Phase I study of the safety and pharmacokinetics of CSL889 (hemopexin) in adults with sickle cell anemia

Vaso-occlusive crisis (VOC) is the primary cause of hospitalization in patients with sickle cell disease (SCD) and is marked by episodes of severe pain.[1] Heme released into the circulation due to intravascular hemolysis plays an important role in VOC[2] through endothelial activation and enhanced blood cell adhesion that leads to vaso-occlusion, ischemia, and severe pain. No treatments have been approved by the US Food & Drug Administration for acute VOC. Supportive care with hydration and pain management with opioid and non-opioid analgesics are the current standard of care for patients with VOC, and if organ dysfunction develops, emergency blood transfusions (simple or exchange) may be indicated. If acute organ damage develops during VOC, patients are at increased risk of mortality and chronic organ dysfunction.[3,4]

Chronic hemolysis in SCD depletes hemopexin, an endogenous plasma protein that scavenges extracellular heme, to levels well below the normal value of approximately 2,000 μg/mL.[5,6] In preclinical studies, hemopexin administration relieved vaso-occlusion caused by both hemoglobin and heme-independent triggers, such as hypoxia-reoxygenation, in Townes SCD mice.[7] Similarly, hemopexin prevented heme-toxicity in the cardiovascular system and facilitated heme recovery and detoxification by the liver through the induction of heme oxygenase in mouse models of hemolysis.[8] In many different experimental models, heme modestly activates toll-like receptor 4 (TLR4) signaling, whereas a combination of heme with TLR4 ligands induces strong signaling,[9,10] but is attenuated by hemopexin supplementation. We investigated the potential for the human plasma-derived hemopexin, CSL889, to counteract heme-induced vaso-occlusion in patients with SCD experiencing acute VOC. Here, we report the results of a phase I first-in-human study that evaluated the pharmacokinetics (PK), safety, and tolerability of CSL889 in adults with SCD (clinicaltrials.gov identifier NCT04285827).

This study was a phase I, multicenter, open-label trial that included participants aged ≥18 to ≤60 years with a diagnosis of SCD (any genotype) and hemoglobin levels ≥6 g/dL (≥60 g/L). An independent ethics committee and institutional review board approved the protocol. Eligibility criteria are provided in *Online Supplementary Table S1*. The study consisted of 2 parts: parts A and B. Part A participants had stable SCD with no VOC within 30 days of screening. Stable SCD was defined as no evidence of disease worsening (including VOC, recent major surgery, hospitalization, serious infection, significant bleeding, cerebrovascular accident, seizure, or intravenous [i.v.] opioids) within 30 days of screening. Participants were administered a single i.v. dose of CSL889 in one of 6 ascending dose cohorts (3, 10, 30, 60, 120, and 200 mg/kg) of 4 participants each. Dose escalation was based on a committee review of safety and PK data. In part B, 4 patients hospitalized for the management of uncomplicated acute VOC (without fever, infection, acute chest syndrome, or stroke) received a single i.v. dose of CSL889 (60 mg/kg; selected according to part A safety and PK data) within 36 hours of admission. For PK assessments in parts A and B, serum hemopexin was measured using an enzyme-linked immunosorbent assay (lower limit of quantification: 2,500 ng/mL) at baseline and 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 168, 336, and 768 hours after the end of CSL889 infusion. This serum hemopexin assay measures total hemopexin and cannot differentiate CSL889 from endogenous hemopexin or heme-bound from free hemopexin. Baseline correction was applied to estimate CSL889 concentrations, considering endogenous hemopexin in each participant. Non-compartmental analysis was performed to estimate the PK parameters of CSL889. Safety was assessed from the start of CSL889 infusion through day 33 by evaluating the frequency, nature, and severity of treatment-emergent adverse events (TEAE). Anti-CSL889 antibody titers were assessed at baseline, day 15, and day 33.

Twenty-five participants were enrolled in part A, of whom 24 (4 in each of 6 cohorts) completed the study. One participant withdrew before receiving CSL889 due to unsuccessful venous access. In part B, all 4 participants completed the study. Baseline participant characteristics and laboratory data are available in *Online Supplementary Tables S2* and *S3*, respectively. Median age of the participants was 32 years (range: 20-57). Most participants (96.4%) were of Black or African American ethnicity, and most (86%) had HbSS genotype. Within the previous 12 months, most participants in part A had ≤2 VOC, and all participants in part B had ≥3 VOC. Half of the participants (50%) in part A and all (100%) in part B were taking hydroxyurea at baseline (stable dose for at least 30 days before CSL889 administration, with no dose adjustments during the study period). Additionally, 3 participants in part B were receiving voxelotor or crizanlizumab, which were continued during the study.

Exposure assessments in part A participants showed low but highly variable baseline endogenous hemopexin levels (range: 7.2-499 μg/mL; mean normal value 2,000 μg/mL). Total hemopexin concentrations increased dose-dependently after CSL889 infusion and decreased to baseline levels over time (Figure 1A). Hemopexin C_{max} also increased with increasing doses of CSL889. The mean total hemopexin C_{max} at 200 mg/kg was approximately twice the

normal level found in healthy humans.[5] The mean C_{max} in participants without VOC in part A and with VOC in part B who received the same dose (60 mg/kg) was comparable within variability based on standard deviation (Figure 1B, C). Time to maximum concentration (T_{max}) of CSL889 after dosing was ≤2.3 hours, and the elimination half-life ($T_{1/2}$) ranged from 0.4 to 3.7 days across the dose levels. In part A, among the 3 highest doses (60, 120, and 200 mg/kg), increases in area under the concentration time curve $(AUC)_{0\text{-inf}}$ were dose-dependent, with increases of 1.6- and 3.0-fold when comparing the 120 mg/kg and 200 mg/kg cohorts with the 60 mg/kg cohort, respectively. AUC from time 0 to the last measurable concentration ($AUC_{0\text{-last}}$) in part B was 21% lower compared to part A (Table 1).

Hemopexin:heme complex levels correlated with total hemopexin levels, confirming target engagement. Total serum heme, measured to estimate the heme scavenging capacity of hemopexin, showed variable levels over time, within and across cohorts, but no clear association with hemopexin levels. A panel of exploratory pharmacodynamic and disease

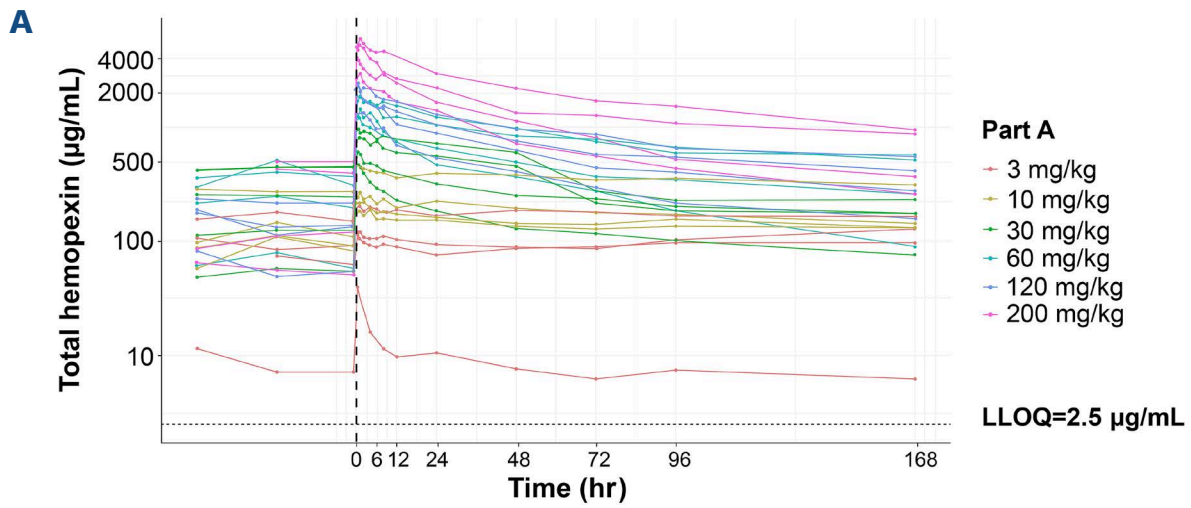


Figure 1. Total hemopexin levels over time. (A) Total hemopexin levels over time in part A participants with sickle cell anemia not in vaso-occlusive crisis (VOC). Participants (N=4 per cohort) received a single intravenous dose of 3, 10, 30, 60, 120, or 200 mg/kg of CSL889. (B) Total hemopexin levels over time in part A participants with stable sickle cell anemia and in part B participants with VOC who received the same dose (60 mg/kg) of CSL889. (C) Total hemopexin area under the concentration time curve $(AUC)_{0\text{-last}}$ of participants with sickle cell disease during (part A; 60 mg/kg) or not during VOC (part B; 60 mg/kg cohort) was similar when considering variability.

biomarkers included markers of cellular activation and adhesion (soluble [s] ICAM-1, VCAM-1, ICAM-3, E-selectin, P-selectin, L-selectin) and inflammation (interleukin [IL]-1β, IL-2, IL-3, IL-6, IL-8, IL-10, TNF-α, sCD40L, HMGB1, sTF). No changes in mean pharmacodynamic biomarker concentrations were observed. No pharmacodynamic or disease markers showed a relationship with CSL889 dose or patient physiology, including disease state (stable *vs*. VOC).

This phase I study identified no safety concerns after CSL889 infusion. No participants developed treatment-emergent anti-CSL889 antibodies. No participants discontinued the study, and no deaths were reported. Overall, 19 of 24 participants in part A and 3 of 4 participants in part B experienced TEAE (60 TEAE in part A and 10 TEAE in part B). The majority of these TEAE (58 of 60 in part A; 10 of 10 in part B) resolved; 2 TEAE (paresthesia and wisdom tooth pain) were ongoing at the final study visit for each participant. Most TEAE were of mild or moderate severity; there was one severe TEAE of back pain in a participant in part A that was assessed as not related to CSL889, and this resolved. Neither the number nor the severity of TEAE increased with dose or VOC status. The most frequent TEAE reported (Common Terminology Criteria for Adverse Events [CTCAE] preferred term) were sickle cell anemia with crisis (25% [6/24] in part A and 50% [2/4] in part B) and headache (17% [4/24] in part A) (Table 2). In part A, 4 TEAE in 3 participants were assessed by the investigators as related to CSL889. Two participants (one from the 30 mg/kg cohort and the other from the 120 mg/kg cohort) experienced transient dizziness shortly after the CSL889 infusion. Another participant in the 30 mg/kg cohort showed a mild transient increase in fibrin D-dimer and a mild decrease in fibrinogen plasma level four hours after infusion. All TEAE that were assessed as related to CSL889 were non-serious and resolved. No participant in part B experienced any TEAE that was considered related to CSL889. Two serious adverse events (SAE) of moderate severity (simultaneous COVID-19 and sickle cell anemia with crisis), unrelated to CSL889, were reported in one participant in part A; both resolved. One participant in part B experienced acute chest syndrome in the context of an illness with diarrhea more than eight days after CSL889 infusion, which was unrelated to CSL889 and resolved. No changes were noted in the electrocardiogram or other lab findings.

The result of this phase I study demonstrates the PK, safety, and tolerability of CSL889 when administered as a single dose of up to 200 mg/kg in patients with stable SCD and at 60 mg/kg in patients with acute VOC. The observed PK data are in line with non-clinical predictions. As expected, baseline hemopexin concentrations were low, although some variability was observed. After CSL889 infusion, increases in total hemopexin concentrations were observed, returning to the baseline range by day 8. PK parameters in participants with VOC were comparable to those in participants with stable SCD at the same dose, when variability is considered. The study did not find any safety concerns. All TEAE observed in the study corresponded to those expected for a population with SCD, including the TEAE of sickle cell anemia with crisis and acute chest syndrome. This study was not designed to investigate efficacy. Single doses given primarily during steady state may not have provided a sensitive setting

Table 1. Hemopexin pharmacokinetic parameters after CSL889 infusion.

Parameter units	Part A N=4 per cohort Mean (SD)						Part B N=4 Mean (SD)
	3 mg/kg[a]	10 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	200 mg/kg	60 mg/kg
$AUC_{0\text{-}Inf}$, h*mg/mL	0.583 (0.4174)	12.304 (3.4798)	21.964 (6.1735)	71.346 (30.5107)	113.340 (45.7888)	212.768 (70.5459)	37.793 (19.5298)
$AUC_{0\text{-}last}$, h*mg/mL	0.469 (0.3156)	6.146 (1.7785)	14.211 (2.6060)	59.557 (20.8918)	83.588 (28.2191)	171.465 (55.3108)	48.286 (19.4514)
C_{max}, μg/mL	44.953 (14.4082)	152.429 (38.4637)	521.711 (97.6298)	1385.322 (243.0488)	1909.998 (416.2172)	4315.742 (1201.0224)	1089.586 (216.0738)
T_{max}, hr	0.759 (0.28, 1.22)	0.475 (0.23, 1.25)	0.400 (0.28, 0.80)	1.642 (1.30, 2.18)	1.700 (1.62, 2.05)	2.142 (1.17, 2.33)	1.309 (1.13, 2.28)
$T_{1/2}$, hr	9.545 (4.5539)	70.558 (4.2393)	48.198 (13.9404)	58.694 (15.8209)	89.776 (38.7196)	77.358 (28.4475)	35.955 (29.5215)
Last point NCA, hr	24	72	96	168	168	168	168

All parameters (baseline-adjusted) are expressed as mean (standard deviation, SD), except T_{max} which is given as median (minimum, maximum). AUC: area under the concentration time curve; $AUC_{0\text{-}inf}$: AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$: AUC from time 0 to the last measurable concentration; C_{max}: maximum observed concentration; hr: hours; N: total population; NCA: non-compartmental analysis; $T_{1/2}$: terminal half-life; T_{max}: time of maximum concentration. [a]N = 2 for $AUC_{0\text{-}inf}$ and $T_{1/2}$.

Table 2. Overview of treatment-emergent adverse events.

	Part A N=4 per cohort						Part A overall N=24	Part B N=4
	3 mg/kg	10 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	200 mg/kg		60 mg/kg
Any TEAE, N* (%)	3 (75.0)	4 (100.0)	2 (50.0)	3 (75.0)	3 (75.0)	4 (100.0)	19 (79.2)	3 (75.0)
Any treatment-emergent SAE, N* (%)	0	1 (25.0)	0	0	0	0	1 (4.2)	1 (25.0)
CSL889-related TEAE, N* (%)	0	0	2 (50.0)	0	1 (25.0)	0	3 (12.5)	0
CSL889-related TEAE leading to study discontinuation, N* (%)	0	0	0	0	0	0	0	0
TEAE in >1 participant overall, N* (%)								
Sickle cell anemia with crisis	1 (25.0)	2 (50.0)	0	2 (50.0)	0	1 (25.0)	6 (25.0)	2 (50.0)
Headache	0	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (25.0)	4 (16.7)	0
Dizziness	0	0	1 (25.0)	0	1 (25.0)	0	2 (8.3)	0
Arthralgia	0	0	1 (25.0)	0	0	1 (25.0)	2 (8.3)	1 (25.0)
Back pain	0	0	0	2 (50.0)	0	0	2 (8.3)	0
COVID-19	0	1 (25.0)	0	0	0	1 (25.0)	2 (8.3)	0
Abdominal pain	0	0	0	1 (25.0)	0	1 (25.0)	2 (8.3)	0
Diarrhea	1 (25.0)	0	0	1 (25.0)	0	0	2 (8.3)	1 (25.0)
Increased fibrin D-dimer	0	0	1 (25.0)	0	1 (25.0)	0	2 (8.3)	0

COVID-19: Coronavirus disease 2019; N: total population; N*: subset; SAE: serious adverse event; TEAE: treatment-emergent adverse events.

for secondary changes in biomarkers.

To conclude, CSL889 had an excellent safety and tolerability profile. The observed half-life suggests that CSL889 may be administered once daily or every other day. These results provide a strong foundation for future trials to evaluate potential efficacy.

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Contributions

FRW and PMS are responsible for study concept, investigation and supervision, and project administration; GJK is responsible for study concept and supervision; VRG is responsible for study concept, investigation and supervision; RW is responsible for the formal analysis, visualization and study supervision; KJ is responsible for project administration, and study investigation and supervision; BJB

is responsible for study investigation and supervision; RK-A, EW, RCGA, AAB, PE, LMDeC and SB are responsible for study investigation; MA is responsible for study supervision; WDH is responsible for visualization. All authors helped design the study methodology, write the original draft, and review and edit the final version of the manuscript for publication.

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Data-sharing statement

CSL will consider on a case-by-case basis requests to share Individual Patient Data (IPD) with external bona-fide, qualified scientific and medical researchers. For information on the process and requirements for submitting a voluntary data-sharing request for IPD, please contact CSL at clinicaltrials@cslbehring.com

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