of SANGUINATE 320 mg/kg for 4 weeks and Cohort 2 received once-weekly infusions for 6 weeks.
- The administration of once-weekly infusions of SANGUINATE was well tolerated. 2/10 patients report treatment emergent adverse events considered related to study drug.. Changes in ECG intervals were seen in a few subjects, but those changes were not considered clinically meaningful. There were no clinically meaningful changes in laboratory values, physical examinations, or concomitant medications.
- The administration of 4 or 6 once-weekly infusions of SANGUINATE at a dose of 320 mg/kg was generally well tolerated. Slight improvements in total and individual VCSS are promising and may warrant further study.

Life-Threatening Anemia In Patients With Hyperhemolysis And Acute Chest Syndrome:

- Over 5 patients with hemoglobin levels below 5 g/dL have received SANGUINATE Under a Phase I safety study in patients who are unable to receive blood transfusions.
- Patients have received multiple doses.
- No serious adverse effects have been reported.

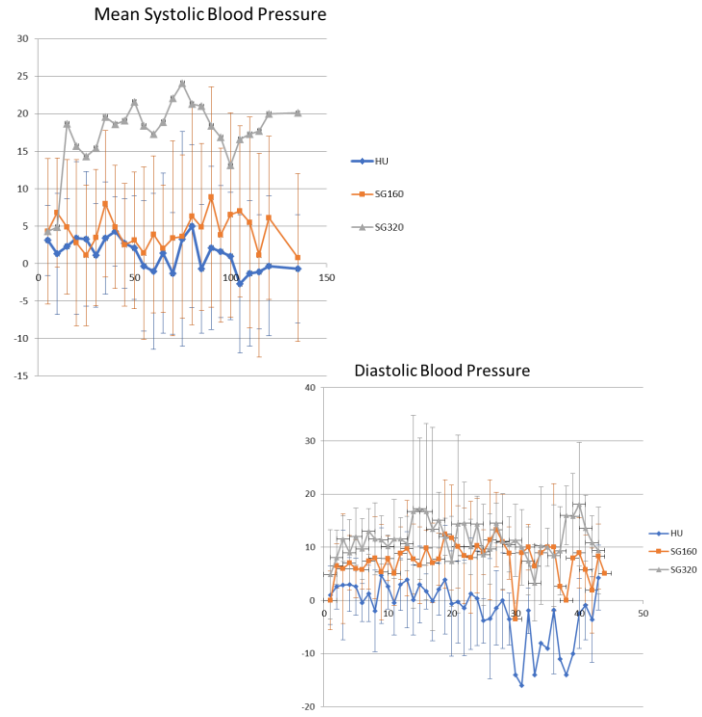
For more info: www.prolongpharma.com

The Conflict of Interest disclosure forms for above authors have been satisfied.

Discussion:

- To date, 63 patients with SCD have been infused with single, multiple or repeated doses of SANGUINATE. All reported adverse events were of mild or moderate severity
- Transient increases in mean arterial pressure have been observed. This is due to the colloid nature of the investigational drug (figure 4).

Figure 4. Impact on Mean Arterial Pressure



Conclusion:

Preliminary data suggesting that SANGUINATE unsickles patients' RBCs during VOC is promising and suggests that this drug may have a role in treatment of the pain crisis. To date, no clear evidence of a clinically meaningful safety concern has been identified. Future studies in VOC and other comorbidities are being explored.