Use of SANGUINATE™ to Treat the Comorbidities of Sickle Cell Disease: Safety Results of a Phase Ib Study in Stable SCD Patients

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INTRODUCTION
A clinical study of SANGUINATE™ (pegylated carboxyhemoglobin bovine) intravenous infusion has been conducted in Sickle Cell Disease (SCD) patients who are not currently experiencing vaso-occlusive crises or other clinically significant SCD-related morbidities (stable SCD patients). SANGUINATE is a carbon monoxide-releasing, oxygen transfer agent that is being developed for the treatment of comorbidities of SCD and other anemia/chronic conditions. This was the first study of SANGUINATE in patients. An initial study in healthy subjects revealed no serious treatment-unrelated adverse effects and showed dose-proportional pharmacokinetics. This study further demonstrated no clinically meaningful adverse effects but was insufficiently powered to provide proof of efficacy.

ANALYSIS/RESULTS
- All patients had many laboratory test values that were abnormal at Baseline.
- There were more adverse events reported but no difference in event-rate between the two SANGUINATE dose groups that were reported in the comparator group.
- Because SANGUINATE is a colloidal solution, there is transient "plasma expansion" effect seen in patients that is not expected in the comparator. This effect increased mean pressure, which is believed to be the reported mild to moderate dose-independent adverse events.
- The most commonly reported adverse events were musculoskeletal and connective tissue disorders, with arthralgia accounting for 10 of 51 reported events.
- ECG status did not show any dose or treatment-related trends.
- Transient increases in mean body temperature did not vary significantly with changes in treatment or dose provided.
- 6 events in 2 patients (mild pulmonary hypertension, mild to moderate tricuspid regurgitation, moderate nausea, moderate epigastralgia, moderate bone pain, and mild pruritus) were identified as possibly related to SANGUINATE. A single reported SAE was identified by investigator.

Serious Adverse Event
The patient, a 69 year-old female with homozygous SCD and a history of both mitral and tricuspid valve insufficiency, received 320 mg/kg SANGUINATE. TRV after dosing was 3.65 m/s, 3.66 m/s, and 3.59 m/s at 0, 2, and 6 hours after the end of the infusion.

Other Noteworthy Events
- There were brief but substantial increases in troponin I levels in 3 patients receiving SANGUINATE 320 mg/kg that were not seen in the patients receiving SANGUINATE 160 mg/kg.
- The clinical interventions were requested in response to the event.
- Two of the patients had Baseline troponin I values (before dosing) of 0.028 ng/mL (above the upper limit of the laboratory reference range (0.018 ng/mL).
- The patient’s self-reported condition was “very good” throughout the period of the event and no clinical signs or symptoms of concern could be identified.
- The patient continued to perform the study procedures with no reductions in exercise capacity or expiratory volume and no increases in reported pain from before the time of dosing.

CONCLUSION
Following assessment of vital signs, TRV, EKG, serum biochemistry, hematology, and urinalysis, as well as analysis of reported adverse events in 27 stable SCD patients treated with a single dose of either 160 mg/kg SANGUINATE, 320 mg/kg SANGUINATE, or 15 mg/kg hydroxyurea, no clear evidence of a clinically meaningful safety concern was identified. Due to its multiple mechanisms of action, SANGUINATE has potential as a broad-range of indications characterized by hypoxia. SANGUINATE has shown signs of therapeutic effects in SCD patients treated under eNOS that warrant more in-depth clinical investigation. Phase 2 studies are approved by the FDA for the treatment of SCD leg ulcers and for the reduction or prevention of delayed cerebral ischemia following subarachnoid hemorrhage in USA. A trial is underway in Thailand for β-Thalassemia. Follow-up Phase 2 studies of the clinical effects of SANGUINATE in SCD patients in Central and South America are planned.

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