Efficacy, Safety, and Health-Related Quality of Life (HRQOL) in Patients With Sickle Cell Disease (SCD) Who Have Received Lovotibeglogene Autotemcel (Lovo-cel) Gene Therapy: Up to 60 Months of Follow-Up

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65th ASH Annual Meeting and Exposition; December 9-12, 2023 - Abstract # 1051

Lovo-cel Studies Using the Refined Manufacturing Process

HGB-206 Group C and HGB-210

Premobilization transfusion regimen

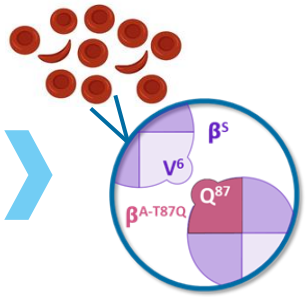
Mobilization (with plerixafor) & apheresis

Busulfan myeloablative conditioning

DP manufactured at a centralized location

DP infusion

Engraftment and reconstitution



Modified RBCs express gene-therapy-derived adult Hb (HbA^{T87Q})

2-year follow up

13-year long-term follow-up study (LTF-307; NCT04628585)[a]

Inclusion criteria

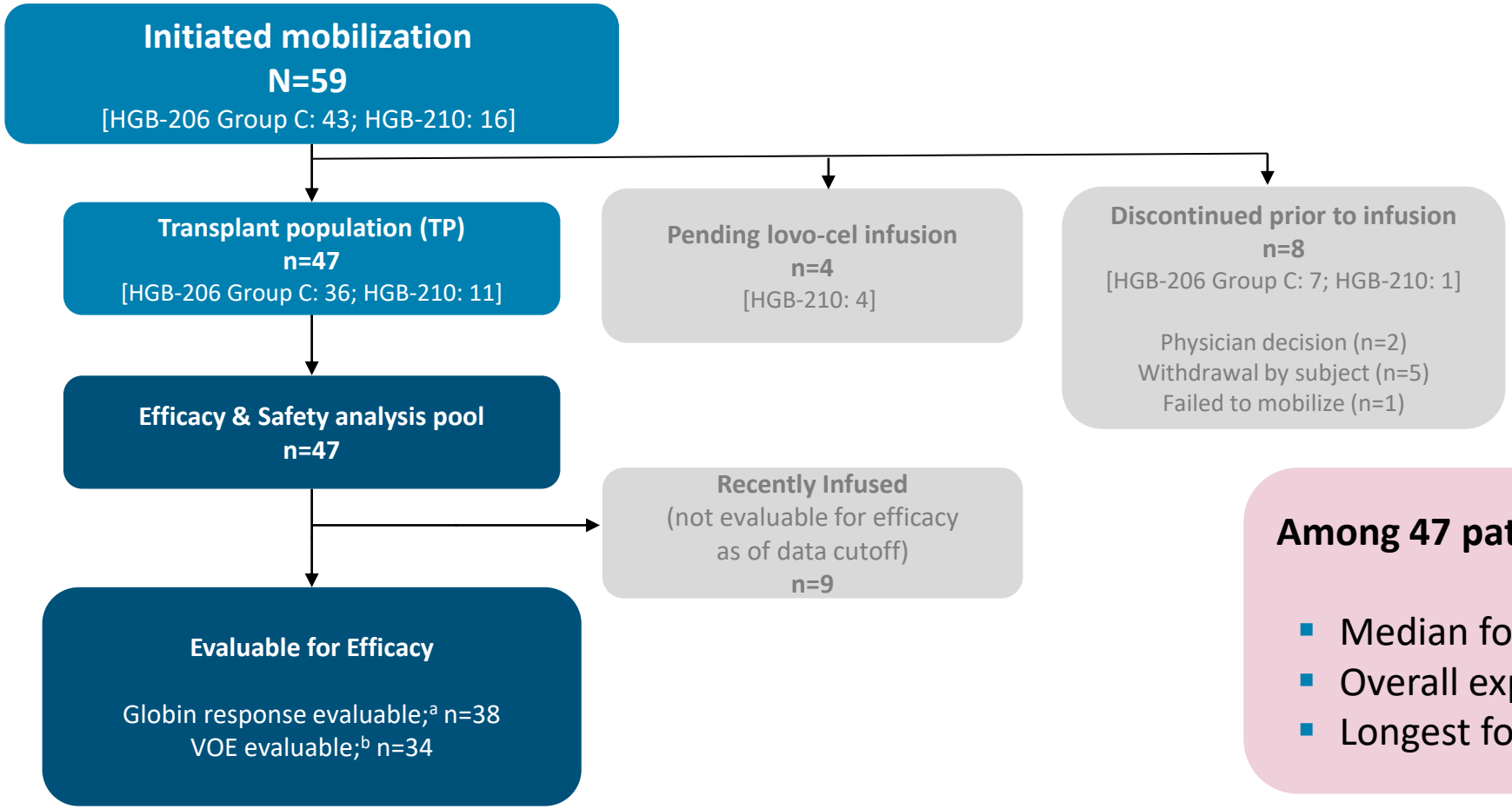
- Age at time of consent: ≥12-≤50 years (HGB-206) or ≥2-≤50 years (HGB-210)
- Diagnosis of SCD, with either β^S/β^S, β^S/β^0, or β^S/β^+ genotype
- ≥4 VOEs[b] in the 24 months prior to informed consent[c]
- Hydroxyurea failure or intolerance
- Karnofsky (≥16 years of age) or Lansky (<16 years of age) performance status ≥60
- Patients with chronic pain were eligible to enroll

- Lovo-cel treats at a genetic level
- Treatment results in production of normal adult Hb with anti-sickling properties through a single amino acid change (T87Q)[1]
- HbAT87Q has near identical oxygen affinity to wild-type HbA[2]
- Lovo-cel is a one-time therapy that integrates into the HSPC genome; effects are expected to be lifelong

[a]All data, except HRQOL, are reported up to 60 months in the total population (HGB-206 Group C and HGB-210); HRQOL data are reported up to 48 months for adult patients in HGB-206 Group C with available baseline and follow-up data. [b]For HGB-206, must have been severe VOEs. [c]Prior to July 30, 2018, patients with SCD and history of overt stroke were also eligible for enrollment into HGB-206.

DP, drug product; Hb, hemoglobin; HbA, adult hemoglobin; HbA^{T87Q}, anti-sickling Hb; HbS, sickle cell hemoglobin; HRQOL, health-related quality of life; HSPC, hematopoietic stem and progenitor cell; pRBC, packed red blood cells; RBC, red blood cell; SCD, sickle cell disease; VOE, vaso-occlusive event. 1. Magrin E, et al. *Nature Medicine.* 2022;28(1):81-88 2. Pawliuk R, et al. *Science.* 2002;294(5550):2368-2371.

Analysis Population



Among 47 patients who received lovo-cel:

- Median follow-up time: **35.5** months (3.0 years)
- Overall exposure: **126.2** patient years
- Longest follow-up: **61.0** months (5.1 years)[c]

[a]Globin Response evaluable patients are those who achieved Globin Response or have at least 18 months follow-up. [b]Patients who had ≥1 adjudicated VOE between 6 to 18 months post drug product infusion or have at least 18 months follow-up. Includes patients with ≥4 VOEs at baseline. Excludes 4 patients from HGB-206 who were enrolled based on history of overt stroke. [c]These data refer to the longest follow-up in HGB-206 Group C and HGB-210 Transplant Population

VOE-CR, complete resolution of VOEs; VOE, vaso-occlusive event; sVOE-CR, complete resolution of severe VOEs.

Demographics & Baseline Characteristics – Transplant Population (N=47)

Demographics & Patient Characteristics	Total N=47
Age at enrollment, median (min, max), years	23 (12, 38)
Adult, ≥18 years, n (%)	37 (78.7)
Adolescent, ≥12 to <18 y, n (%)	10 (21.3)
Sex, n (%)	
Male	28 (59.6)
Female	19 (40.4)
Follow-up post infusion, median (min, max), months	35.5 (0.3, 61.0)
Genotype for β-globin, n (%)	
β^S/β^S	46 (97.9)
β^S/β^0	1 (2.1)
Genotype for α-globin, n (%)	
αα/αα	32 (68.1)
αα/-α3.7	13 (27.7)
-α3.7/-α3.7	2 (4.3)
History of stroke, n (%)	6 (12.8)
Prior hydroxyurea use, n (%)	40 (85.1)
Baseline Clinical Characteristics	
Annualized number of adjudicated VOEs,[a,b] median (min, max)	3.5 (0.0, 16.5)
Annualized number of adjudicated sVOEs,[a,b] median (min, max)	3.0 (0.0, 13.0)
Annualized number of packed RBC transfusions,[a] median (min, max)	3.0 (0.0, 17.0)
Total Hb, median (min, max),[c] g/dL	8.70 (6.1, 12.5)

[a]In the 24 months prior to consent. [b]As confirmed by the Independent Event Adjudication Committee after patient enrollment. [c]Baseline total Hb is defined as average of 2 most recent qualifying Hb assessments made prior to or during screening that met the following criteria: assessments were separated by at least 1 month; assessments were drawn no earlier than 24 months prior to informed consent and could include the Hb result from screening; and the subject did not receive a packed RBC transfusion within 3 months prior to each Hb assessment.

Hb, hemoglobin; RBC, red blood cell; sVOE, severe vaso-occlusive event; VOE, vaso-occlusive event.

Population: Transplant population

Data as of Feb 13, 2023

Mobilization, Drug Product, and Engraftment Characteristics

Characteristic	Total	Median (min, max)
Mobilization and Engraftment		
No. of mobilization cycles	n=47	2.0 (1, 4)
Estimated average daily busulfan AUC, µmol*min/day	n=46	4834.2 (167,[a] 7322)
Total CD34+ cell dose, $\times 10^6$ cells/kg	n=45	6.5 (3.0, 14.0)
Time to neutrophil engraftment,[b] days	n=44[c]	20 (12, 35)
Time to platelet engraftment,[d] days	n=38[c]	35 (19, 136)
Duration of hospitalization,[e] days	n=46	36.0 (26, 65)
Drug Product Characteristics		
VCN, copies/diploid genome	n=47	4.0 (2.3, 6.6)
% LVV+ cells	n=46	81.6 (63, 93)

- Over 85% of patients required ≤2 mobilization cycles
- Peripheral blood VCN remained stable (**median >1 copies/diploid genome through follow-up**)

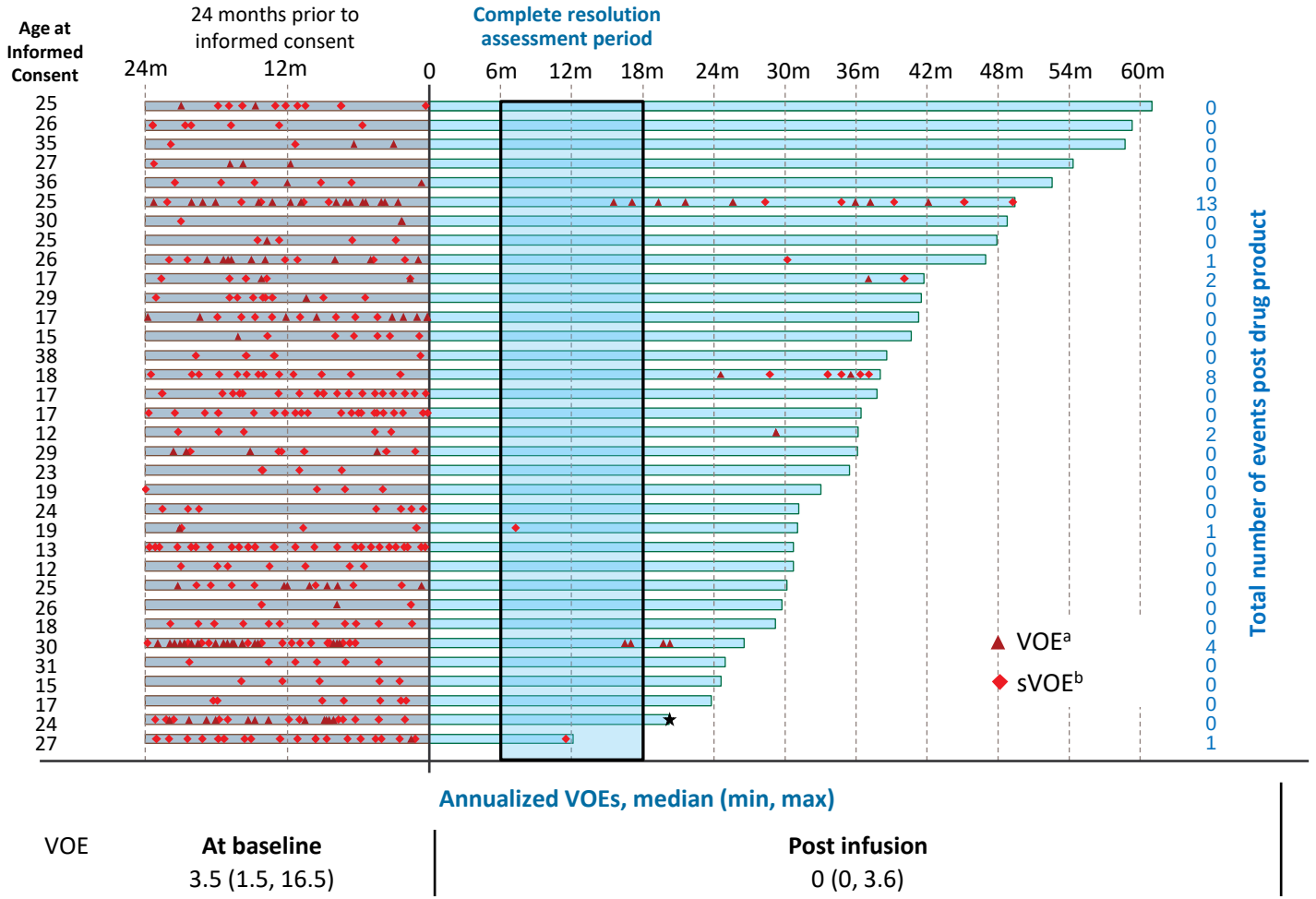
[a]The minimum value of the estimated average busulfan daily AUC was incorrectly recorded at the time of data cut; a correction will be implemented in future data cuts. [b]Neutrophil engraftment was defined as achieving 3 consecutive laboratory values of $\geq 0.5\times10^9$ cells/L (after initial post-infusion nadir) obtained on different days by day 43 post infusion; time to neutrophil engraftment was measured from infusion (day 1) to the first day of the 3 consecutive measurements. [c]Following data cutoff, all patients achieved neutrophil and platelet engraftment. [d]Platelet engraftment was defined as achieving 3 consecutive laboratory values of $\geq 50\times10^9$ cells/L (after initial postinfusion nadir) obtained on different days without receiving any platelet transfusions for 7 days immediately preceding and during the evaluation period; time to platelet engraftment was measured from infusion (day 1) to the first day of the 3 consecutive measurements. [e]Duration of hospitalization from conditioning to discharge.

AUC, area under the curve; LVV, lentiviral vector; VCN, vector copy number

Population: Transplant population

88.2% (30/34) of Patients Achieved Complete Resolution of All VOEs

Primary Endpoint (6 – 18 months)



- All 34 patients had stable peripheral blood VCN, total Hb, and HbA^{T87Q} after lovo-cel infusion through last follow up

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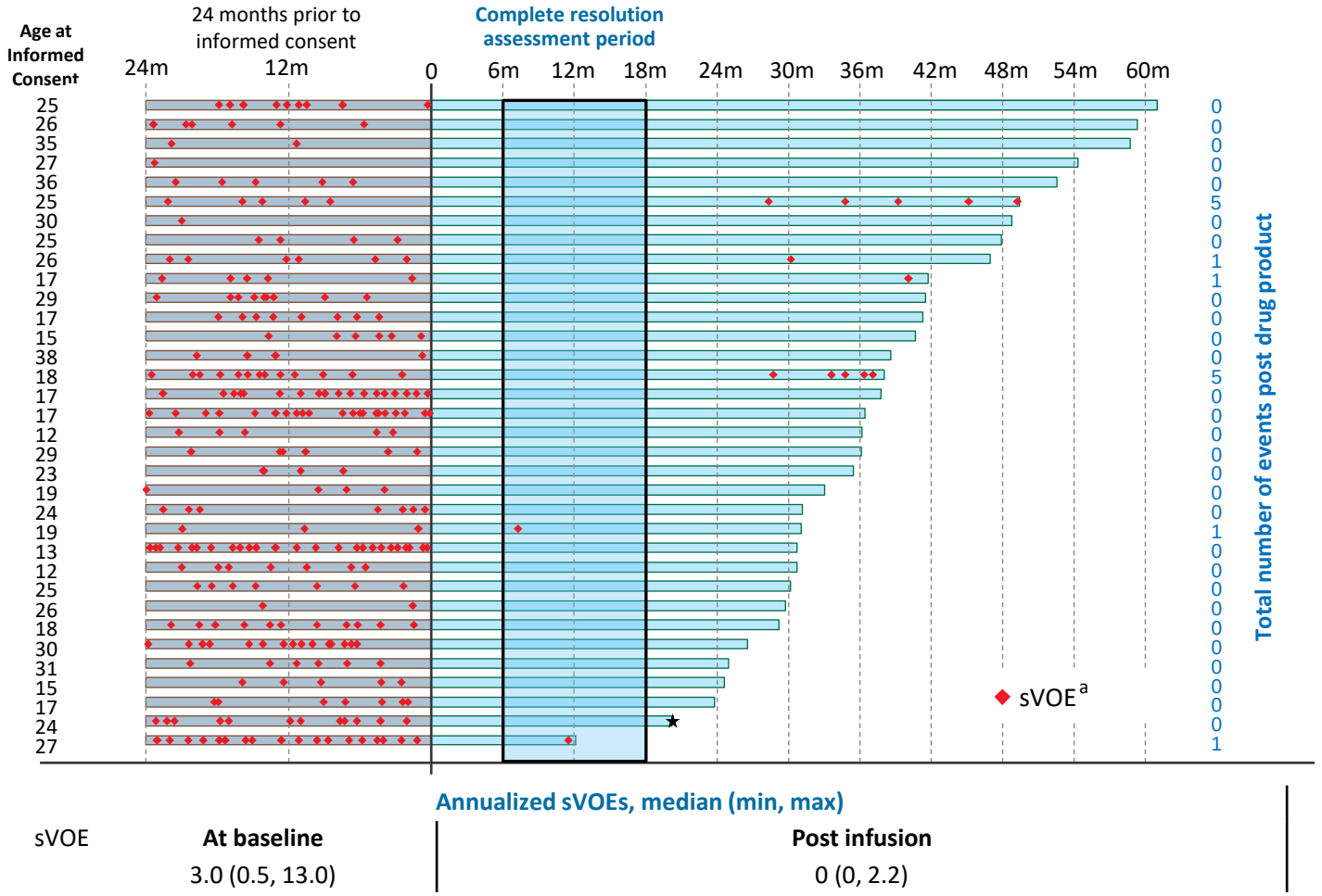
- **88.2%** (30/34; 95% CI: 72.5-96.7) of patients achieved complete resolution of all VOEs[c] during the 6 – 18 month assessment period
- **100%** (10/10) of adolescent patients (≥12 to <18 y) demonstrated complete resolution of VOEs during the 6 – 18 month assessment period
- Four additional patients experienced VOEs after the 6 – 18 month assessment period
- All patients who experienced VOEs post treatment experienced a reduction of at least 50% compared with baseline

★ Death, due to significant baseline SCD-related cardiopulmonary disease; not considered related to lovo-cel.

An Independent Event Adjudication Committee confirmed VOEs met protocol criteria. [a]Any of the following: acute episodes of pain with no medically determined cause other than a vaso-occlusion lasting 2 hours and requiring care at a medical facility; acute chest syndrome requiring oxygen treatment and/or blood transfusion; acute hepatic sequestration; acute splenic sequestration; or acute priapism lasting 2 hours and requiring care at a medical facility. [b]Defined as a VOE requiring ≥24-hour hospital or emergency room (ER) observation unit visit or at least 2 visits to a day unit or ER over a 72-hour period, with both visits requiring intravenous treatment; all VOEs of priapism were also considered sVOEs. [c]Maintained VOE-free status for median (min, max) of 35.8 (20.6, 61.0) months.

94.1% (32/34) of Patients Achieved Complete Resolution of Severe VOEs (sVOE)

Key Secondary Endpoint (6 – 18 months)



★ Death, due to significant baseline SCD-related cardiopulmonary disease; not considered related to lovo-cel.

6-18 Month Assessment Period

- **94.1%** (32/34; 95% CI, 80.3-99.3) of patients experienced **complete resolution of sVOEs**[b]

6 Months to Last Follow Up

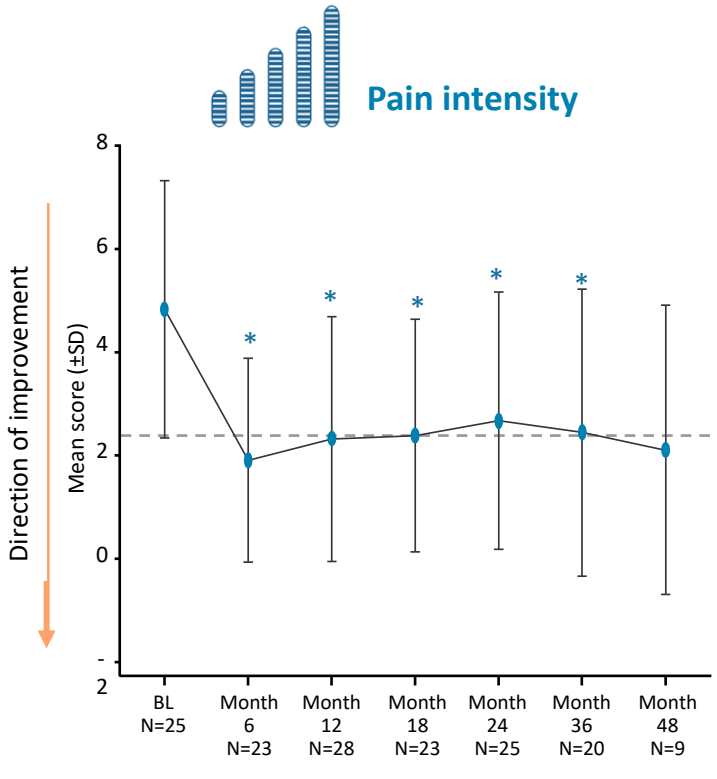
- **85.3%** (29/34) of patients had no VOE[c]-related hospital admissions from 6 months post infusion to last follow-up (median follow up: 36.3 months).

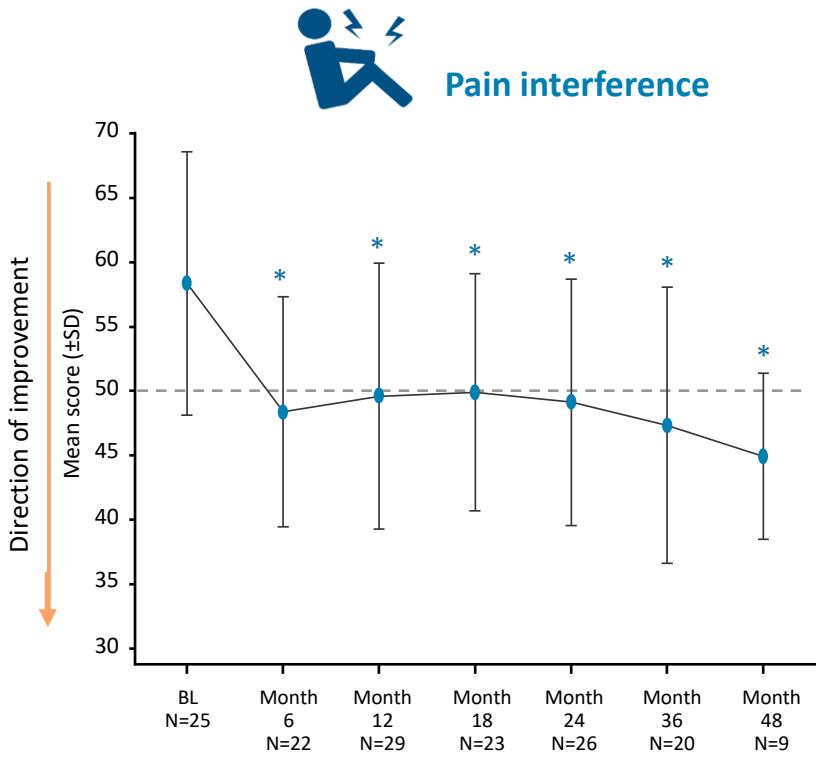
- Among the 8 patients with VOEs post lovo-cel infusion, annualized median (min, max):
  - **Hospital admissions:** reduced from **2.5** (1, 13) to **0.41** (0, 2)
  - **Hospital days:** reduced from **15.75** (3.5, 136.0) to **2.20** (0.0, 25.4)

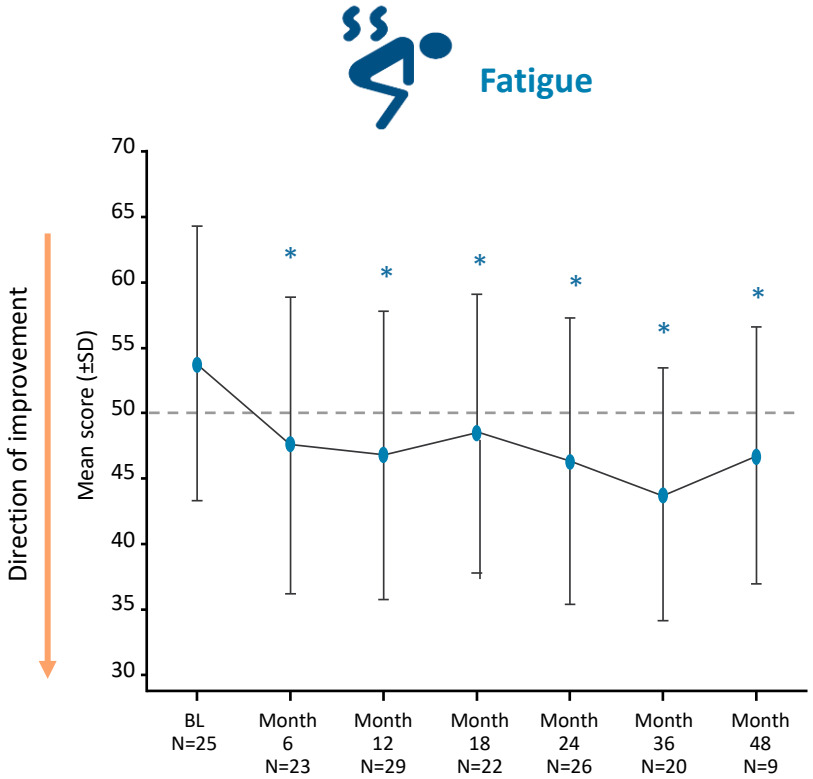
An Independent Event Adjudication Committee confirmed VOEs met protocol criteria. [a]Defined as a VOE requiring ≥24-hour hospital or emergency room (ER) observation unit visit or at least 2 visits to a day unit or ER over a 72-hour period, with both visits requiring intravenous treatment; all VOEs of priapism were also considered sVOEs. [b]Maintained for a median (min, max) of 35.8 (20.2, 61.0) months. [c]Any of the following: acute episodes of pain with no medically determined cause other than a vaso-occlusion lasting 2 hours and requiring care at a medical facility; acute chest syndrome requiring oxygen treatment and/or blood transfusion; acute hepatic sequestration; acute splenic sequestration; or acute priapism lasting 2 hours and requiring care at a medical facility.

Patient-Reported Outcomes

Improvements in Pain Intensity, Pain Interference, and Fatigue (PROMIS-57)







At 36 months (N=20), clinically meaningful improvements in pain intensity, pain interference, and fatigue were noted in 57%, 64%, and 64% of patients, respectively

Includes a subset of adult HGB-206 Group C patients with available baseline and follow-up HRQOL data (PROMIS-57); dashed line indicates population normative value for the specified assessment; pain intensity was raw score; pain interference was T score; fatigue was T score; month 36 selected for reporting due to smaller sample size at month 48.

**P*-value<0.05; exploratory analysis of change from baseline using Wilcoxon rank sum test.

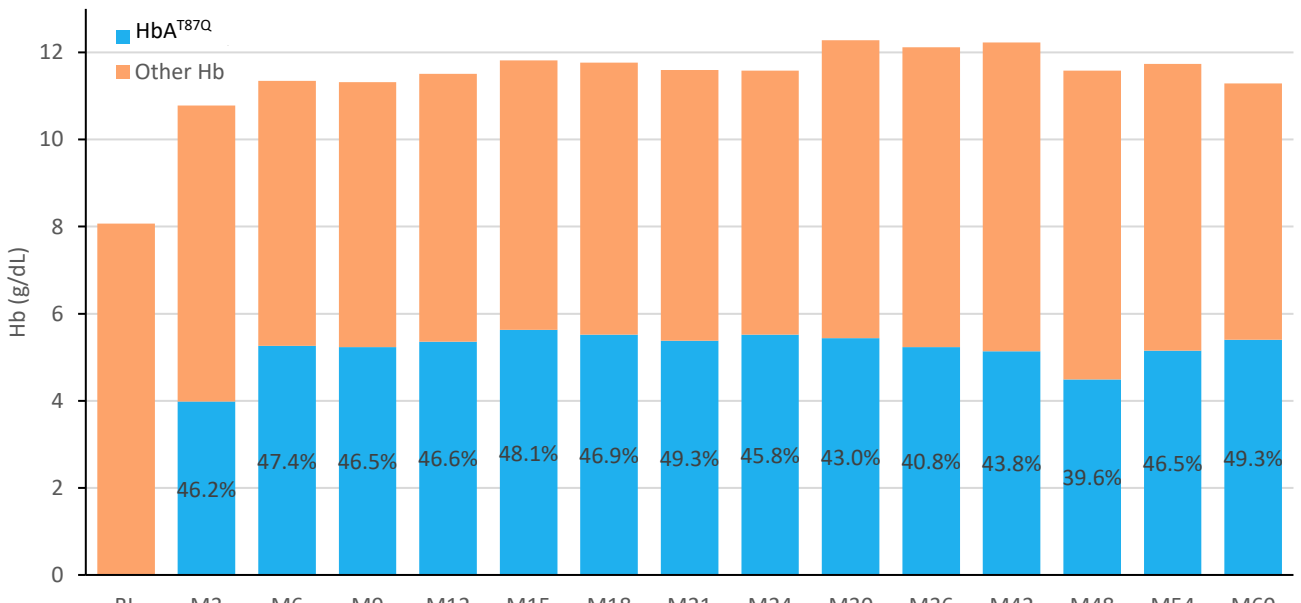
BL, baseline; HRQOL, health-related quality of life; PROMIS-57, Patient-Reported Outcomes Measurement Information System questionnaire.

Population: Transplant population

Biologic Response

HbA^{T87Q} Levels and Globin Response Were Maintained Over Time

HbA^{T87Q} & Total Hb levels



Median percent HbA^{T87Q} of non-transfused total Hb was ≈40% or more[a]

- All patients maintained stable HbA^{T87Q} levels from 6 months to last follow-up and as far out as month 60

- **86.8%** (33/38) of patients[b] achieved globin response

  (Globin response defined as meeting the following criteria for a continuous period of ≥6 months: weighted average HbA^{T87Q} ≥30% of non-transfused total Hb; AND weighted average increase in non-transfused total Hb of ≥3 g/dL vs baseline total Hb OR weighted average non-transfused total Hb of ≥10 g/dL)

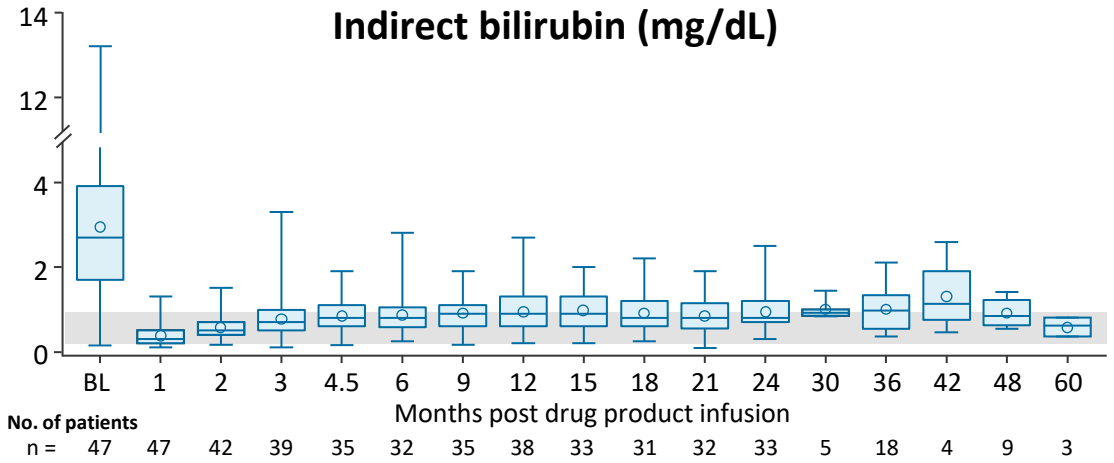
- **100%** (33/33) of patients demonstrated a durable globin response through last follow up[c]

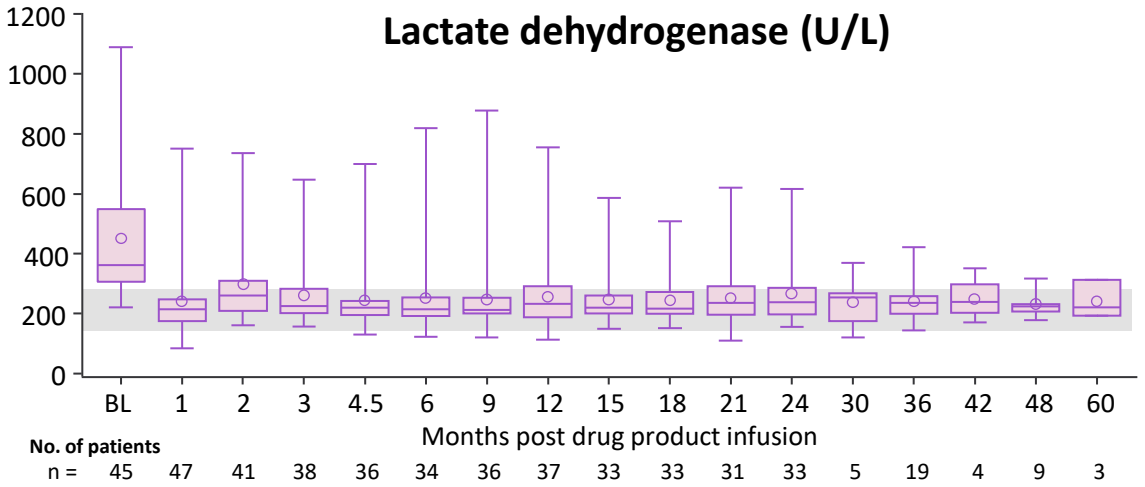
- No patients with a history of stroke experienced a stroke post treatment[d]

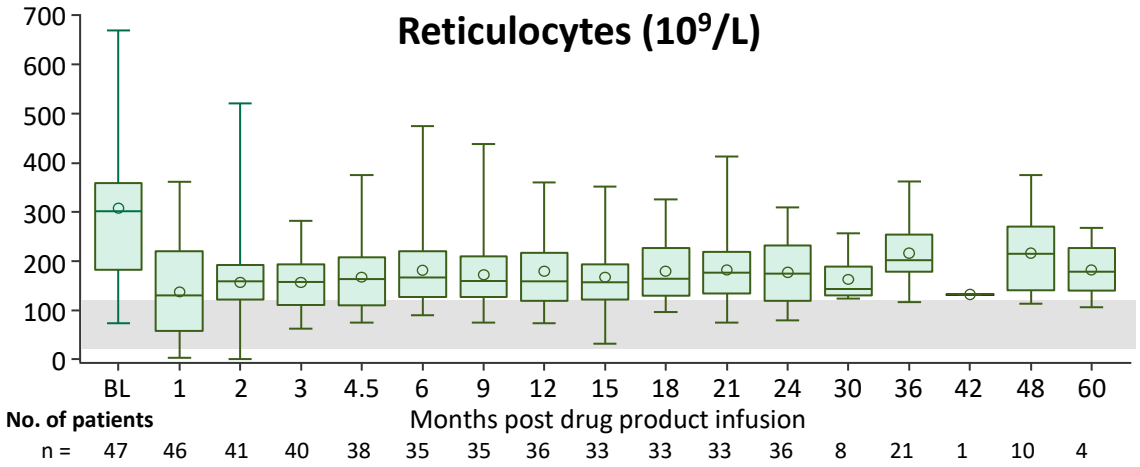
Percentages represent the median HbA^{T87Q} fraction as a percentage of non-transfused total Hb. Values below each bar represent the median total Hb or HbS % of non-transfused total Hb at each visit and are not equivalent to the sum of the individual Hb fraction medians. The baseline was an average of 2 qualified, total Hb values (measured in g/dL) during the 24 months before study enrollment. [a]Median (min, max) % HbAT87Q at last visit (n=42) was 44.7 (27.6, 63.2). [b]Assessed in patients who achieved globin response or had ≥18 months follow-up. [c]Three patients achieved globin response but later had transfusions due to an unrelated accident or illness (n=2), or death not related to study drug (n=1). [d]Patients who were receiving chronic transfusions due to a history of overt stroke and maintained globin response, did not require transfusions post engraftment, and have experienced no strokes to the time of the data cut.

BL, baseline; DP, drug product infusion; Hb, hemoglobin; HbA, adult Hb; HbA^{T87Q}, anti-sickling Hb; HbS, sickle cell hemoglobin; M, month.

Biologic Response
Hemolysis Markers Approached Normal Levels







- Reticulocytes, indirect bilirubin, and lactate dehydrogenase approached normal levels

In each graph, the bottom and top edges of the box indicate the first and third quartiles. The open circle and the horizontal line inside the box indicate the mean and median, respectively. The whiskers extend to the maximum and minimum values. Grey boxes indicate bounds of normal for reticulocytes. Normal range for indirect bilirubin and lactate dehydrogenase varies by sex and age.

BL, baseline.

Summary of Safety in the Transplant Population

	Total N=47
TEAEs	n (%)
Any grade	47 (100)
Grade ≥3	44 (93.6)
Lovo-cel–related AEs[a]	**4 (8.5)**
Anemia[b,c]	2 (4.3)
Abdominal discomfort	1 (2.1)
Blood pressure diastolic decreased	1 (2.1)
Myelodysplastic syndrome[b,c]	1 (2.1)
Nasal congestion	1 (2.1)
Patients with any serious AE	**26 (55.3)**
Patients with lovo-cel–related serious AEs[a]	2 (4.3)

[a]Sponsor assessed
[b]Serious AE
[c]Two patients had β^s/β^s and α-thalassemia trait ($-\alpha^{3.7}/-\alpha^{3.7}$). One was diagnosed with myelodysplastic syndrome (MDS) by the principal investigator based on findings of cytopenia, dysplasia, and karyotype.

- A majority of TEAEs occurred within 1 year post lovo-cel infusion and were known consequences of conditioning with busulfan
- There were no cases of veno-occlusive liver disease, graft failure, or graft-versus-host disease
- There were no vector-related complications; no insertional oncogenesis, or vector-mediated replication-competent lentivirus
- There was one death, due to significant baseline SCD-related cardiopulmonary disease; it was not considered related to study drug

AE, adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

Update: Pediatric Patient With Two Alpha-Globin Gene Deletions

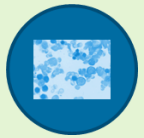
- 16-year-old male with β^s/β^s and α-thalassemia trait ($-\alpha^{3.7}/-\alpha^{3.7}$); noted to have low peripheral blood counts and marrow erythroid dysplasia at month 12 assessment in July 2021.[1] Followed closely with serial blood counts and bone marrow morphologic and genetic testing
- Patient was diagnosed with MDS in January 2023 (30 months after lovo-cel) by a local tumor board based on anemia, erythroid-restricted dysplasia, and clonality identified by karyotype
- As of July 2023, patient's treating physician and family have elected to continue monitoring and not proactively treat for MDS

Patient is clinically well; no VOEs post transplant

Total Hb is stable >10g/dL (10.1-11.3g/dL) and there is no leukopenia or thrombocytopenia (January to October 2023)

At 36 months post lovo-cel, **only a single variant[a] of unknown significance was observed in bone marrow (frequency, ≈1.4%)**

No driver mutations or aneuploidy associated with MDS by RHP,[2] WES, or karyotype; FISH continues to show low level aneuploidy in bone marrow



Erythroid-restricted dysplasia consistent with **stress dyserythropoiesis;** stable at 20%-25% from M12-M36

[a]46,XY,del(1)(q25),ins(5;1)(q22;q32q42)[1]/46,XY[19])

FISH, fluorescence in situ hybridization; M, month; MDS, myelodysplastic syndrome; RHP, rapid heme panel; VOE, vaso-occlusive event; WES, whole exome sequencing.

1. Walters M, et al. Presented at: ASH. Dec 10-13 2022. 2. Kluk MJ, et al. *J Mol Diagn.* 2016;18(4):507-515. 3. Misra S, et al. *J Medical Soc*. 2023;37:1-8.

Conclusions

- One-time treatment with lovo-cel resulted in near-complete resolution of VOEs and sVOEs for all patients, with complete resolution of VOEs and sVOEs in 88% and 94% of patients, respectively
- 100% of adolescent patients demonstrated complete resolution of VOEs and sVOEs
- A majority of patients remain VOE-free through last follow-up
- Biologic efficacy was sustained for up to 60 months, with patients demonstrating stable therapeutic levels of HbA^{T87Q}, increased levels of total Hb, and normalization of hemolysis markers
- The safety profile of lovo-cel treatment was consistent with underlying SCD and myeloablative conditioning
- Improvements in pain intensity, pain interference, and fatigue occurred early and were sustained up to 36 months

Long-term follow-up data confirm previous findings about the efficacy, safety, and patient experience with lovo-cel, including in adolescent patients

Hb, hemoglobin; HbA^{T87Q}, anti-sickling Hb; SCD, sickle cell disease; sVOE, severe vaso-occlusive event; VOE, vaso-occlusive event.

Thank you to the study site members as well as the study participants and their families

Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University

- Peter Chase
- Robert Liem
- Savannah Winkler
- Christine Inguglia
- Kevin Guerrero
- Leticia Alvarado
- Alexis Thompson

Medical University of South Carolina

- Brandi Day
- Michelle Hudspeth
- Jennifer Jaroscak
- Linda Wozniak

Children's Hospital of Philadelphia

- Janet Kwiatkowski
- Timothy Olson
- Pranaya Venkatapuram
- Jaladhikumar Patel

UCSF Benioff Children's Hospital

- Mark Walters
- Cyrus Bascon
- Marci Moriarty
- Frans Kuypers

Children's Healthcare of Atlanta

- Suhag Parikh
- Lilian Okparaocha
- Judson Russell
- Megan Hanby
- Judith Talib
- Amber Kaminki

Hackensack University Medical Center

- Stacey Rifkin-Zenenberg
- Andrea Ricourt
- Elana Smilow
- Paola Noziglia

Cohen Children's Medical Center

- Banu Aygun
- Shifath Ferdausi
- Antonella Farrell
- Evangelia Atsidaftos

Columbia University Medical Center

- Markus Mapara
- Monica Bhatia
- Beatriz Raposo Corradini
- Matt Chiaramonte
- Elizabeth Shelton

National Institutes of Health, Molecular and Clinical Hematology Branch

- John Tisdale
- Matt Hsieh
- Fahn Bryant
- Naoya Uchida
- Stephanie Helwing
- Rick Gustafson
- Wynona Coles

University of North Carolina

- Kimberly Kasow
- Catherine Cheng

University of Alabama

- Julie Kanter
- Emily Warner
- Michele Blue
- Emily Burke
- Marteesa Williams

University of Minnesota

- Ashish Gupta
- Lauren Matzke
- Caitlyn Thompson
- Danielle Jin

ProtaGene GmbH

- Ivan Labik
- Michelle Maennl

Independent reads of bone marrow

- Robert Hasserjian
- Shunyou Gong

bluebird bio, Inc.

- Brandi Blount
- Pooja Satija
- Susanne Mardirosian
- Emily Pereira
- Sally Yacout
- Manisha Pradhananga
- Teresa Curto
- Farinaz Sadeghzadeh
- Branwen Hall
- Brian Boogie
- Lin Pan
- Leah Eardley
- Lachana Wells
- Suus Plezier Jonkheer
- Ankit Lodaya
- Pooja Khemchandani
- Michelle Fisher

These studies were funded by bluebird bio, Inc. Medical writing and editorial support were provided by Nathan Yardley, PhD, Allyson Lehrman, DPM, and Kimberly Church of Apollo Medical Communications, part of Helios Global Group, and funded by bluebird bio, Inc.