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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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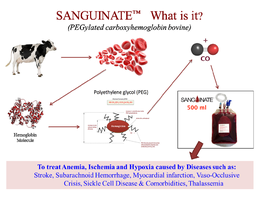
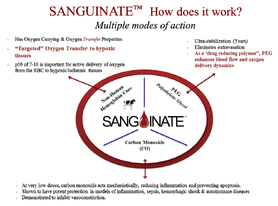
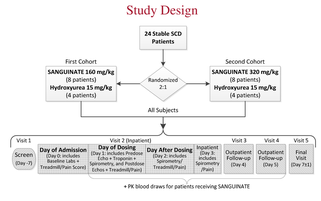
INTRODUCTION

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 crisis 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 anemic/ischemic conditions. This was the first study of SANGUINATE in patients. An earlier study in healthy subjects revealed no serious treatment-emergent 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 than were reported in the comparator group.
- Because SANGUINATE is a colloid solution, there is a transient "plasma expansion" effect seen in patients that is not expected in the comparator. This colloid effect increases osmotic pressure, which is believed to generate 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.
- Mean oxygen saturation, mean pulse rate, mean respiratory rate, and mean body temperature did not vary significantly with changes in treatment or dose provided.
- 6 events in 2 patients (*moderate 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 49 year old female with homozygous SCD and a history of both mitral and tricuspid valve insufficiency, received IV SANGUINATE (320 mg/mL). Her tricuspid regurgitant jet velocity (TRV) determined by Doppler ultrasound echocardiography was 2.42 m/s before dosing. TRV after dosing was 3.63 m/s, 3.66 m/s, and 3.59 m/s at 0, 2, and 6 hours after the end of the infusion.

- No clinical interventions were required in response to the event.
- The diagnosis of pulmonary hypertension was not confirmed by right heart catheterization.
- 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.

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.

- No clinical interventions were required in response to the event.
- Two of the patients had Baseline troponin I values (before dosing) near or above the upper limit of the laboratory reference range (0.028 ng/mL).
- Because of the short duration of the elevations, and because they were not accompanied by any clinically identified or patient reported adverse experiences, these were not reported by the Investigators as serious adverse events.
- One patient receiving hydroxyurea also had a brief increase in troponin I level above the upper limit of the laboratory reference range at 72 hours after dosing.

CONCLUSION

Following assessment of vital signs, TRV, EKG, serum biochemistry, hematology, and urinalysis, as well as analysis of reported adverse events in 22 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 has been identified. Due to its multiple mechanisms of action, SANGUINATE has potential use in a broad range of indications characterized by hypoxia. SANGUINATE has shown signs of therapeutic effect in 3 SCD patients treated under eINDs that warrant more in-depth clinical investigation. Phase 2 studies are approved by the US 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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