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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#P618

Background: Leg ulcers are a common complication of sickle cell disease (SCD). The pathophysiology of SCD leg ulcer is complex and ma y 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 as 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; VSCC)
- Quality of Life: Quality of life was assessed using the Short Form-12 v2 Health Survey (SF-12)

Results:

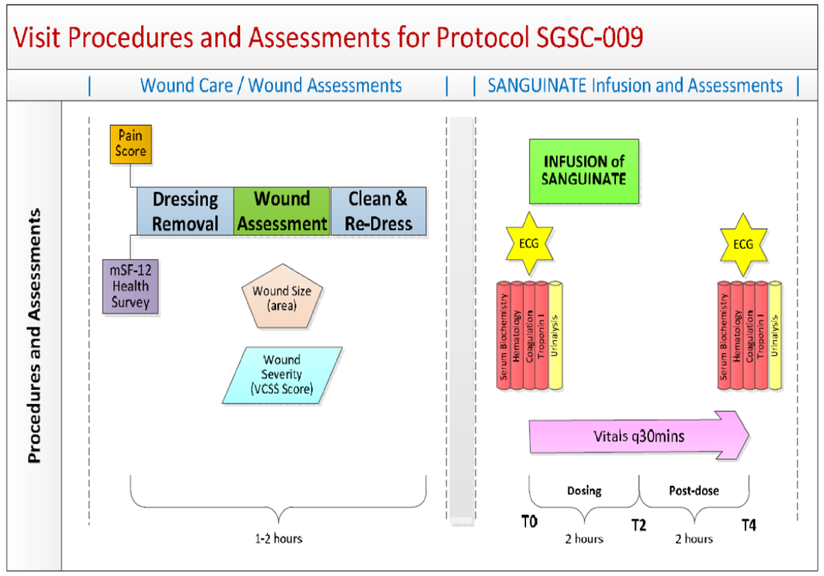
The administration of once-weekly infusions of PEG-COHb was well tolerated. Treatment emergent adverse events (mild pyrexia, moderate worsening anemia) considered related to study drug were report in 2/10 patients. Increases in mean arterial pressure were anticipated due to the oncotic effects of this 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.

Study Site Enrollment Information

Center Number	Investigator Center Address	Number of Subjects Screened	Number of Subjects Enrolled
001	Lineth Lopez, MD Centro Hemato-Oncológico Panamá Panamá, Calle 53 Marbella, Edificio Royal Center Quinto Piso, Torre B, Sección B	Cohort 1 – 7 Cohort 2 – 3	Cohort 1 – 5 Cohort 2 – 3
002	Gladys Maria Paulino, MD Hospital General de la Plaza de la Salud Av. Ortega y Gasset, Ensanche La Fe 10514 Santo Domingo República Dominicana	Cohort 1 – 0 Cohort 2 – 2	Cohort 1 – 0 Cohort 2 – 2



Conclusion

The administration of 4 or 6 once-weekly infusions of PEG-COHb 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 with prolonged repeated doses of PEG-COHb.

Demographic Characteristics by Cohort (Safety Population)

Characteristics	Cohort 1 N=5	Cohort 2 N=5	All Subjects N=10
Gender, n (%)			
Male	2 (40.0)	2 (40.0)	4 (40.0)
Female	3 (60.0)	3 (60.0)	6 (60.0)
Race, n (%)			
Other: Multiracial	5 (100)	5 (100)	10 (100)
Ethnicity, n (%)			
Hispanic or Latino	5 (100)	5 (100)	10 (100)
Age (years)			
Mean (SD)	43.4 (7.89)	43.4 (11.44)	43.4 (9.26)
Median	42.0	42.0	42.0
Min, Max	37, 57	30, 59	30, 59

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation

Overall Summary of Treatment-emergent Adverse Events by Cohort (Safety Population)

Number of:	Cohort 1 N=5 n (%)	Cohort 2 N=5 n (%)	All Subjects N=10 n (%)
TEAEs	8	11	19
Subjects with at least 1 TEAE	4 (80.0)	4 (80.0)	8 (80.0)
SAEs	0	1	1
Subjects with SAEs	0	1 (20.0)	1 (10.0)
Subjects with moderate or severe TEAEs	2 (40.0)	3 (60.0)	5 (50.0)
Subjects with treatment-related TEAEs	1 (20.0)	1 (20.0)	2 (20.0)
Subjects with AEs that lead to withdrawal from the study	0	0	0
Deaths	0	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Note: A TEAE was defined as an AE that started on or after the date of the first dose of study drug. Since a subject could have had more than 1 TEAE, the number of TEAEs can be greater than the number of subjects in the Safety population. A subject was only counted once within each category. Treatment-emergent AEs were coded using MedDRA version 19.0.

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