USE OF PEGYLATED-CARBOXYHEMOGLOBIN BOVINE FOR THE TREATMENT OF SICKLE CELL DISEASE ASSOCIATED LEG ULCERS: RESULTS FROM A PHASE II SAFETY STUDY

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Background: Leg ulcers are a common complication of sickle cell disease (SCD). The pathophysiology of SCD leg ulcer is complex and may include obstruction of blood vessels by sickled red cell, chronic anemia, depleted nitric oxide bioavailability (resulting in impaired endothelial function), infection, thrombosis and excessive vasoconstriction. These events lead to progressive peripheral de-vascularization and tissue necrosis, such that even minor lower-leg wounds can become persistent ulcers, with no tendency to heal after months of appropriate treatment.

PEGylated-Carboxyhemoglobin bovine (PEG-COHb; SANGUINATE®) is an oxygen carrying agent with anti-inflammatory activity. A study of safety and effectiveness was undertaken in SCD patients with chronic leg ulcers to determine the safety of this investigational drug administered in a once weekly infusion for either 4 or 6 weeks.

Aim: To assess the safety and efficacy of repeated doses of PEG-COHb on SCD leg ulcers.

Methods: The study was an escalating, repeated-dose, open-label, Phase 2 study to test PEG-COHb at 320 mg/kg (8) in subjects suffering from leg ulceration associated with SCD. It was conducted in Panama and the Dominican Republic. All enrolled subjects underwent a 3-week Run-In Period, during which they received standard of care treatment for wound management. During the Treatment Period, subjects were assigned sequentially to Cohort 1 or Cohort 2. Cohort 1 received 4 once-weekly doses by 2-hour intravenous infusion of SANGUINATE®. Following the completion of Cohort 1, the safety findings were reviewed prior to initiating Cohort 2. Cohort 2 received 6 once-weekly infusions. In addition to the study drug, subjects continued to receive standard of care during the Treatment Period. One week after the end of Treatment, subjects returned to the study center for a Final Visit.

The following assessments were done:
- Safety: Safety was assessed by recorded adverse events (AEs), laboratory assessments (hematology, chemistry, and urinalysis), vital signs, concomitant medications, and 12-lead electrocardiograms (ECGs)
- Efficacy: Wound pain, wound appearance and condition, wound size, wound vascular status (Venous Clinical Severity Score; VCSS)
- Quality of Life: Quality of life was assessed using the Short Form-12 (SF-12) Health Survey.

Results: The administration of once-weekly infusions of PEG-COHb was well tolerated. Treatment emergent adverse events (mild pyrexia, moderate worsening anemia) considered related to study drug were report in 2/10 patients. Increases in mean arterial pressure were anticipated due to the oncotic effects of this colloidal drug, but with no consistent pattern to the changes. 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.

There were no statistically significant changes from Baseline in leg ulcer pain and wound surface area for either Cohort. All of the wound assessments remained relatively consistent throughout the study. There were slight decreases in total VCSS at most time points, indicating slight improvement in vascular status. Results were similar for the individual scores.

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

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