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

Authors

Bart J. Biemond,[1] Rachel Kesse-Adu,[2] Ezanul Wahab,[3] Roberta C.G. Azbell,[4] Alexander A. Boucher,[5] Perla Eleftheriou,[6] Laura M. De Castro,[7] Shayla Bergmann,[8] William D. Hedrich,[9] Francine R. Wilson,[9] Kerstin Jung,[10] Michael Araco,[11] Rongrong Wang,[9] Paul M. Shore,[9] Gregory J. Kato[9] and Victor R. Gordeuk[12]

[1]Department of Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [2]Department of Hematology, Guy's and St Thomas' Hospital, London, UK; [3]MAC Clinical Research, Manchester, UK; [4]Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, The OSU Wexner Medical Center, Columbus, OH, USA; [5]Department of Medicine, University of Minnesota, Minneapolis, MN, USA; [6]University College London Hospital, London, UK; [7]Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [8]Medical University of South Carolina, Charleston, SC, USA; [9]CSL Behring, King of Prussia, PA, USA; [10]CSL Innovation GmbH, Marburg, Germany; [11]CSL Innovation, Victoria, Australia and [12]Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

Correspondence:
P.M. SHORE - Paul.Shore@cslbehring.com
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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