Efficacy and Safety of Betibeglogene Autotemcel (beti-cel) Gene Therapy in 63 Patients with Transfusion-Dependent β-Thalassemia (TDT): 7-Year Post-Infusion Follow-up of Phase 1/2 and Phase 3 Studies

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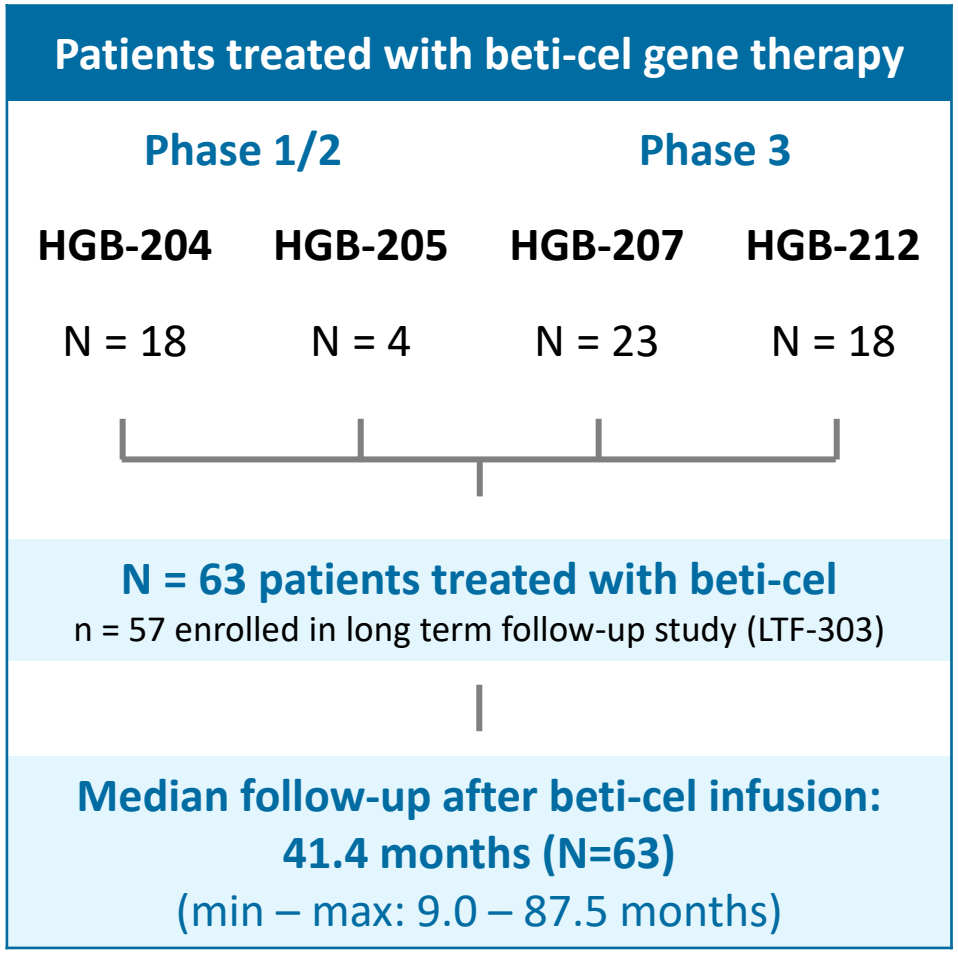
Jennifer Schneiderman: Participated on advisory Board for bluebird bio, scientific consultant for Mallinckrodt/Therakos, Inc.

Beti-cel gene therapy is a one-time treatment option for patients with TDT

- TDT is a severe, genetic disease caused by mutations in the *HBB* gene encoding β-globin
  - β-globin mutations result in absent or significantly reduced HbA, which normally accounts for ~95% of total Hb in blood after 6 months of age[1]
  - Results in lifelong transfusion dependence, iron overload, and associated complications and comorbidities
- Autologous gene therapy with beti-cel aims to establish lifelong, functional HbA allowing for transfusion independence
- 63 adult and pediatric patients with TDT (median age 17 years) have been treated with beti-cel across 4 clinical studies
  - All studies are completely enrolled and include 2 years of follow up
  - 57 patients completed parent study and enrolled in long-term follow-up study (LTF-303) for an additional 13 years of follow up



Hb, hemoglobin; HbA, adult hemoglobin; TDT, transfusion-dependent β-thalassemia.

1. Cappellini MD, et al. Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition – 2021). Thalassaemia International Federation.

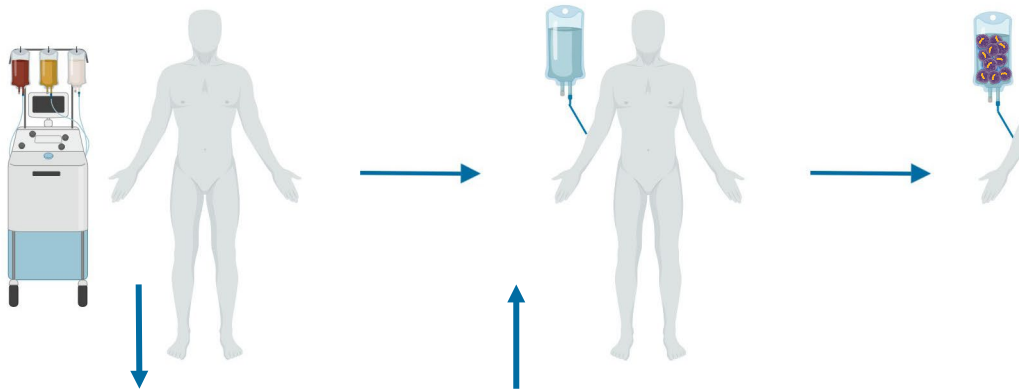
Beti-cel adds copies of a modified *HBB* gene into patients' HSCs through transduction of autologous CD34+ cells with BB305 lentiviral vector

HSC collection
Mobilization (G-CSF + plerixafor) and apheresis

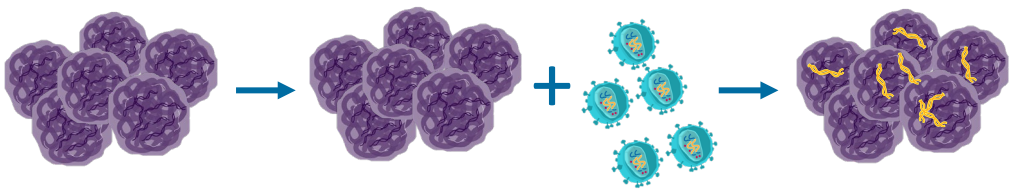
Busulfan myeloablative conditioning

beti-cel IV infusion

Transduced HSCs engraft and reconstitute RBCs which contain HbA^{T87Q}



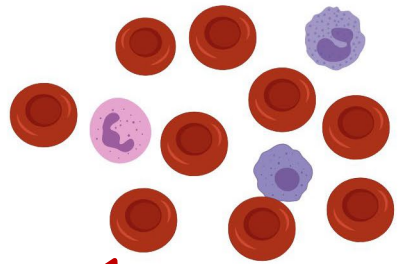
Drug product centralized manufacturing



Select CD34+ cells

HSCs transduced with BB305 lentiviral vector (encodes for $\beta^{A\text{-}T87Q}$-globin)

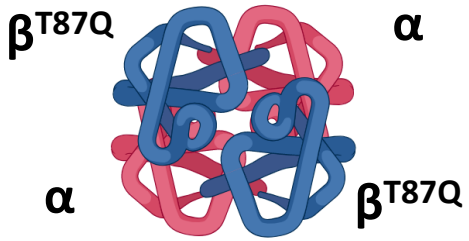
Cryopreserve, test, release drug product



2-year follow-up on parent study

13-year long-term follow-up study

HbA^{T87Q}
Gene therapy-derived functional HbA



Beti-cel–derived HbA^{T87Q} has oxygen affinity similar to that of endogenous HbA[1]

G-CSF, granulocyte colony-stimulating factor; HbA, adult hemoglobin; HSC, hematopoietic stem cell; IV, intravenous; RBC, red blood cell.

1. Pawliuk R, et al. *Science.* 2001;294(5550):2368-71.

Refined manufacturing resulted in improved beti-cel drug product characteristics in Phase 3 studies

		Phase 1/2 (N = 22)	Phase 3 (N = 41)
Baseline patient characteristics			
Genotype, n (%)	non-β^0/β^0	**14** (64)	**29** (71)
	β^0/β^0	**8** (36)	**12** (29)
Age at consent, median (min – max), years		**20** (12 – 35)	**13** (4 – 34)
Liver iron concentration, median (min – max), mg Fe/g dw		**7.1** (0.4 – 26.4)	**4.9** (1.0 – 41.0)
Cardiac T2*, median (min – max), msec		**34** (10 – 54)	**37** (15 – 75)
Splenectomy, n (%)		**9** (41)	**7** (17.1)
Fertility preservation, n (%) †		**13** (59.1)	**30** (73.2)

		Phase 1/2 (N = 22)	Phase 3 (N = 41)
HSC collection and busulfan conditioning			
Mobilization cycles per patient, n (%) ‡	**1**	**18** (82)	**32** (78)
	2	**4** (18)	**8** (20)
	3	**0** (0)	**1** (2)
Estimated daily average busulfan AUC over 4 days median (min – max), µM*min		**4175** (3030 – 5212)	**4310** (3605 – 9086)
Drug product (average per patient)			
Vector copy number median (min – max), c/dg		**0.8** (0.3 – 2.1)	**3.0** (1.2 – 7.0)
CD34⁺ cells transduced median (min – max), %		**32** § (17 – 58)	**78** (34 – 94)
Cell dose median (min – max), x 10^6 CD34⁺ cells/kg		**8.9** (5.2 – 18.1)	**9.4** (5.0 – 42.1)

AUC, area under the curve; c/dg, copies per diploid genome; Fe/g dw, iron content per gram dry weight; HSC, hematopoietic stem cell.
† Fertility preservation was an optional procedure; ‡ Data as of 12 June 2019 for Phase 1/2 and 9 March 2021 for Phase 3 (HGB-207 and HGB-212); §N=18; not evaluated in HGB-205.

Patient demographics by study

		HGB-204 (N = 18)	HGB-205 (N = 4)	HGB-207 (N = 23)	HGB-212 (N = 18)	All Studies (N=63)
Baseline patient characteristics						
Genotype, n (%)	non-β^0/β^0	**10** (56)	**4** (100)	**23** (100)	**6** (33)	**43** (68)
	β^0/β^0	**8** (44)	**0**	**0**	**12** (67)	**20** (32)
Age at consent, median (min–max), years		**20** (12 – 35)	**18** (16 – 19)	**15** (4 – 34)	**13** (4 – 33)	**17** (4 – 35)
Pre-study pRBC transfusion volume, [†] annualized median, mL/kg/year		**171.2** (124 – 273)		**207.9** (142 – 274)	**194** (75 – 289)	-
Number of pre-study pRBC transfusions, [†] n/year		**13.0** (10.0 – 17.5)		**16.0** (11.5 – 37.0)	**17.3** (11.0 – 39.5)	-
Liver iron concentration, median (min–max), mg Fe/g dw		**5.7** (0.4 – 26.4)	**11.2** (3.9 – 14.0)	**5.3** (1.0 – 41.0)	**3.6** (1.2 – 13.2)	**5.3** (0.4 – 41.0)
Cardiac T2*, median (min–max), msec		**35** (10 – 54)	**33** (29 – 46)	**37** (21 – 57)	**37** (15 – 75)	**36** (10 – 75)
Splenectomy, n (%)		**6** (33)	**3** (75)	**4** (17)	**3** (17)	**16** (25)
Fertility preservation, [‡] n (%)		**9** (50)	**4** (100)	**15** (65)	**15** (65)	**43** (68)

Fe/g dw, iron content per gram dry weight; pRBC, packed red blood cell.

[†] Data as of 12 June 2019 for Phase 1/2 and 9 March 2021 for Phase 3 (HGB-207 and HGB-212). [‡] Fertility preservation was an optional procedure.

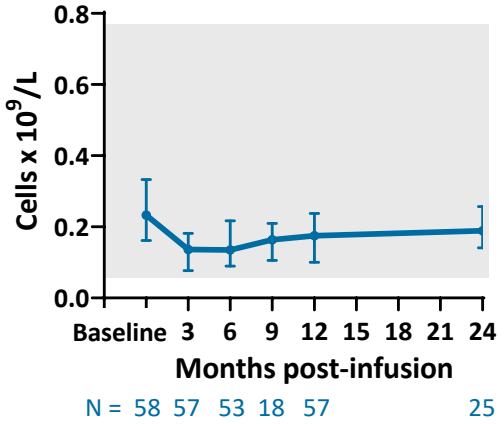
Hematopoietic recovery after beti-cel infusion

Engraftment and hospitalization
(pooled Phase 1/2 [n=22] and Phase 3 [n=41])

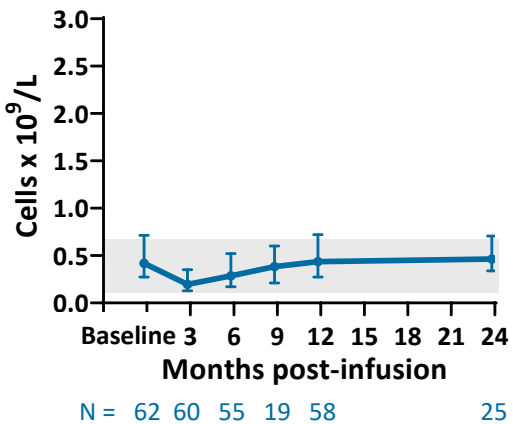
Time to event post-infusion, median (min – max), days	N=63
Neutrophil engraftment ANC ≥500 cells/μL x 3 days	**23** (13 – 39)
Platelet engraftment ≥20,000 platelets/μL x 3 days	**45** (19 – 191) †
Duration of hospitalization ‡	**43** (27 – 92)
Phase 1/2	**40** (27 – 69)
Phase 3	**44** (29 – 92)

Lymphocyte subsets generally within normal range after beti-cel §

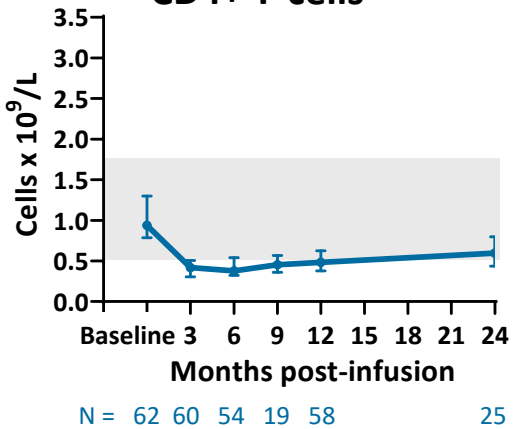
CD3- CD16+ CD56+ NK cells



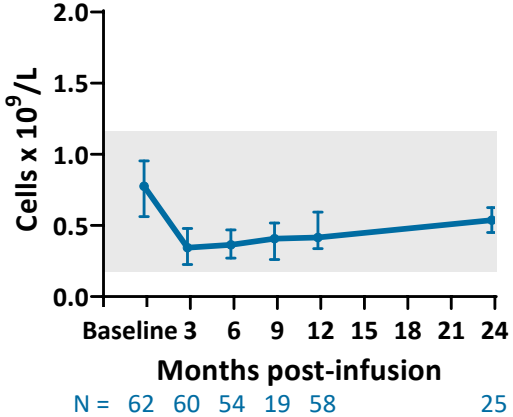
CD19+ B-cells



CD4+ T-cells



CD8+ T-cells

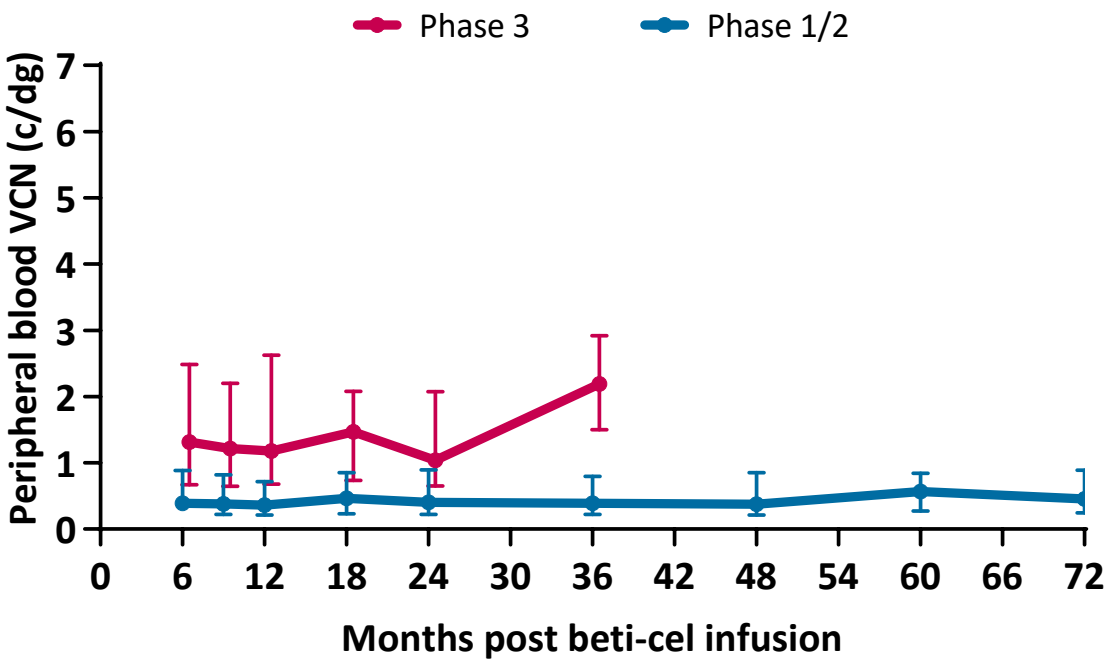


ANC, absolute neutrophil count; NK, natural killer. † One patient achieved neutrophil engraftment on day 24 but did not achieve platelet engraftment until day 191. ‡ Defined as the time from admission for conditioning through post-infusion discharge. § Median (Q1, Q3) depicted; grey bars indicate normal range.

Persistent vector-positive cells and durable HbA^{T87Q} levels support stable total Hb

Peripheral blood vector copy number

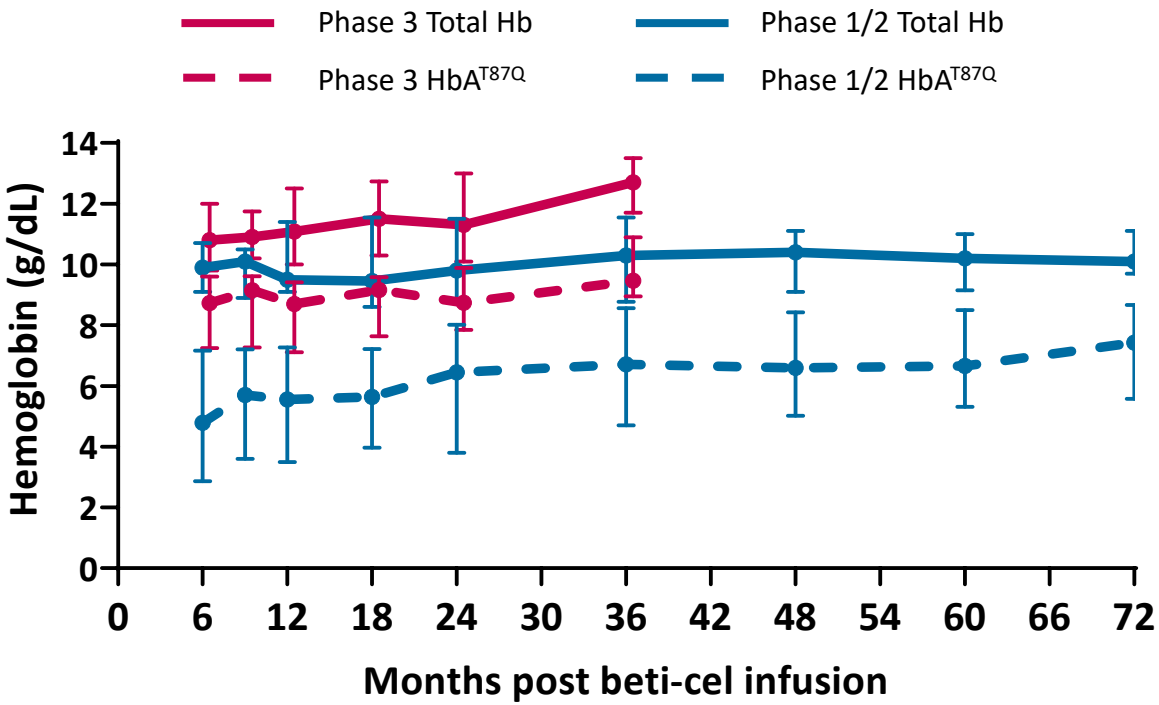
Median PB VCN in Phase 3: 1.2 c/dg at M12 and 1.0 c/dg at M24



n =	39	39	35	35	17			
n =	22	22	21	22	22	22	19	14

Total unsupported Hb and gene therapy-derived HbA^{T87Q}

Median total Hb in Phase 3: 11.1 g/dL at M12 and 11.3g/dl at M24

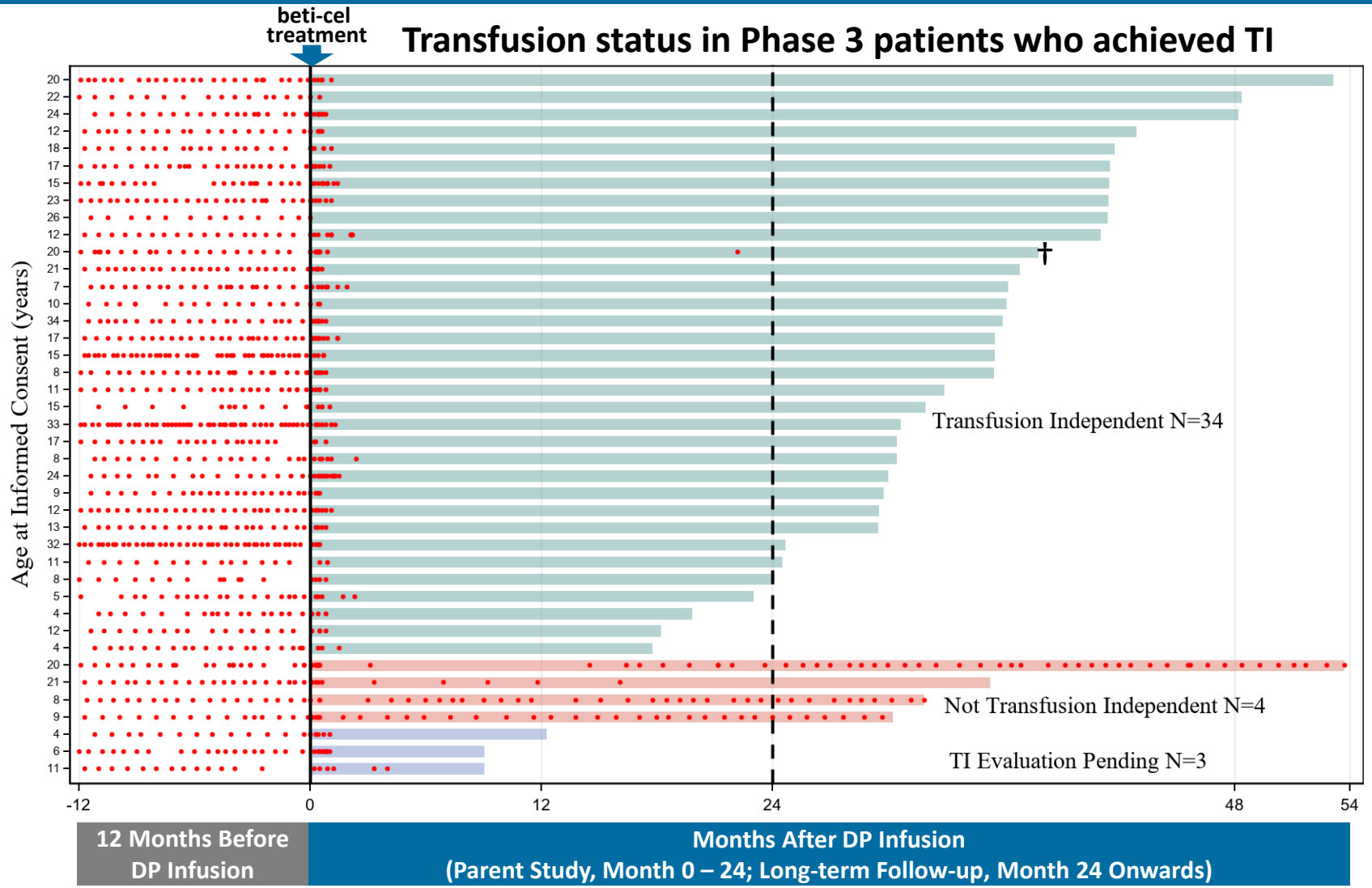


Total Hb n =	39	36	31	31	18			
HbA^{T87Q} n =	37	39	35	35	17			
Total Hb n =	13	17	18	18	19	19	18	14
HbA^{T87Q} n =	22	22	21	22	22	22	17	14

c/dg, copies per diploid genome; Hb, hemoglobin; VCN, vector copy number.
Median (Q1 – Q3) depicted. Unsupported Hb is defined as no prior packed red blood cell transfusion in the prior 60 days.

Data as of August 18, 2021

Phase 3 studies: maintenance of TI for up to 4 years of follow-up



	Phase 3 (N=41)	Phase 1/2 (N=22)
TI-evaluable patients who completed the study and achieved TI, % (n/N)	89.5 (34/38)	68.2 (15/22)
Patients who achieved and remained TI, %	100	100
Duration of TI, median (min – max), months	31.6 (13.3 –49.1)	65.9 (19.8 – 84.5)
Weighted average Hb during TI, median (min – max), g/dL	11.3 (9.5 – 13.7)	10.3 (9.1 – 13.2)

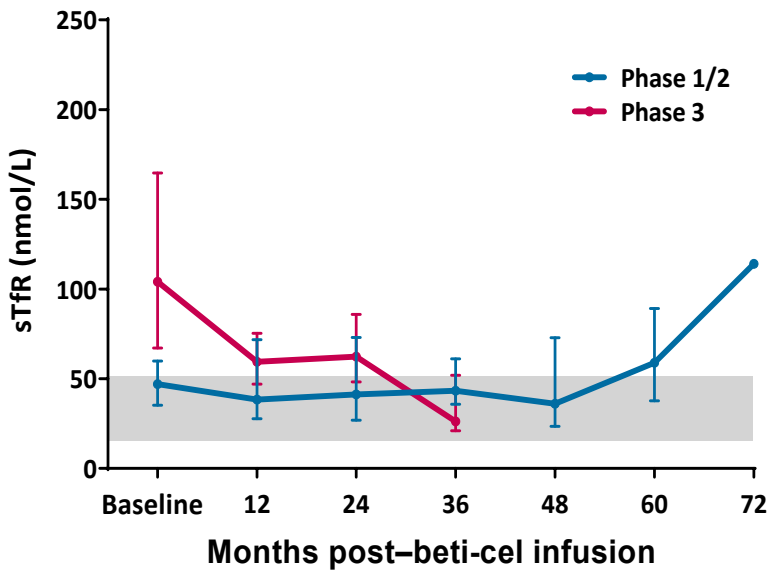
† Patient's total Hb level at Month 22 was 13.4 g/dL. After a planned orthopedic surgery, the patient had blood loss, which required 1 packed red blood cell transfusion.

DP, drug product; Hb, hemoglobin; TI, transfusion independence (defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months).
Red dots depict transfusion episode. Black dotted line denotes completion of parent study and enrollment in LTF-303.

Data as of August 18, 2021

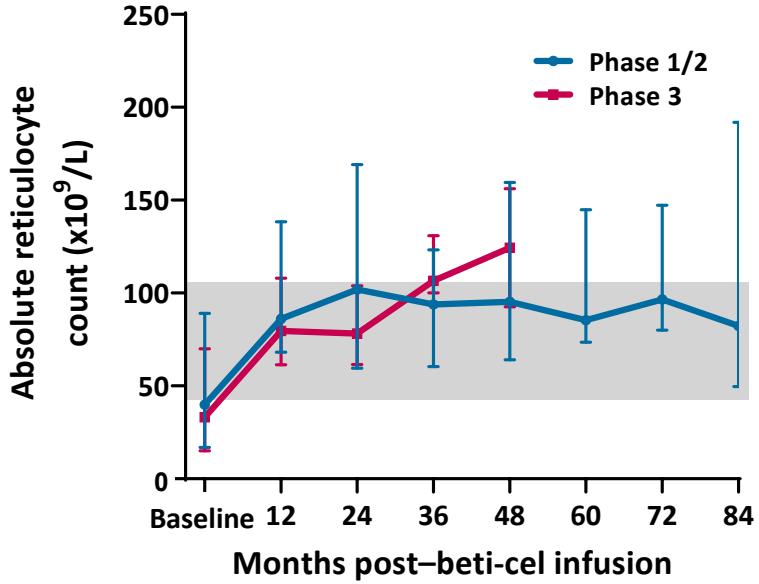
Improved erythropoiesis in patients who achieved TI

Soluble transferrin receptor



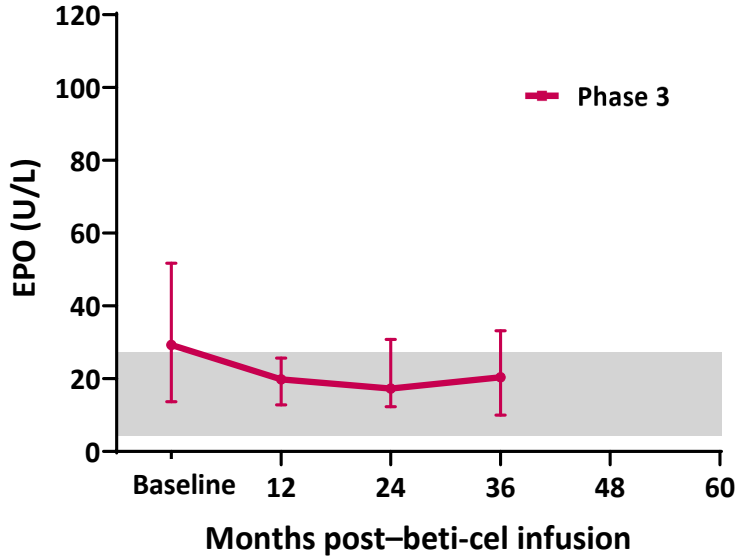
n =	11	11	12	10	4	8	1
n =	34	30	31	7			

Reticulocyte count



n =	15	14	15	15	15	15	10	3
n =	33	32	29	18	2			

Erythropoietin†

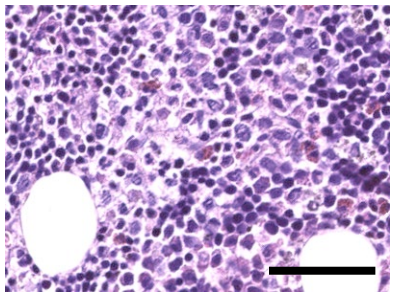
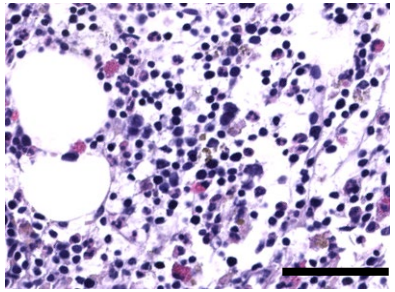
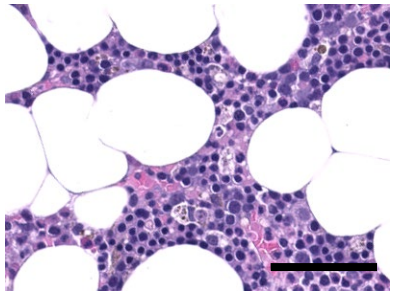
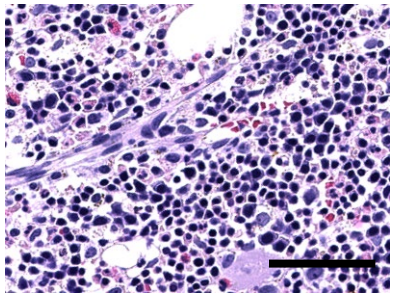
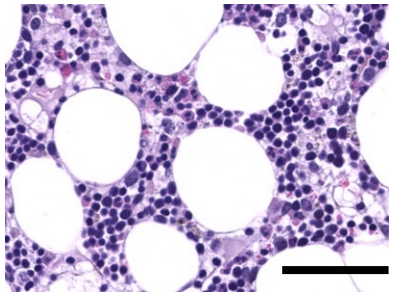
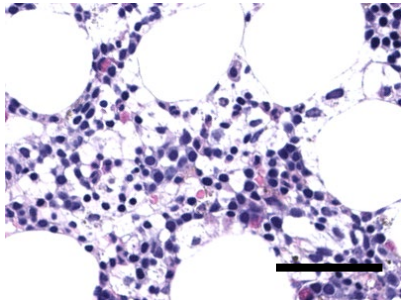


n =	29	29	27	9

EPO, erythropoietin; sTfR, soluble transferrin receptor; TI, transfusion independence.
Median (Q1, Q3) depicted. Grey bars indicate normal range. † Erythropoietin data were not collected in Phase 1/2 studies.

Bone marrow histology and myeloid to erythroid ratio improved in Phase 3 patients who achieved TI

Bone marrow assessment post beti-cel infusion

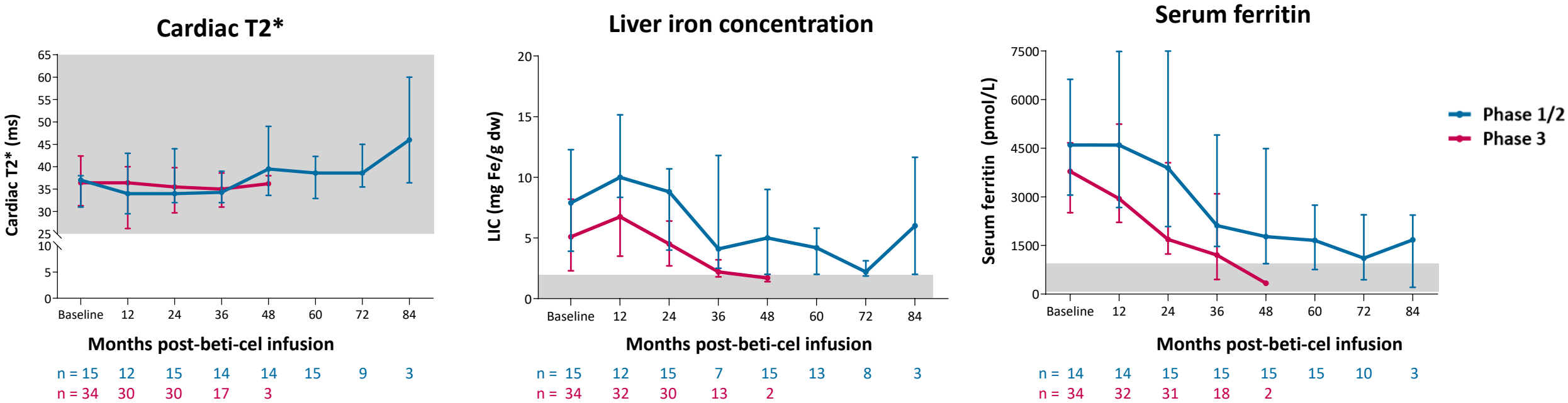
Screening	Month 12	Month 24
		
Hypercellular; M:E 1:5.5	Normocellular; M:E 1:1.3	Normocellular; M:E 1.2:1
		
Hypercellular; M:E 1:2:2	Hypocellular; M:E 1:1:1	Normocellular; M:E 1:2:1

Scale bars: 50 µm.
M:E ratio in healthy individuals[1]: 3-4:1

17/26 TI patients (65%) had normocellular histology at M24

M:E, myeloid to erythroid ratio; TI, transfusion independence.
1. Origa R. GeneReviews®. 2018. https://www.ncbi.nlm.nih.gov/books/NBK1426/ (accessed Jan 10, 2022).

Reduced iron burden in patients who achieved TI



Iron management in patients who achieved TI

- **76% (37/49) restarted iron chelation after beti-cel infusion**
  - Time to starting chelation after beti-cel infusion was 8.2 (0.8 – 25) months
  - 21/37 patients who restarted iron chelation have since stopped; duration of chelation was 24.6 (0.2 – 62.3) months
- **25% (12/49) of patients received phlebotomy for iron removal, including 6 patients receiving iron chelation**
  - 6 patients received only phlebotomy
  - Time to starting phlebotomy after beti-cel infusion was 9.8 (3.2 – 31.6) months

LIC, liver iron concentration; TI, transfusion independence. Median (min – max) reported. Patients received iron removal therapy at the discretion of the investigator. Median (Q1, Q3) depicted. Last-observation-carried-forward imputed values are included. Grey bars indicate normal range.

Safety profile after beti-cel infusion

- All patients were alive at last follow-up
- 18% (11/63) of patients experienced ≥1 AE considered related or possibly related to beti-cel
  - All events were grade 1/2 except two events of grade 3 thrombocytopenia (one was serious)
  - No beti-cel-related AEs beyond 2 years post-infusion
- VOD was reported in 11% (7/63) patients
  - 5 patients had serious VOD (3 grade 4; 2 grade 3)
  - 2 patients had non-serious VOD (grade 2)
  - All events resolved
- No malignancies, insertional oncogenesis, or vector-derived replication competent lentivirus
- Polyclonal reconstitution: no single clone meets criteria for clonal predominance †
- Two male patients, one of whom underwent fertility preservation, reported the births of healthy children with their partners

AEs in ≥ 2 patients from infusion to last follow-up	N = 63 n (%)
AEs considered possibly related or related to beti-cel ‡	
Abdominal pain	5 (8)
Thrombocytopenia	3 (5)
Serious AEs	
VOD	5 (8)
Pyrexia	5 (8)
Neutropenia	3 (5)
Thrombocytopenia	3 (5)
Sepsis §	3 (5)
Appendicitis	2 (3)
Febrile neutropenia	2 (3)
Major depression	2 (3)
Stomatitis	2 (3)

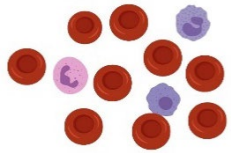
AE, adverse event; c/dg, copies per diploid genome; VOD, veno-occlusive liver disease. † Criteria for clonal predominance for an individual subject is defined as an insertional site-specific vector copy number > 0.5 c/dg, estimating >50% clonal contribution. ‡ The following AEs possibly related or related to beti-cel occurred in 1 patient (1.6%): immune thrombocytopenia, leukopenia, neutropenia, tachycardia, dysplasia, non-cardiac chest pain, pain in extremity, dysponea, and hot flush. § Sepsis events included neutropenic sepsis, bacterial sepsis and sepsis not otherwise specified.

Summary of data from patients treated with beti-cel gene therapy in Phase 1/2 and 3 studies

63 patients treated in 4 clinical studies evaluating safety and efficacy of beti-cel for TDT with genotypes spanning a broad range of TDT severity and across several age groups

One-time beti-cel gene therapy enabled durable TI with up to 7 years follow-up

- Persistent vector-positive hematopoietic cells
- Stable gene therapy-derived HbA, HbA^{T87Q}



Reduction of ineffective erythropoiesis and iron overload in patients who achieved TI

- Soluble transferrin receptor and erythropoietin demonstrated improvement
- Improvement of LIC, serum ferritin, and cardiac T2* toward normal levels

Absence of drug product-related AEs >2 years post-infusion supports a favorable long-term safety profile

- Safety profile consistent with known effects of single-agent busulfan myeloablation
- No vector-derived replication-competent lentivirus or events of insertional oncogenesis or hematologic malignancy reported

Beti-cel is a potentially curative gene therapy for patients with TDT through the achievement of durable TI and normal or near-normal Hb levels

AE, adverse event; Hb, hemoglobin; HbA, adult hemoglobin; LIC, liver iron concentration; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence.

Data as of August 18, 2021

Thank you to the study participants and their families

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IRCCS Bambino Gesù Children's Hospital, Rome, Italy

University College London Hospital, London, UK

UCL Great Ormond Street Hospital, London, UK

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

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- Dana Martin
- Kailey Walsh
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