Poster 055

Efficacy and Safety of Betibeglogene Autotemcel in Pediatric Patients With Transfusion-Dependent β-Thalassemia

Ashutosh Lal,[1]* Mark C. Walters,[1] Alexis A. Thompson,[2,3] Timothy S. Olson,[2,3] John B. Porter,[4] Jennifer Schneiderman,[5] Suradej Hongeng,[6] Andreas E. Kulozik,[7] Marina Cavazzana,[8-10] Martin G. Sauer,[11] Adrian J. Thrasher,[12] Isabelle Thuret,[13] John E. J. Rasko,[14-16] Evangelia Yannaki,[17] Shamshad Ali,[18] Ge Tao,[18] Himal L. Thakar,[18] Ami Deora,[18] Clark Paramore,[18] Richard A. Colvin,[18] Franco Locatelli,[19,20] Janet L. Kwiatkowski[2,3]

[1]University of California San Francisco Benioff Children's Hospital, Oakland, CA; [2]Children's Hospital of Philadelphia, Philadelphia, PA; [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [4]University College London Hospital, London, UK; [5]Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL; [6]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [7]University of Heidelberg and DKFZ, Heidelberg, Germany; [8]Inserm Assistance Publique Hôpitaux de Paris, Paris, France; [9]Imagine Institute, Paris, France; [10]Hospital Necker, University Paris Descartes, Paris, France; [11]Hannover Medical School, Hannover, Germany; [12]University College London Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [13]Hospital Timone, Marseille, France; [14]Centenary Institute, Camperdown, Australia; [15]The University of Sydney, Sydney, Australia; [16]Royal Prince Alfred Hospital, Camperdown, Australia; [17]G. Papanikolaou General Hospital, Thessaloniki, Greece; [18]bluebird bio, Inc., Somerville, MA; [19]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; [20]Catholic University of the Sacred Heart, Rome, Italy

*Presenting author.

OBJECTIVE

- To report efficacy, safety, and health-related quality of life (HRQOL) data from pediatric and adult patients treated with betibeglogene autotemcel (beti-cel) who were followed for up to 9 years after treatment

CONCLUSIONS

- Beti-cel efficacy was durable up to 9 years post infusion, with no loss of transfusion independence (TI) due to loss of expression
- The majority of patients treated with beti-cel achieved TI with a safety profile consistent with known side effects of hematopoietic stem cell collection and the busulfan conditioning regimen
- Cell collection, safety and efficacy outcomes, and drug product (DP) characteristics with beti-cel treatment were generally similar across study, genotype, and pediatric and adult subgroups in the phase 3 studies
- Improvements in HRQOL were demonstrated in both pediatric and adult patients up to 36 months
- Beti-cel is a potentially curative gene therapy for patients with transfusion-dependent β-thalassemia (TDT) across ages and genotypes through achievement of TI and normal or near-normal hemoglobin (Hb)
- These data will inform real-world beti-cel treatment decisions for patients with TDT across genotypes and different age groups

ACKNOWLEDGMENTS

Thank you to the study site members as well as the study participants and their families. These studies were funded by bluebird bio, Inc. Medical writing and editorial support were provided by Allyson Lehrman, DPM, and Kimberly Church of Apollo Medical Communications, part of Helios Global Group, and funded by bluebird bio, Inc.

INTRODUCTION

- Beti-cel is a gene therapy approved by the U.S. Food and Drug Administration indicated for pediatric and adult patients with TDT[1]
- Beti-cel gene therapy addresses the underlying cause of TDT by adding functional copies of a modified version of the β-globin gene to autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) via a third-generation, self-inactivating lentiviral vector (LVV), BB305[2]
- Following one-time beti-cel therapy, HbA^{T87Q}, normal Hb containing an amino acid substitution (T→Q) at position 87, is produced in red blood cells (RBCs).[2] HbA^{T87Q} has similar oxygen binding affinity to HbA[3]
- Durable TI in patients with TDT, improvements in HRQOL, and a favorable risk/benefit profile have been previously reported with beti-cel treatment[4-6]

METHODS

- Patients with TDT underwent HSPC collection after mobilization with granulocyte colony-stimulating factor and plerixafor, followed by pharmacokinetic-adjusted myeloablative busulfan conditioning and beti-cel infusion[2,6,7]
- Patients who completed either a phase 1/2 (HGB-204 [NCT01745120]; HGB-205 [NCT02151526]) or phase 3 (HGB-207 [NCT02906202]; HGB-212 [NCT03207009]) beti-cel parent study and subsequently participated in the long-term, 13-year follow-up LTF-303 study (NCT02633943) were included in these analyses

Efficacy and safety

- Analyses were conducted by age subgroup according to patient age at enrollment (pediatric: <12 years; adolescent: ≥12 to <18 years; adult: ≥18 years) to examine:
  - Achievement and maintenance of TI (defined as a weighted average Hb ≥9 g/dL without packed RBC transfusions for ≥12 months)
  - Transduction efficiency and HbA^{T87Q} expression
  - Safety outcomes
- HRQOL was assessed at baseline and every 6 months using the outcome measures shown in **Table 1**
- Data are reported through month 36 for patients in the HGB-204, HGB-207, and HGB-212 studies who had baseline and posttreatment HRQOL scores

Table 1. HRQOL scales[8-11]

Instrument[a]	Population normative mean score	MCID	Ages for which instrument was used in current analyses, y
PedsQL	82.9	4.4	<18
EQ-5D-Y	Not established	Not established	
SF-36	50	2	≥18
FACT-G	80.1	Not established	
FACT-BMT	Not established	Not established	
EQ-5D-3L	Not established	Not established	

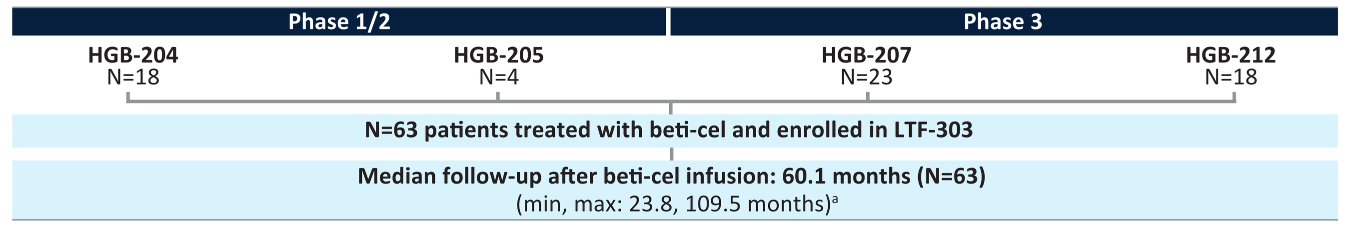
[a]Higher scores indicate better HRQOL.
EQ-5D-3L, EuroQol 5 Dimensions 3 Levels questionnaire; EQ-5D-Y, EuroQol 5 Dimensions Youth questionnaire; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplantation; FACT-G, FACT-General; HRQOL, health-related quality of life; MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SF-36, 36-Item Short Form Health Survey.

RESULTS

Baseline characteristics and follow-up

- As of January 30, 2023, 63 patients had received beti-cel in a phase 1/2 or phase 3 study and enrolled in LTF-303 (**Figure 1; Table 2**)

Figure 1. Pooled analysis population



[a]Median follow-up for phase 3 patients (N=41): 48.3 months (min, max: 23.8, 71.9 months).

Table 2. Baseline characteristics for patients treated in beti-cel studies

	Phase 1/2 (N=22)	Phase 3 (N=41)
Gender, n (%)		
Male	7 (31.8)	21 (51.2)
Female	15 (68.2)	20 (48.8)
Genotype, n (%)		
Non-β^0/β^{0a}	14 (63.6)	29 (70.7)
β^0/β^0	8 (36.4)	12 (29.3)
Age at enrollment, median (min, max), y	20 (12, 35)	13 (4, 34)
Pediatric, <12 y, n (%)	0	16 (39.0)
Adolescent, ≥12 to <18 y, n (%)	5 (22.7)	11 (26.8)
Adult, ≥18 y, n (%)	17 (77.3)	14 (34.1)
Fertility preservation, n (%)[b]	13 (59.1)	30 (73.2)

[a]Includes non-β^0/β^0 patients phenotypically similar to β^0/β^0 (IVS-1-110 homozygous or IVS-1-110/β^0 genotype). [b]Fertility preservation was an optional procedure.

Transduction efficiency and pharmacodynamic endpoints

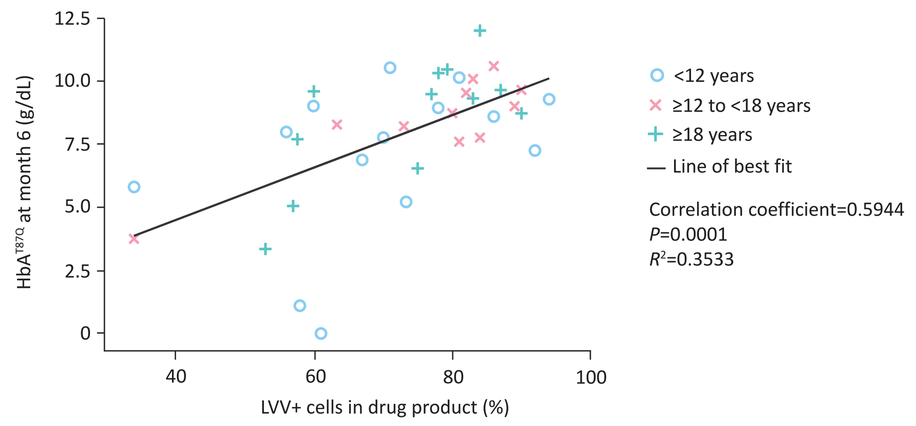
- Approximately 80% of phase 3 pediatric and adolescent patients and 64% of adult patients who received beti-cel required only 1 mobilization cycle to achieve DP dose (**Table 3**)
- The median percentage of DP cells transduced with the BB305 LVV, peripheral blood (PB) vector copy number (VCN), and HbA^{T87Q} were comparable across age subgroups
- Overall, HbA^{T87Q} expression at month 6 was significantly correlated with the proportion of infused LVV+ cells in the DP in the phase 3 studies (**Figure 2**)

Table 3. Transduction efficiency and pharmacodynamic endpoints by age (phase 3 patients)

	Pediatric, <12 y (n=16)	Adolescent, ≥12 to <18 y (n=11)	Adult, ≥18 y (n=14)
Number of mobilization cycles, n (%)			
1 cycle	14 (87.5)	9 (81.8)	9 (64.3)
2 cycles	2 (12.5)	2 (18.2)	5 (35.7)[a]
DP cells transduced, median (min, max), %	72.2 (34, 94)	82.0 (34, 90)	77.5 (53, 90)
Month 6 PB VCN, median (min, max), c/dg	0.8 (0.2, 3.3)[b]	1.9 (0.2, 4.5)	1.4 (0.2, 3.4)
Month 6 HbA^{T87Q}, median (min, max), g/dL	8.0 (5.2, 10.5)[b]	8.7 (3.8, 10.6)	9.4 (3.4, 12.0)[b]

[a]One patient needed 3 mobilization cycles, but cells from only 2 of these cycles were used for DP manufacturing. [b]n=12.
c/dg, copies/diploid genome; DP, drug product; PB, peripheral blood; VCN, vector copy number.

Figure 2. HbA^{T87Q} expression at month 6 vs the proportion of LVV+ cells in the DP (phase 3 studies)



DP, drug product; LVV, lentiviral vector.

Achievement and maintenance of transfusion independence

Phase 3 studies

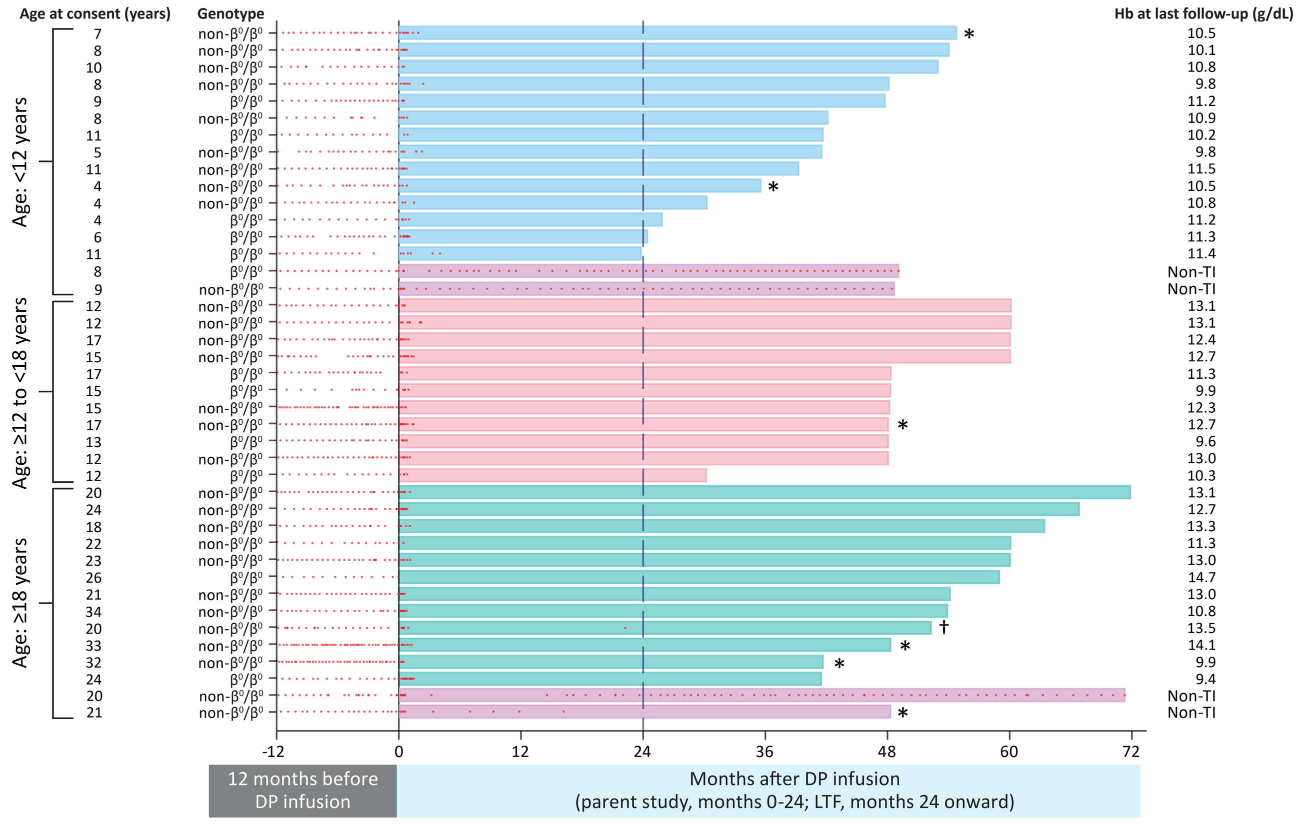
- In the phase 3 studies, in which the commercial DP manufacturing process was used, 90.2% (37/41) of patients achieved and maintained TI through last follow-up (up to 6 years); TI rate and median weighted average Hb were generally similar across study, genotype, and age subgroups (**Table 4; Figure 3**)

Table 4. Proportion of phase 3 patients who achieved TI with beti-cel and total Hb by study, genotype, and age

	N	TI evaluable, n	TI rate, n/N (%)	Weighted average Hb during TI, median (min, max), g/dL
By study				
Phase 3 patients	41	41	**37/41 (90.2)**	11.03 (9.6, 13.7)
HGB-207	23	23	**21/23 (91.3)**	12.06 (9.8, 13.0)
HGB-212	18	18	**16/18 (88.9)**	10.47 (9.6, 13.7)
By genotype				
Non-β^0/β^0	29	29	**26/29 (89.7)**	11.92 (9.8, 13.4)
β^0/β^0	12	12	**11/12 (91.7)**	10.54 (9.6, 13.7)
By age				
Pediatric, <12 y	16	16	**14/16 (87.5)**	10.41 (9.8, 11.4)
Adolescent, ≥12 to <18 y	11	11	**11/11 (100)**	11.80 (10.0, 13.4)
Adult, ≥18 y	14	14	**12/14 (85.7)**	12.65 (9.6, 13.7)

Hb, hemoglobin; TI, transfusion independence.

Figure 3. Transfusion status by age (phase 3 studies)



Numbers at the ends of lanes represent unsupported total Hb (g/dL) at last follow-up. Red dots depict transfusion episodes. Vertical dashed line denotes completion of parent study and rollover to LTF-303. There were 15 patients with HbE/β^0 genotype enrolled in all studies; 6 were enrolled in phase 3 studies, and all 15 achieved TI.
*Indicates non-β^0/β^0 patients (n=6) phenotypically similar to β^0/β^0 (IVS-1-110 homozygous or IVS-1-110/β^0 genotype). †After a planned orthopedic surgery, the patient had blood loss, which required 1 pRBC transfusion.
DP, drug product; Hb, hemoglobin; LTF, long-term follow-up; pRBC, packed red blood cell; TI, transfusion independent.

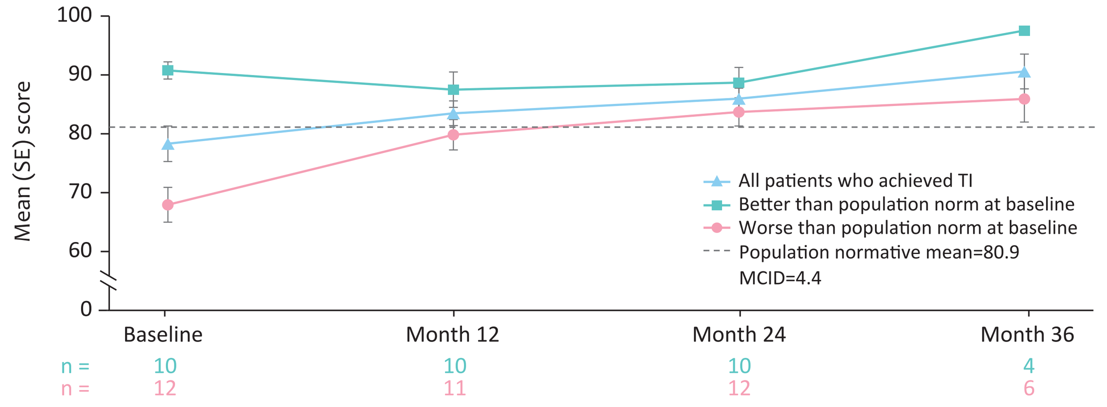
Phase 1/2 studies

- In phase 1/2 studies, prior to making improvements to the drug manufacturing process for phase 3 studies, 68.2% (15/22) of patients achieved TI, and median (min, max) weighted average Hb during TI was 10.50 g/dL (9.1, 13.2)
  - 14 of these patients sustained TI through last follow-up, which was up to 9 years
  - One patient, with human immunodeficiency virus complicated by gastrointestinal infection and bleeding, no longer meets protocol-defined TI as a result of Hb level <9 g/dL at year 6. PB VCN was stable with continued HbA^{T87Q} production. The patient is not receiving transfusions as of last follow-up (late-breaking data)

Health-related quality of life

- Mean pediatric HRQOL scores also showed clinically meaningful improvement at month 36 (**Figure 4**)
- In pediatric and adult patients who achieved TI, mean HRQOL scores increased numerically across all other measures except for the EQ-5D-3L composite index score, for which there was little change from baseline (**Table 5**)
- Clinically meaningful improvements (mean score increase >2) were reported in 36-Item Short Form Survey mental and physical component summary scores at month 36 (**Table 5**)

Figure 4. PedsQL total score over time



MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SE, standard error; TI, transfusion independence.

Table 5. Patient-reported HRQOL at months 24 and 36 in patients treated with beti-cel who achieved TI

	N	Baseline, mean (SE)	N	Month 24, mean (SE)	N	Month 36, mean (SE)
Pediatric HRQOL measures[a]						
PedsQL[b]						
Physical health summary score	22	81.11 (2.89)	22	+2.98 (3.20)	10	+14.69 (3.52)
Psychosocial health summary score	22	76.82 (3.23)	22	+10.15 (3.58)	10	+15.83 (3.74)
EQ-5D-Y						
Health state today	15	81.53 (4.66)	15	+9.33 (4.98)	5	+13.00 (6.64)
Adult HRQOL measures[c]						
SF-36						
Mental component	12	50.95 (1.74)	12	+2.54 (2.70)	11	+4.57 (2.35)
Physical component	12	53.77 (1.43)	12	+1.66 (1.58)	11	+2.35 (1.27)
FACT						
FACT-BMT total score	11	125.76 (11.27)	11	+3.12 (8.99)	10	+5.68 (12.29)
FACT-G total score	11	94.21 (8.60)	11	+1.59 (7.58)	10	+3.02 (8.53)
EQ-5D-3L						
Composite index score	12	0.92 (0.04)	12	+0.04 (0.04)	11	+0.03 (0.06)
Health state today	12	85.17 (3.02)	12	+7.83 (3.97)	11	+6.91 (4.0)

[a]Data from studies HGB-204, HGB-207, and HGB-212 in the subgroup of patients (<18 years of age) who achieved and maintained TI through last follow-up. [b]MCID=4.36; population normative mean=80.9. [c]Data from studies HGB-204, HGB-207, and HGB-212 in the subgroup of adult patients (≥18 years of age) who achieved and maintained TI through last follow-up.
EQ-5D-3L, EuroQol 5 Dimensions 3 Levels questionnaire; EQ-5D-Y, EuroQol 5 Dimensions Youth questionnaire; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplantation; FACT-G, FACT-General; HRQOL, health-related quality of life; MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SE, standard error; SF-36, 36-Item Short Form Survey; TI, transfusion independence.

Safety

- Overall, 19.0% (12/63) of patients experienced ≥1 beti-cel–related adverse event (AE) (**Table 6**), the most common of which were abdominal pain and thrombocytopenia
- Most beti-cel–related AEs were reported in the first 24 months after infusion; none were reported after 48 months
- Five patients, 3 of whom were adolescents, experienced serious veno-occlusive liver disease assessed as related to busulfan; all 5 received defibrotide and recovered
  - Of these, only 1 adult patient had received prophylaxis; the other 3 adolescent patients and 1 adult patient did not receive prophylaxis
- No malignancies, insertional oncogenesis, or vector-derived replication-competent lentivirus were reported

Table 6. Summary of beti-cel–related AEs by age

	Pediatric, <12 y (n=16)	Adolescent, ≥12 and <18 y (n=16)	Adult, ≥18 y (n=31)	Overall (N=63)
Any related AE, n (%)	3 (18.8)	3 (18.8)	6 (19.4)	12 (19.0)
Abdominal pain	0	2 (12.5)	3 (9.7)	5 (7.9)
Thrombocytopenia	1 (6.3)	0	2 (6.5)	3 (4.8)
Dysplasia	0	1 (6.3)	0	1 (1.6)
Dyspnea	0	0	1 (3.2)	1 (1.6)
Hot flush	0	0	1 (3.2)	1 (1.6)
Immune thrombocytopenia	0	0	1 (3.2)[a]	1 (1.6)[a]
Focal nodular hyperplasia	1 (6.3)	0	0	1 (1.6)
Leukopenia	0	0	1 (3.2)	1 (1.6)
Neutropenia	0	0	1 (3.2)	1 (1.6)
Noncardiac chest pain	0	0	1 (3.2)	1 (1.6)
Pain in extremity	0	0	1 (3.2)	1 (1.6)
Tachycardia	1 (6.3)	0	0	1 (1.6)

[a]Occurred between months 24 and 36.
AE, adverse event.

REFERENCES

1. Zynteglo (betibeglogene autotemcel). Prescribing information. bluebird bio, Inc.; 2022. **2.** Locatelli F, et al. *N Engl J Med*. 2022;386(5):415-427. **3.** Pawliuk R, et al. *Science*. 2001;294(5550):2368-2371. **4.** Olson TS, et al. Presented at: Tandem TCT Meetings; Feb 15-19, 2023; Orlando, FL. Poster 385. **5.** Locatelli F, et al. Presented at: ASH; Dec 10-13, 2022; New Orleans, LA. Poster 3665. **6.** Kwiatkowski JL, et al. Presented at: ASH; Dec 11-14, 2021; Atlanta, GA, and Virtual. Poster 3085. **7.** Thompson AA, et al. *N Engl J Med*. 2018;378(16):1479-1493. **8.** Sobota A, et al. *Am J Hematol*. 2011;86(1):92-95. **9.** Webster K, et al. *Health Qual Life Outcomes*. 2003;1:79. **10.** EuroQol Research Foundation. EQ-5D-3L User Guide, 2018. Accessed Jan 22, 2024. https://euroqol.org/publications/user-guides. **11.** Varni JW, et al. *Ambul Pediatr*. 2003;3(6):329-341.

DISCLOSURES

AL: Received research funding from BMS, Forma Therapeutics, Agios, bluebird bio, Celgene, La Jolla Pharmaceuticals, and Novartis; consultancy for Graphite Bio. **MCW:** Consultancy for BioLabs and AllCells; consultancy and holder of stock options at Ensoma; membership on board of directors or advisory committees at Vertex Pharmaceuticals. **AAT:** Consultancy for and received research funding from bluebird bio, Beam, Novartis, Editas, and CRISPR/Vertex. **TSO:** Consultancy for bluebird bio, Vertex Pharmaceuticals, and Medexus Pharmaceuticals; member of Data Safety Monitoring Board for Elixirgen Pharmaceuticals; membership on board of directors or advisory committees at Team Telomere. **JBP:** Honoraria for Protagonist, Vifor, Silence Therapeutics, La Jolla Pharmaceuticals; consultancy and honoraria for Celgene, bluebird bio, and Agios; honoraria and membership on board of directors or advisory committees for BMS and Novartis. **JS:** Consultancy for Therakos Mallinckrodt; membership on board of directors or advisory committees at bluebird bio. **AEK:** Honoraria for Vertex Pharmaceuticals, BMS, and Celgene; received honoraria and research funding from bluebird bio. **MC:** Current employee of and equity holder in Smart Immune; consultancy for Cellectis and Noga. **AJT:** Consultancy for Orchard Therapeutics, Rocket Pharmaceuticals, and 4BIO Capital; consultancy and current equity holder in Generation Bio.

IT: Participation in clinical trials for bluebird bio, Celgene, and Novartis; membership on board of directors or advisory committees at Vertex Pharmaceuticals. **JEJR:** Consultancy for Gilead, Roche, Novartis, bluebird bio, Spark Therapeutics, Cynata, and Pfizer; current equity holder at Genea and Rarecyte. **EY:** Received research funding from bluebird bio. **SA**, **GT**, **HLT**, **AD**, **CP**, **RAC:** Current employees of and equity holders in bluebird bio. **FL:** Honoraria at Jazz Pharmaceuticals; honoraria and membership on speakers bureau for Novartis; membership on speakers bureau for Medac, Sobi, Miltenyi, bluebird bio, Amgen, and Neovii. **JLK:** Consultancy for Agios, BMS, Celgene, Chiesi, Silence Therapeutics, and BioMarin; received research funding from Apopharma, Bioverativ, and Sangamo; consultancy and received research funding from bluebird bio, Imara, Forma, and CRISPR/Vertex. **SH**, **MGS:** Nothing to disclose.