haematologica
Journal of the Ferrata Storti Foundation

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Received: October 21, 2025.
Accepted: February 27, 2026.

Citation: Bart J. Biemond, Rachel Kesse-Adu, Ezanul Wahab, Roberta C. G. Azbell, Alexander A. Boucher, Perla Eleftheriou, Laura M. De Castro, Shayla Bergmann, William D. Hedrich, Francine R. Wilson, Kerstin Jung, Michael Araco, Rongrong Wang, Paul M. Shore, Gregory J. Kato and Victor R. Gordeuk. Phase I study of the safety and pharmacokinetics of CSL889 (hemopexin) in adults with sickle cell anemia. Haematologica. 2026 Mar 19. doi: 10.3324/haematol.2025.300088 [Epub ahead of print]

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

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Running title: Safety and PK of hemopexin in SCD

Disclosures

Bart J. Biemond reports research funding from Novartis, Pfizer, BMS and Novo Nordisk; honoraria for advisory board meetings, lecturers or podcasts from Pfizer, Celgene, BMS, Novo Nordisk and Sanofi.

Rachel Kesse-Adu reports honoraria for meetings, lectures and educational materials from Pfizer, Novartis, Novo Nordisk and Vertex.

Ezanul Wahab has no disclosures.

Roberta C. G. Azbell has no disclosures.

Alexander A. Boucher reports research funding from Innovative Hematology, Inc and Takeda.

Perla Eleftheriou reports honoraria for advisory board meetings, talks at conferences and webinars from Pfizer, Novo Nordisk and Vertex.

Laura M. De Castro reports clinical trial funding from Novartis, CSL Behring and Pfizer.

Shayla Bergmann reports honoraria for advisory board meeting and talks from Sobi, Sanofi, Bayer, Takeda, NovoNordisk along with clinical trial funding from Sanofi, Takeda, Bayer, Pfizer, NovoNordisk, Novartis, CSL Behring, and Forma.

William D. Hedrich, **Francine R. Wilson**, **Kerstin Jung**, **Michael Araco**, **Rongrong Wang**, **Paul M. Shore**, and **Gregory J. Kato** are employees of CSL.

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Funding

This study was funded by CSL Behring.

Acknowledgements

The authors acknowledge Dr. Henry Fok, Dr. Payal Desai, Dr. Anita Rijneveld, Dr. Peter Dewland, and Dr. Pui Man Leung for their contributions toward patient enrollment in this study. The authors would also like to acknowledge Jeanine Jochems, Jeannine McCune, and Stefan

Costin. Medical writing assistance for this manuscript was provided by Shereen Cynthia D'Cruz, Ph.D., CMPP™ of CSL Behring.

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.

Keywords: hemopexin; sickle cell disease; vaso-occlusive crisis

ClinicalTrials.gov number, NCT04285827

Letter to the Editor

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. There are no FDA-approved treatments 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 about 2000 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 are investigating the potential for CSL889 (human plasma-derived hemopexin) to counteract heme-induced vaso-occlusion in patients with SCD experiencing acute VOC. Here, we report the results of a phase 1, first-in-human study that evaluated the pharmacokinetics (PK), safety, and tolerability of CSL889 in adults with SCD [NCT04285827].

This study was a phase 1, multicenter, open-label trial that included participants aged 18 to 60 years (inclusive) 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 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 [IV] opioids) within 30 days of screening. Participants were administered a single IV 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 IV dose of CSL889 (60 mg/kg; selected based on part A safety and PK data) within 36 hours of admission. For PK assessments in part A and B, serum hemopexin was measured using an enzyme-linked immunosorbent assay (lower limit of quantification: 2500 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 (TEAEs). 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 Tables S2 and S3, respectively. The median (range) age of the participants was 32 years (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 to 499 μg/mL; mean normal value 2000 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), area under the concentration time curve $(AUC)_{0\text{-inf}}$ increased dose-dependently, with increases of 1.6- and 3.0-fold while comparing 120 mg/kg and 200 mg/kg cohorts with the 60 mg/kg cohort,

respectively. The area under the concentration time curve 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 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 versus VOC).

This phase 1 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 TEAEs (60 TEAEs in part A and 10 TEAEs in part B). The majority of these TEAEs (58 of 60 in part A; 10 of 10 in part B) resolved; 2 TEAEs (paresthesia and wisdom tooth pain) were ongoing at the final study visit for each participant. Most TEAEs were of mild or moderate severity; there was 1 severe TEAE of back pain in a participant in part A that was assessed as not related to CSL889 and resolved. Neither the number nor the severity of TEAEs increased with dose or VOC status. The most frequent TEAEs reported (CTCAE [common terminology criteria for adverse events] 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 TEAEs in 3 participants were assessed by the investigators as related to CSL889; 2

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; and 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 4 hours after infusion. All the TEAEs that were assessed as related were non-serious and resolved. No participant in part B experienced any TEAE that was considered related to CSL889. Two serious adverse events (SAEs) of moderate severity (simultaneous COVID-19 and sickle cell anemia with crisis), unrelated to CSL889, were reported in 1 participant in part A; both resolved. One participant in part B experienced acute chest syndrome in the context of an illness with diarrhea > 8 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 1 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 is in line with nonclinical predictions. Baseline hemopexin concentrations were low as expected, although variability was observed. After CSL889 infusion, increased 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 TEAEs 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 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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Tables

Table 1. Hemopexin pharmacokinetic parameters after CSL889 infusion.

	Mean (SD)						
	Part A, N = 4 per cohort						Part B, N = 4
Parameter, units	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}, hours	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)
$T_{1/2}$, hours	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, hours	24	72	96	168	168	168	168

All parameters (baseline-adjusted) are expressed as mean (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; N, total population; NCA, noncompartmental analysis; SD, standard deviation; $T_{1/2}$, terminal half-life; T_{max}, time of maximum concentration

[a]N = 2 for $AUC_{0\text{-}inf}$ and $T_{1/2}$

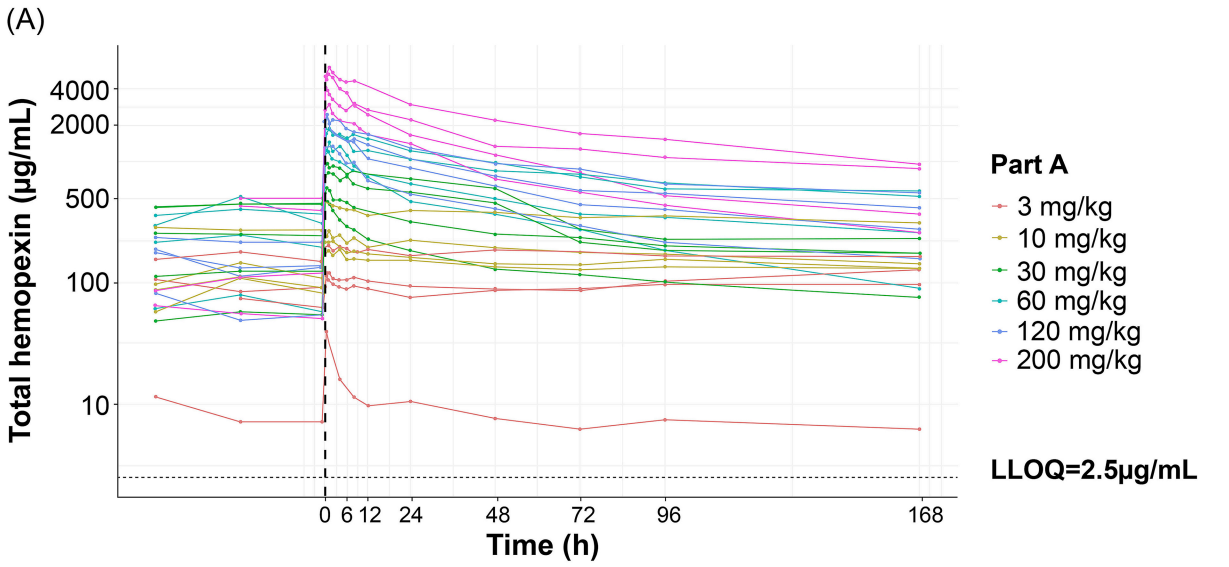
Table 2. Overview of treatment-emergent adverse events.

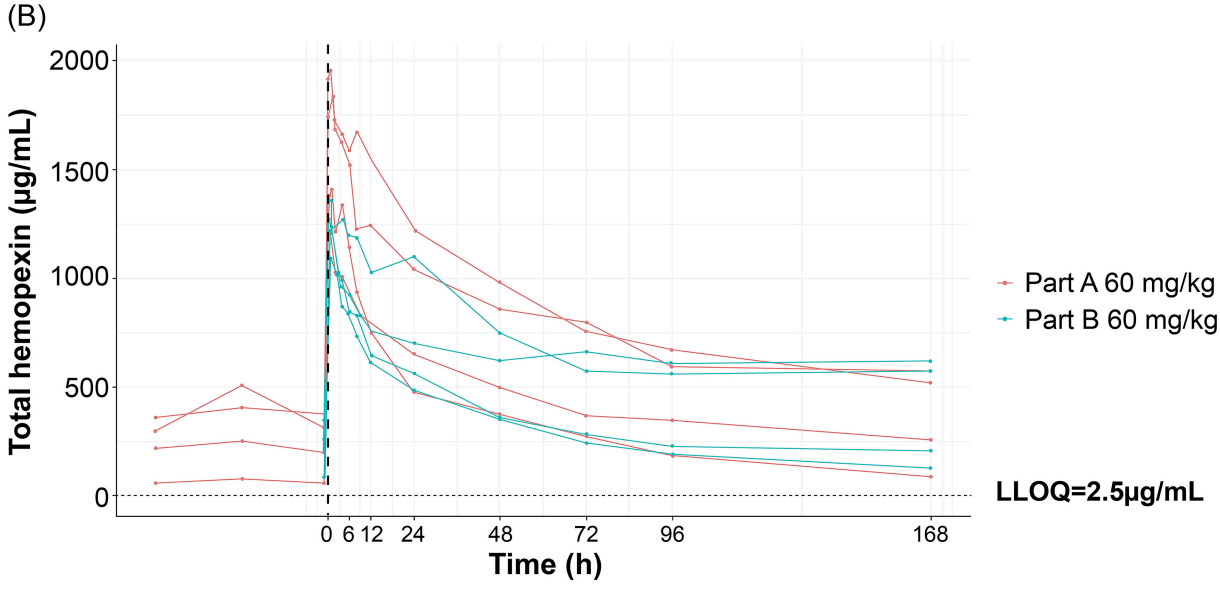
	Part A, N = 4 per cohort						Part A Overall (N = 24)	Part B, N = 4
	3 mg/kg	10 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	200 mg/kg		60 mg/kg
Any TEAE, n (%)	3 (75.0)	4 (100.0)	2 (50.0)	3 (75.0)	3 (75.0)	4 (100.0)	19 (79.2)	3 (75.0)
Any treatment-emergent SAE, n (%)	0	1 (25.0)	0	0	0	0	1 (4.2)	1 (25.0)
CSL889-related TEAEs, n (%)	0	0	2 (50.0)	0	1 (25.0)	0	3 (12.5)	0
CSL889-related TEAEs leading to study discontinuation, n (%)	0	0	0	0	0	0	0	0
TEAEs in > 1 participant overall								
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

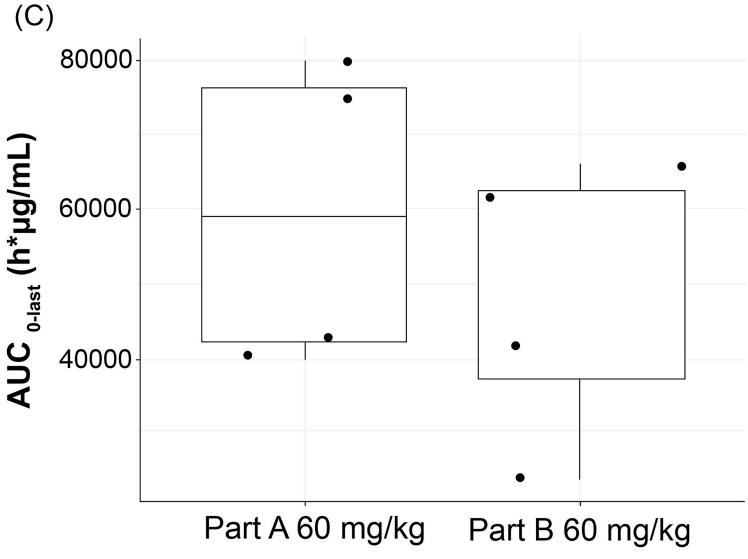
COVID-19: Coronavirus disease 2019; N: total population; n: subset; SAE: serious adverse event; TEAEs: treatment-emergent adverse events.

Figure Legend

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


(A)
Total hemopexin (μg/mL)
4000
2000
500
100
10
0 6 12 24 48 72 96 168
Time (h)
Part A
3 mg/kg
10 mg/kg
30 mg/kg
60 mg/kg
120 mg/kg
200 mg/kg
LLOQ=2.5μg/mL


(B)
Total hemopexin (μg/mL)
2000
1500
1000
500
0
0 6 12 24 48 72 96 168
Time (h)
Part A 60 mg/kg
Part B 60 mg/kg
LLOQ=2.5μg/mL


(C)
AUC 0-last (h*μg/mL)
80000
60000
40000
Part A 60 mg/kg
Part B 60 mg/kg

Supplemental Information

Table S1. Eligibility criteria

Inclusion criteria:

- Diagnosis of SCD as documented in the patient's medical record.
- Aged 18 to 60 years, inclusive.
- Part A: Stable SCD for at least 30 days before Day 1. Stable SCD is defined as the patient being at his or her medical baseline, with no evidence of worsening of disease over the last 30 days (including VOC, recent major surgery, hospitalization, serious infection, significant bleeding, cerebrovascular accident, seizures, or IV opioids).
- Part B: Uncomplicated VOC requiring parenteral opioid treatment and admission to hospital for management. Uncomplicated VOC is defined as sickle cell pain without the following associated clinical features:
  - Fever (>38.5°C).
  - Hypotension (<90/60 mmHg).
  - Hypoxia (<90% oxygen saturation on room air, or requiring oxygen therapy to maintain oxygen saturation above 90%).
  - New neurological signs and/or symptoms clinically suggestive of stroke or transient ischemic attack.
  - Signs and/or symptoms of acute chest syndrome, accompanied by any new pulmonary infiltrate on chest radiography (chest X-ray to be performed if clinically indicated and according to local clinical guidelines).
- Hemoglobin ≥6 g/dL (≥60 g/L).
- Patient is either not taking one of the study permitted SCD therapies (hydroxyurea, L-glutamine, crizanlizumab, and/or voxelotor) or has been taking one or more of those for at least 30 days before Day 1 and is on a stable, well tolerated regimen that is planned to continue without change throughout the study.

Exclusion criteria:

- History of primary hemorrhagic stroke.
- History or evidence of inherited bleeding diathesis or significant coagulopathy at risk for bleeding.
- Weight >110 kg (242 lbs).
- Surgery within 30 days before Day 1 or any preplanned surgeries during the study (minor surgeries may be permitted under local anesthesia before screening, with permission of the medical monitor).
- Female patients who are pregnant or breastfeeding.
- Female patients of childbearing potential or fertile male patients either not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 30 days after receipt of CSL889.
- Treatment with any other drug/biologic that is newly approved for SCD during the conduct of this study within 90 days before Day 1. Exceptions: crizanlizumab (Adakveo®) and voxelotor (Oxbryta®) are permitted (where prescribed).

- Treatment with another investigational product within 30 days or within 5 half-lives of the product (whichever is greater) before Day 1.
- Vaccination within 30 days before Day 1, or planned vaccination during the study.
- Body-mass index <16 kg/m^2 or weight <50 kg (110 lbs).
- History of anaphylactic-type reactions, transfusion related reaction, asthma, or autoimmune disease.

IV: intravenous; SCD: sickle cell disease; VOC: vaso-occlusive crisis.

Table S2. Participant baseline characteristics

	Part A (N = 24)	**Part B (N = 4)**	**Overall (N = 28)**
Age, median (min, max)	32.0 (23, 57)	23.5 (20, 38)	32.0 (20, 57)
Sex, n (%)			
Female	14 (58.3)	1 (25.0)	15 (53.6)
Male	10 (41.7)	3 (75.0)	13 (46.4)
Race, n (%)			
Asian	1 (4.2)	0	1 (3.6)
Black or African American	23 (95.8)	4 (100.0)	27 (96.4)
Ethnicity, n (%)			
Not Hispanic or Latino	22 (91.7)	4 (100.0)	26 (92.9)
Unknown	2 (8.3)	0	2 (7.1)
Weight (kg), mean (SD)	71.2 (11.24)	71.5 (13.33)	71.3 (11.29)
Height (cm), mean (SD)	169.8 (8.57)	172.0 (11.34)	170.1 (8.80)
BMI, kg/m^2, mean (SD)	24.77 (4.190)	24.20 (4.085)	24.69 (4.105)
SCD genotype, n (%)			
HbSS	21 (87.5)	3 (75.0)	24 (85.7)
$HbS\beta^0$-thal	2 (8.3)	0	2 (7.1)
HbSC	0	1 (25.0)	1 (3.6)
$HbS\beta^+$-thal	1 (4.2)	0	1 (3.6)
VOC in past 12 months, n (%)*			
0	14 (58.3)	0	14 (50.0)
1 to 2	4 (16.7)	0	4 (14.3)
3 to 5	3 (12.5)	2 (50.0)	5 (17.9)
6 to 8	1 (4.2)	0	1 (3.6)
≥ 9	2 (8.3)	2 (50.0)	4 (14.3)
Baseline hydroxyurea use, n (%)			
Yes	12 (50.0)	4 (100.0)	16 (57.1)
No	12 (50.0)	0	12 (42.9)

*Percentages may not sum to 100% due to rounding.

BMI: body mass index; HbSC: heterozygous for the β^S mutation and hemoglobin C; HbSS: homozygous for the hemoglobin S allele; $HbS\beta^+$-thal: heterozygous for the β^S mutation and β^+-thalassemia mutation; $HbS\beta^0$-thal: heterozygous for the β^S mutation and β^0-thalassemia mutation; N: total population; n: subset; max: maximum; min: minimum; SCD: sickle cell disease; SD: standard deviation; VOC: vaso-occlusive crisis.

Table S3. Baseline laboratory parameters

Parameter, units	Mean (SD)							
	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
Hematology								
Leukocytes, 10^9/L	7.158 (2.3794)	8.778 (4.2398)	5.548 (1.6702)	6.650 (3.1684)	6.137 (2.0663)*	7.260 (3.0192)	6.956 (2.7750)	9.415 (2.2789)
Neutrophils, 10^9/L	3.093 (2.1660)	5.158 (2.8976)	2.393 (1.2281)	2.870 (1.2412)	2.563 (1.0909)*	3.350 (1.6919)	3.267 (1.8949)	5.405 (3.2769)
Lymphocytes, 10^9/L	3.013 (0.7712)	2.663 (1.3316)	2.585 (0.9489)	3.203 (1.6062)	3.070 (1.8790)*	3.025 (1.2924)	2.920 (1.1832)	2.908 (1.2835)
Monocytes, 10^9/L	0.770 (0.2931)	0.633 (0.3174)	0.375 (0.1063)	0.405 (0.3142)	0.300 (0.0794)*	0.550 (0.3801)	0.514 (0.2956)	0.583 (0.2692)
Eosinophils, 10^9/L	0.178 (0.1886)	0.220 (0.0816)	0.150 (0.1283)	0.128 (0.1357)	0.180 (0.0917)*	0.290 (0.2573)	0.191 (0.1527)	0.388 (0.2720)
Basophils, 10^9/L	0.030 (0.0356)	0.108 (0.0340)	0.050 (0.0346)	0.040 (0.0258)	0.030 (0.0100)*	0.045 (0.0387)	0.051 (0.0393)	0.040 (0.0469)
Platelets, 10^9/L	310.3 (95.35)	417.0 (81.51)	459.8 (100.85)	307.8 (154.70)	281.7 (142.00)*	312.8 (167.32)	351.1 (130.21)	400.7 (50.08)*
Erythrocytes, 10^{12}/L	2.668 (0.5449)	2.833 (0.5878)	2.643 (0.3059)	2.678 (0.5208)	3.007 (1.0997)*	3.153 (0.8123)	2.822 (0.6130)	2.978 (0.4222)
Hematocrit, ratio	0.2418 (0.0482)	0.2845 (0.0093)	0.2938 (0.0390)	0.2960 (0.0468)	0.2447 (0.0602)*	0.2808 (0.0683)	0.2748 (0.0479)	0.2928 (0.0144)
Hemoglobin, g/L	72.5 (12.66)	91.3 (2.63)	91.3 (11.93)	93.5 (11.09)	77.7 (11.68)*	89.8 (22.29)	86.3 (14.30)	91.8 (5.32)
Erythrocyte mean corpuscular hemoglobin, fmol	1.7050 (0.1571)	2.0743 (0.4378)	2.1736 (0.4009)	2.2000 (0.3456)	1.6859 (0.3445)*	1.7826 (0.2200)	1.9478 (0.3659)	1.9378 (0.2226)

Parameter, units	Mean (SD)							
	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
Reticulocytes, %	16.00 (4.63)	9.20 (1.41)	8.58 (4.46)	9.10 (5.88)	8.83 (3.33)	9.35 (4.27)	10.23 (4.64)	9.18 (2.41)
Coagulation Parameters								
Prothrombin time, seconds	15.55 (0.866)	15.25 (0.900)	14.73 (1.072)	14.35 (0.619)	15.63 (0.427)	14.15 (1.502)	14.94 (1.030)	15.50 (0.497)
INR, ratio	1.268 (0.0914)	1.233 (0.0943)	1.153 (0.1072)	1.115 (0.0619)	1.243 (0.0427)	1.088 (0.1539)	1.183 (0.1114)	1.223 (0.0538)
Activated partial thromboplastin time, seconds	28.08 (4.524)	30.00 (2.264)	27.33 (5.082)	26.88 (3.762)	32.48 (2.943)	48.63 (41.825)	32.23 (17.252)	31.40 (3.556)
D-Dimer, µg/L	1365.0 (491.85)	813.5 (651.26)	464.5 (245.99)	410.8 (121.23)	597.5 (302.04)	2291.0 (3141.97)*	933.8 (1186.99)	489.0 (194.91)
Fibrinogen, g/L	2.483 (0.9575)	2.430 (0.8596)	2.503 (0.4076)	2.820 (0.5692)	2.460 (0.5512)	2.825 (0.5368)	2.587 (0.6218)	2.715 (0.4037)
Blood Chemistry								
Albumin, g/L	39.5 (2.08)	41.3 (1.50)	40.0 (3.46)	39.3 (4.57)	40.8 (3.10)	38.3 (2.22)	39.8 (2.84)	40.3 (1.26)
Total bilirubin, µmol/L	51.48 (23.037)	67.55 (59.596)	31.85 (30.794)	52.83 (37.797)	31.53 (22.713)	29.10 (16.125)	44.05 (33.982)	37.15 (15.020)
Direct bilirubin, µmol/L	13.73 (3.452)	8.90 (0.942)	7.98 (2.716)	9.85 (1.258)	8.80 (2.752)	11.20 (7.730)	10.08 (3.931)	12.07 (5.220)*
Alanine aminotransferase, IU/L	20.3 (6.95)	25.5 (3.79)	23.3 (11.76)	20.8 (10.14)	16.3 (6.13)	21.5 (3.11)	21.3 (7.36)	20.0 (12.11)

Parameter, units	Mean (SD)							
	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
Aspartate aminotransferase, IU/L	47.3 (12.74)	33.3 (4.57)	25.0 (6.27)	31.3 (10.90)	27.8 (9.60)	43.3 (12.87)	34.6 (12.06)	29.7 (11.37)*
Creatinine, µmol/L	70.48 (34.072)	58.68 (9.613)	45.93 (10.369)	48.85 (8.500)	51.45 (9.522)	54.58 (8.468)	54.99 (16.590)	54.35 (14.943)
Ferritin, pmol/L	477.2716 (339.1519)	390.0690 (91.3870)	544.2943 (336.1897)	401.0690 (222.5069)	289.9899 (236.6031)	176.5457 (92.2495)	379.8732 (246.4689)	926.7060 (660.2343)
Iron, µmol/L	19.00 (12.624)	19.38 (12.508)	14.80 (8.335)	26.13 (11.319)	15.93 (5.301)	12.18 (6.897)	17.90 (9.861)	21.23 (3.853)
Total iron binding capacity, µmol/L	52.90 (12.071)*	47.38 (10.553)	43.05 (5.145)	50.75 (7.726)	52.20 (12.965)	47.25 (4.553)	48.75 (8.822)	43.10 (7.488)
Haptoglobin, mg/dL	3.0 (0.00)	3.3 (0.50)	3.3 (0.50)	3.0 (0.00)	3.0 (0.00)	17.3 (27.84)	5.5 (11.41)	4.0 (2.00)
Transferrin, µmol/L	30.03 (6.715)	29.58 (7.519)	28.88 (2.470)	31.38 (5.302)	31.65 (8.878)	29.75 (3.894)	30.21 (5.567)	27.95 (3.152)
Transferrin saturation, %	36.0 (31.21)	36.5 (29.37)	26.8 (17.35)	40.8 (14.31)	27.0 (10.42)	21.8 (14.95)	31.5 (19.89)	38.8 (8.73)
Lactate dehydrogenase, IU/L	548.0 (212.73)	351.0 (112.91)	305.8 (79.72)	309.3 (46.12)	369.0 (155.05)	412.5 (232.98)	382.6 (161.15)	380.0 (112.31)*
Total protein, g/L	77.5 (3.70)	70.8 (2.63)	73.8 (9.74)	72.0 (4.08)	72.3 (2.87)	70.0 (6.06)	72.7 (5.42)	67.5 (6.56)

The values are expressed as mean (SD). *n = 3 per cohort.

N: total population; SD: standard deviation; INR: prothrombin international normalized ratio