ELSEVIER

Blood 142 (2023) 1051–1053

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

801.GENE THERAPIES

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

Julie Kanter, MD[1], *Alexis A. Thompson, MD MPH*[2,3], *Janet L. Kwiatkowski, MD MSCE*[2,4], *Suhag Parikh, MD*[5], *Markus Mapara, MD*[6], *Stacey Rifkin-Zenenberg, DO*[7], *Banu Aygun, MD*[8,9], *Kimberly A. Kasow, DO*[10], *Ashish O. Gupta, MBBS, MPH*[11], *Lixin Zhang, PhD*[12], *Emily Sheldon-Waniga, PhD*[12], *Meghan Gallagher, MSc*[12], *Katiana Gruppioni, MPH*[12], *Anjulika Chawla, MD FAAP*[12], *Heidi Elliot*[12], *Francis J. Pierciey, MSc*[12], *Mark C. Walters, MD*[13], *John F. Tisdale, MD*[14]

[1] Division of Hematology and Oncology, University of Alabama, Birmingham, AL
[2] Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[3] Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA
[4] Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA
[5] Cellular Therapies for Nonmalignant Diseases Clinic, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, GA
[6] Blood and Marrow Stem Cell Transplantation Program, Division of Hematology & Oncology, Columbia University Irving Medical Center, New York, NY
[7] Pediatric Hematology/Oncology Division, Hackensack University Medical Center, Hackensack, NJ
[8] Department of Pediatrics, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY
[9] Sickle Cell Program, Cohen Children's Medical Center of New York, New Hyde Park, NY
[10] University of North Carolina, Chapel Hill, NC
[11] Division of Pediatric Blood and Marrow Transplant and Cellular Therapies, University of Minnesota, Minneapolis, MN
[12] bluebird bio, Inc., Somerville, MA
[13] UCSF Benioff Children's Hospital, Oakland, CA
[14] Cellular and Molecular Therapeutics Branch, National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Introduction: Lovo-cel gene therapy uses autologous transplantation of hematopoietic stem and progenitor cells (HSPC) transduced with the BB305 lentiviral vector encoding a modified β-globin gene, which produces an anti-sickling hemoglobin (Hb), HbA ^{T87Q}. The phase 1/2 HGB-206 (NCT02140554) and phase 3 HGB-210 (NCT04293185) studies of lovo-cel are the largest clinical trials of gene therapy in SCD to date. We report efficacy and safety from these studies, including the first data from adult and pediatric patients (age 12 to <18 years) in HGB-210, and HRQOL data from HGB-206.
Methods: This analysis includes patients from HGB-206 Group C and HGB-210 who received lovo-cel using the current HSPC mobilization and manufacturing process. Patients with SCD and recurrent severe vaso-occlusive events (VOEs) or history of overt stroke underwent plerixafor mobilization and apheresis followed by myeloablative busulfan conditioning and lovo-cel infusion. After 24 months of follow-up post lovo-cel infusion, patients enrolled in the long-term study LTF-307 (NCT04628585). Lab evaluations, SCD-related outcomes (eg, resolution of VOEs), globin response (a composite endpoint evaluating HbA ^{T87Q} percentage and total Hb), and safety are reported up to 60 months. An independent Event Adjudication Committee confirmed VOEs met protocol criteria. HRQOL data from Patient-Reported Outcomes Measurement Information System (PROMIS)-57 domains of pain interference, fatigue, and pain intensity are reported up to 48 months.
Results: This analysis includes47 patients (HGB-206 Group C, n=36; HGB-210, n=11; male, 59.6%; median [range] age, 23 y [12-38]) who received a lovo-cel infusion as of Feb 13, 2023. Median (range) follow-up was 35.5 months (0.3-61.0). Median (range) time to neutrophil and platelet engraftment was 20 days (12-35) and 35 days (19-136). Peripheral blood vector copy number remained stable (median >1 c/dg through follow-up). Median HbA ^{T87Q} levels were ≥4.5 g/dL from 6 months post infusion to last study visit. Median (range) total Hb level increased from 8.7 g/dL (6.1-12.5) at relative baseline to 11.8 g/dL (8.4-15.0) at last visit; median percent HbA ^{T87Q} of nontransfused total Hb was ≈40% or more (**Figure**).

Of 33 evaluable patients (ie, ≥18 months follow-up and ≥4 VOEs in the 2 years before enrollment), 30 (90.9%) and 32 (97.0%) had complete resolution of VOEs and severe VOEs during the 6-18 months post infusion, vs a median (range) of 3.5 (1.5-16.5) and 3.0 (0.5-13.0) events/year in the 2 years before enrollment. Additional efficacy analyses in subgroups (eg, stroke history, α-globin genotype) will be presented.

Among patients who had globin response or who had ≥18 months follow-up (n=38), 33 (86.8%) achieved globin response. Hemolysis markers (eg, reticulocytes, total bilirubin, lactate dehydrogenase) approached normal levels.

Among all 47 patients, 44 (93.6%) had ≥1 AE of grade ≥3 after lovo-cel infusion; the most common of which were stomatitis (33 [70.2%] patients) and thrombocytopenia (28 [59.6%]). Serious AEs were reported for 26 (55.3%) patients, the most common of which was chronic pain/acute exacerbation of chronic pain (3 [6.4%]; 2 chronic neuropathic pain and 1 chronic pain associated with anxiety). One patient with -α3.7/-α3.7 genotype was diagnosed with myelodysplastic syndrome with stable complete blood counts 30 months post infusion; updated data to be presented. No veno-occlusive liver disease, graft failure, replication-competent lentivirus, or vector-mediated insertional oncogenesis was observed. Lovo-cel treatment regimen largely reflected known side effects of HSPC collection and busulfan conditioning regimen.

A total of 25 patients (all from HGB-206 Group C; age ≥18 y) had evaluable HRQOL data. Mean scores for PROMIS-57 domains of pain intensity, pain interference, and fatigue improved (ie, decreased) over time up to 48 months (**Table**).

Conclusion: One-time treatment with lovo-cel resulted in sustained HbA ^{T87Q} production and near-complete resolution of VOEs and severe VOEs up to 18 months post treatment; the safety profile was consistent with underlying SCD and myeloablative conditioning. Patients reported sustained improvements in pain intensity, pain interference, and fatigue. Ongoing long-term follow-up will continue to provide important information on efficacy, safety, and patient experience post lovo-cel treatment.

Disclosures Kanter: *Bausch:* Consultancy; *Watkins, Lourie, Roll & Chance:* Consultancy; *NHLBI:* Research Funding; *Austin Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Fulcurm:* Consultancy; *Takeda:* Research Funding; *Glycomimetics:* Membership on an entity's Board of Directors or advisory committees; *ECOR-1:* Consultancy; *BEAM:* Consultancy, Research Funding; *Chiesi:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Vertex:* Consultancy; *Guidepoint Global:* Honoraria; *Bluebird Bio:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novo Nordisk:* Research Funding; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *HRSA:* Research Funding; *CDC:* Research Funding; *National Alliance of Sickle Cell Centers:* Other: President. **Thompson:** *Beam:* Consultancy, Research Funding; *global blood therapeutics:* Divested equity in a private or publicly-traded company in the past 24 months; *CRISPR/Vertex:* Consultancy, Research Funding; *Novartis:* Research Funding; *Editas:* Consultancy, Research Funding; *bluebird bio, Inc.::* Consultancy, Research Funding. **Kwiatkowski:** *Forma Therapeutics:* Consultancy, Research Funding; *Bluebird Bio:* Research Funding; *Bristol Myers Squibb:* Consultancy; *Chiesi Farmaceutici:* Consultancy; *Agios Pharmaceuticals:* Consultancy, Research Funding; *BioMarin Pharmaceutical:* Consultancy; *Vertex Pharmaceuticals:* Consultancy; *Regeneron Pharmaceuticals:* Consultancy; *Editas Medicine:* Research Funding; *Pfizer:* Research Funding. **Mapara:** *Crispr/vertex:* Consultancy; *Incyte:* Consultancy; *Bluebird bio:* Consultancy. **Rifkin-Zenenberg:** *Vertex:* Membership on an entity's Board of Directors or advisory committees. **Aygun:** *bluebird bio:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *GBT:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Kasow:** *Aruvant:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Gupta:** *Vertex Pharmaceuticals:* Consultancy; *Bluerock Therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Zhang:** *bluebird bio, Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Sheldon-Waniga:** *bluebird bio, Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Gallagher:** *bluebird bio, Inc:* Current Employment, Current equity holder in publicly-traded company. **Gruppioni:** *bluebird bio, Inc:* Current Employment, Current equity holder in private company. **Chawla:** *bluebird bio, Inc:* Current Employment, Current equity holder in private company. **Elliot:** *bluebird bio, Inc:* Current Employment, Current equity holder in private company. **Pierciey:** *bluebird bio, Inc:* Current Employment, Current equity holder in private company. **Walters:** *AllCells, Inc:* Consultancy, Other: Medical Director; *BioChip Labs:* Consultancy, Other: Medical Director; *Ensoma, Inc:* Consultancy; *Vertex Pharmaceuticals:* Consultancy.

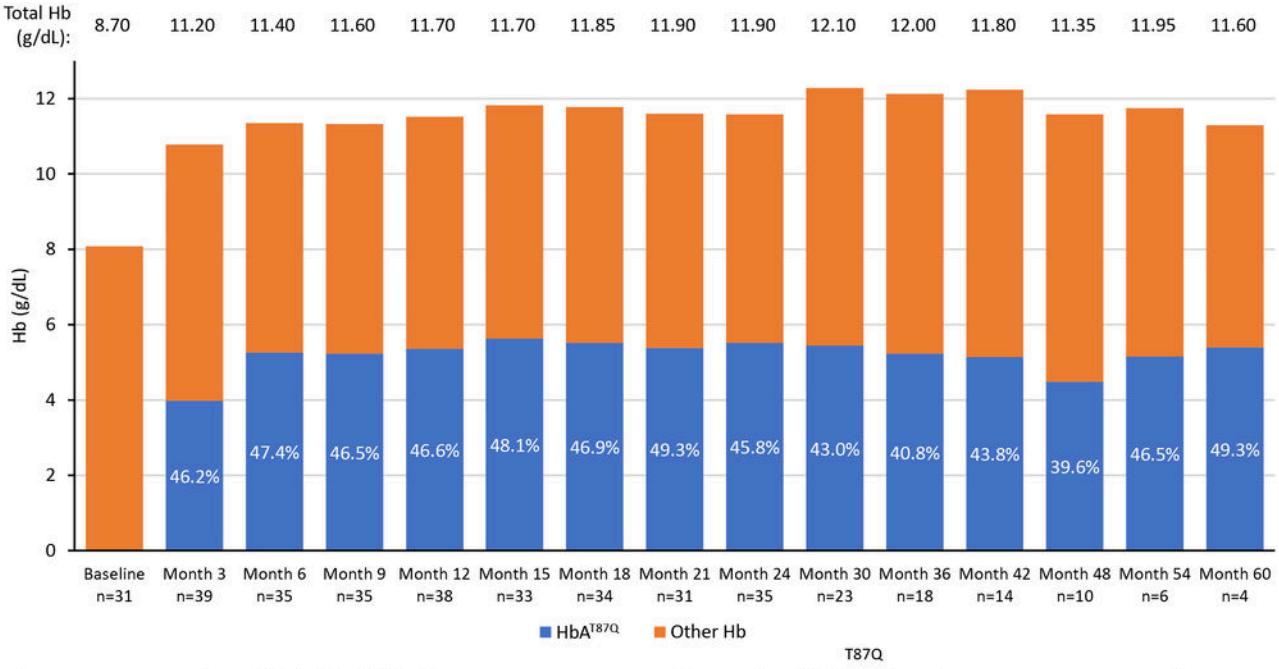
OffLabel Disclosure: This presentation will include discussion of treatments not yet approved by the FDA.

Table. PROMIS-57 patient-reported HRQOL for HGB-206 Group C

	Pain intensity[a]	Pain interference[b]	Fatigue[b]
Baseline score, mean (SD) (n=25)	4.8 (2.49)	58.4 (10.24)	53.8 (10.57)
Change from baseline, mean (SD)			
Month 6 (n=20)	-3.0 (2.32)	-10.2 (8.80)	-6.2 (9.74)
Month 12 (n=22)	-2.4 (2.48)[c]	-9.3 (11.84)	-6.9 (11.78)
Month 24 (n=19)	-2.3 (2.70)[d]	-9.5 (9.41)	-8.7 (9.45)
Month 36 (n=14)	-2.2 (2.29)	-9.9 (11.86)	-7.7 (11.51)
Month 48 (n=9)	-1.9 (2.89)	-11.0 (8.13)	-1.4 (8.80)

Data are reported as of Feb 13, 2023.
[a]Based on a 0-10 numeric rating scale. Data are presented as raw score/change in raw score; a decrease in score represents improvement. [b]Data are presented as T-score/change in T-score; a decrease in score represents improvement. [c]n=21. [d]n=18.
PROMIS-57, Patient-Reported Outcomes Measurement Information System; HRQOL, health-related quality of life.

Figure. Total Hb and HbA^{T87Q} fraction for HGB-206 Group C and HGB-210 combined



Data are reported as of Feb 13, 2023. Percentages represent the median HbA fraction as a percentage of nontransfused total Hb. Values above each bar represent the median 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.

Hb, hemoglobin; HbA, adult Hb; HbA^{T87Q}, anti-sickling Hb.

Figure 1

https://doi.org/10.1182/blood-2023-174229