Offenlegung Interessenskonflikte

Priv.-Doz. Dr. med. Ferras Alashkar

1. Anstellungsverhältnis oder Führungsposition

2. Beratungs- bzw. Gutachtertätigkeit

Bristol Myers Squibb/Celgene, Global Blood Therapeutics/Pfizer, Novartis, Vertex

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

4. Patent, Urheberrecht, Verkaufslizenz

5. Honorare

Agios, Bristol Myers Squibb/Celgene, Global Blood Therapeutics/Pfizer, Novartis, Vertex

6. Finanzierung wissenschaftlicher Untersuchungen

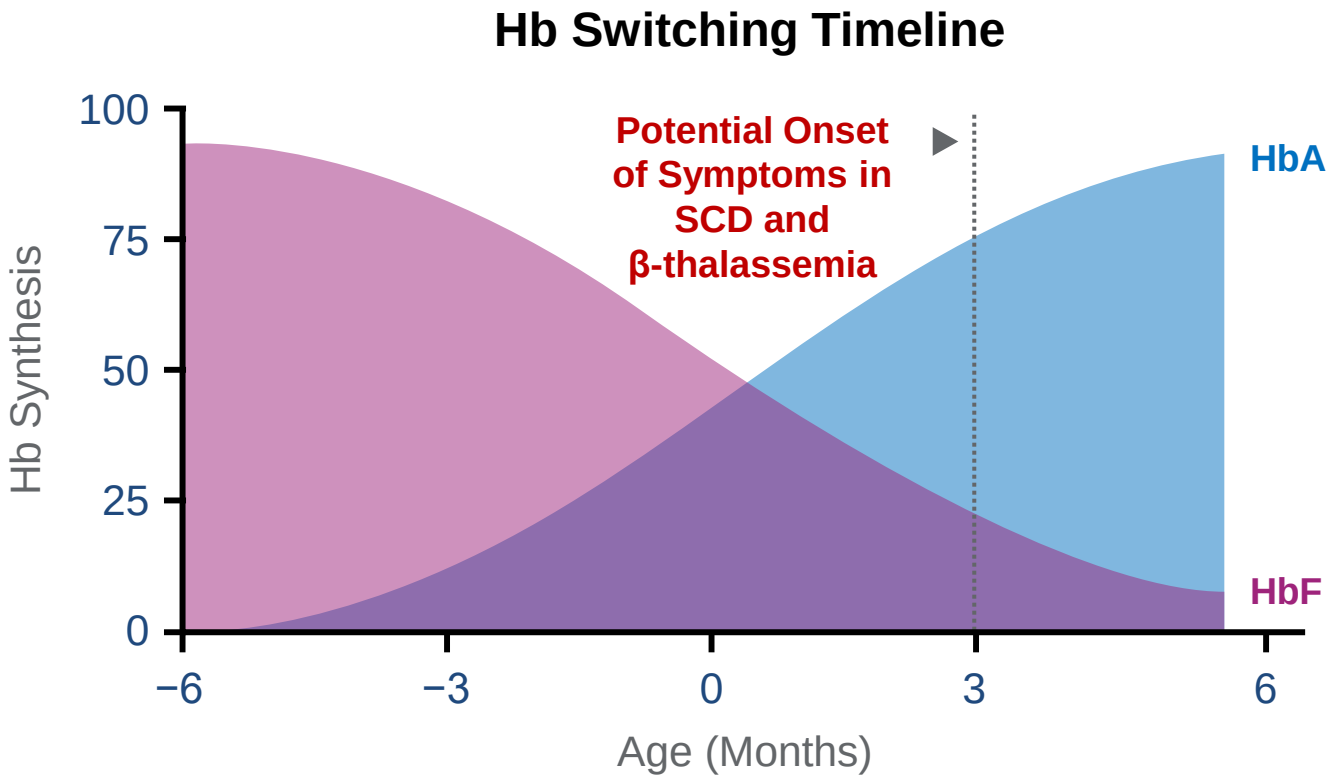
Global Blood Therapeutics/Pfizer

7. Andere finanzielle Beziehungen

8. Immaterielle Interessenkonflikte

Disease Symptoms Arise as Hb Switches From Fetal to Adult[1,2]

- **Infants with SCD or β-thalassemia are typically asymptomatic while their HbF levels remain high**[1,2]
- Shortly **after birth**, the **predominant Hb switches from HbF to HbA** as levels of γ-globin decrease and β-globin increase[1]
- The switch from HbF to HbA is modulated by β-globin genes including *BCL11A*[1,3]

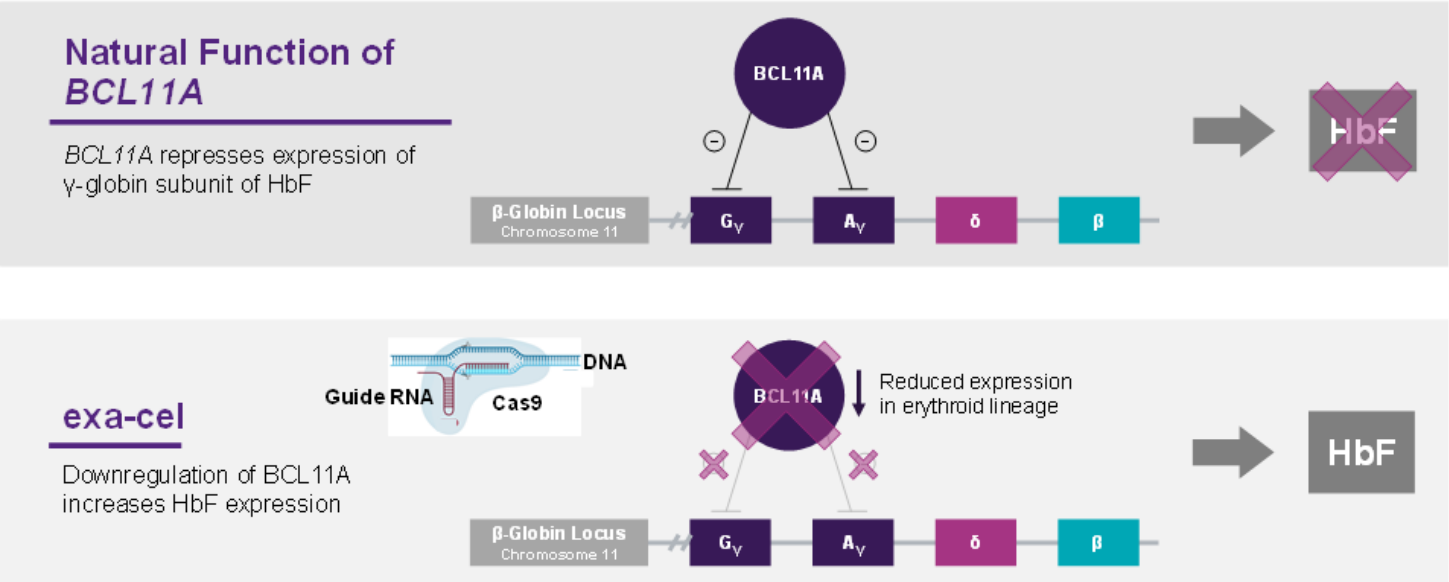


This chart is for illustrative purposes only and not representative of all patients with SCD or β-thalassemia

Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; SCD, sickle cell disease.

1. Sankaran VG, et al. *Cold Spring Harb Perspect Med*. 2013;3(1):a011643. 2. Kato GJ, et al. *Nat Rev Dis Primers*. 2018;4:18010. 3.Galarneau G, et al. Nat Genet. 2010;42:1049-1051. .

Gene Editing Typically Relies on Generating double-stranded breaks in the DNA and Repair by Naturally Occurring DNA Repair Systems[a,1-3]



After generation of a DNA double-strand break, NHEJ creates insertions or deletions (indels) of one or more nucleotides within the *BCL11A* enhancer locus

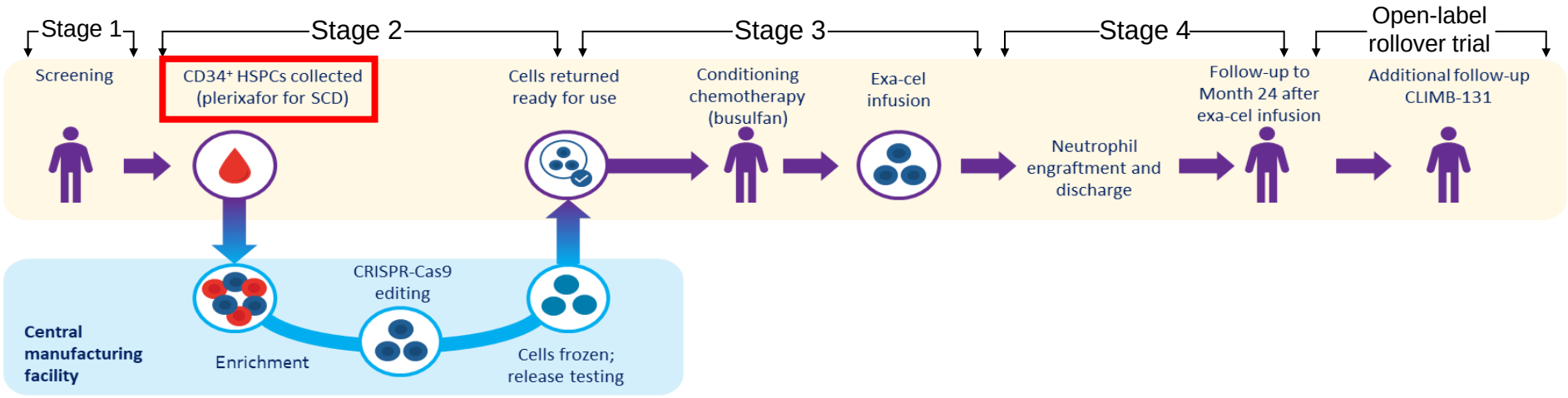
- GATA1 transcription factor binding is disrupted
- *BCL11A* expression is downregulated

[a]Specific to gene-editing approaches with nucleases involved (e.g., CRISPR/Cas9, zinc finger nucleases, transcription activator-like effector nucleases).

***BCL11A*,** B-cell lymphoma/leukemia 11A; **Cas9,** CRISPR-associated 9 nuclease; **CRISPR,** clustered regularly interspaced short palindromic repeats; **DNA,** deoxyribonucleic acid; **exa-cel,** exagamglogene autotemcel; **HbF,** fetal hemoglobin; **NHEJ**, non-homologous end joining; **RNA,** ribonucleic acid

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Pivotal Phase 3 Trial of Exa-cel in Participants With Severe SCD



Study Design	• Global, multicenter, open-label, single-arm, 2-year Phase 3 trial of a single infusion of exa-cel (NCT03745287)
Participants	• Dosing completed with **46 participants** dosed (as of data cutoff: March 2024) • **12 to 35 years of age with severe SCD and a history of ≥2 severe VOCs per year in the previous 2 years**
Primary Efficacy Endpoint	Proportion of participants **free of severe VOCs for ≥12 consecutive months (VF12)**
Key Secondary Efficacy Endpoint	Proportion of participants **free from in-patient hospitalization for severe VOCs for ≥12 consecutive months (HF12)**
Analyses	• **Full Analysis Set: participants who received exa-cel infusion** • **Primary Efficacy Set:** participants **followed for ≥16 months after exa-cel infusion** (evaluable for primary & key secondary endpoints)

Participants who complete CLIMB SCD-121 can enroll in CLIMB-131 for 13 years of additional follow-up

Primary and key secondary efficacy endpoints: assessed starting 60 days after last RBC transfusion for post-transplant support or SCD management.
CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; exa-cel, exagamglogene autotemcel; HSPC, haematopoietic stem and progenitor cell; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Demographics and Baseline Clinical Characteristics

	Full Analysis Set[a] N = 46	Primary Efficacy Set[b] N = 39
Age at screening, years, mean (SD)	**21.4 (6.0)**	**21.2 (6.0)**
≥12 and <18 years, n (%)	12 (26.1)	11 (28.2)
≥18 and ≤35 years, n (%)	**34 (73.9)**	**28 (71.8)**
Sex, n (%)		
Male	25 (54.3)	23 (59.0)
Female	21 (45.7)	16 (41.0)
Genotype, n (%)		
β^s/β^s	**41 (89.1)**	**36 (92.3)**
β^s/β^0	3 (6.5)	2 (5.1)
β^s/β^+	2 (4.3)	1 (2.6)
α-globin gene deletion status, n (%)		
One-gene deletion	16 (34.8)	12 (30.8)
Two-gene deletions	2 (4.3)	2 (5.1)
Historical VOC episodes per year,[c] mean (range)	**4.2 (2.0, 18.5)**	**4.1 (2.0, 18.5)**
Historical in-patient hospitalizations for severe VOCs per year,[a] mean (range)	**2.7 (0.0, 9.5)**	**2.6 (0.5, 8.5)**

[a] Full Analysis Set includes participants who received exa-cel infusion.
[b] Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion (evaluable for primary & key secondary endpoints).
[c] Annualised over 2 years before screening.

Exa-cel, exagamglogene autotemcel; SD, standard deviation; VOC, vaso-occlusive crises.

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Treatment and Engraftment Results

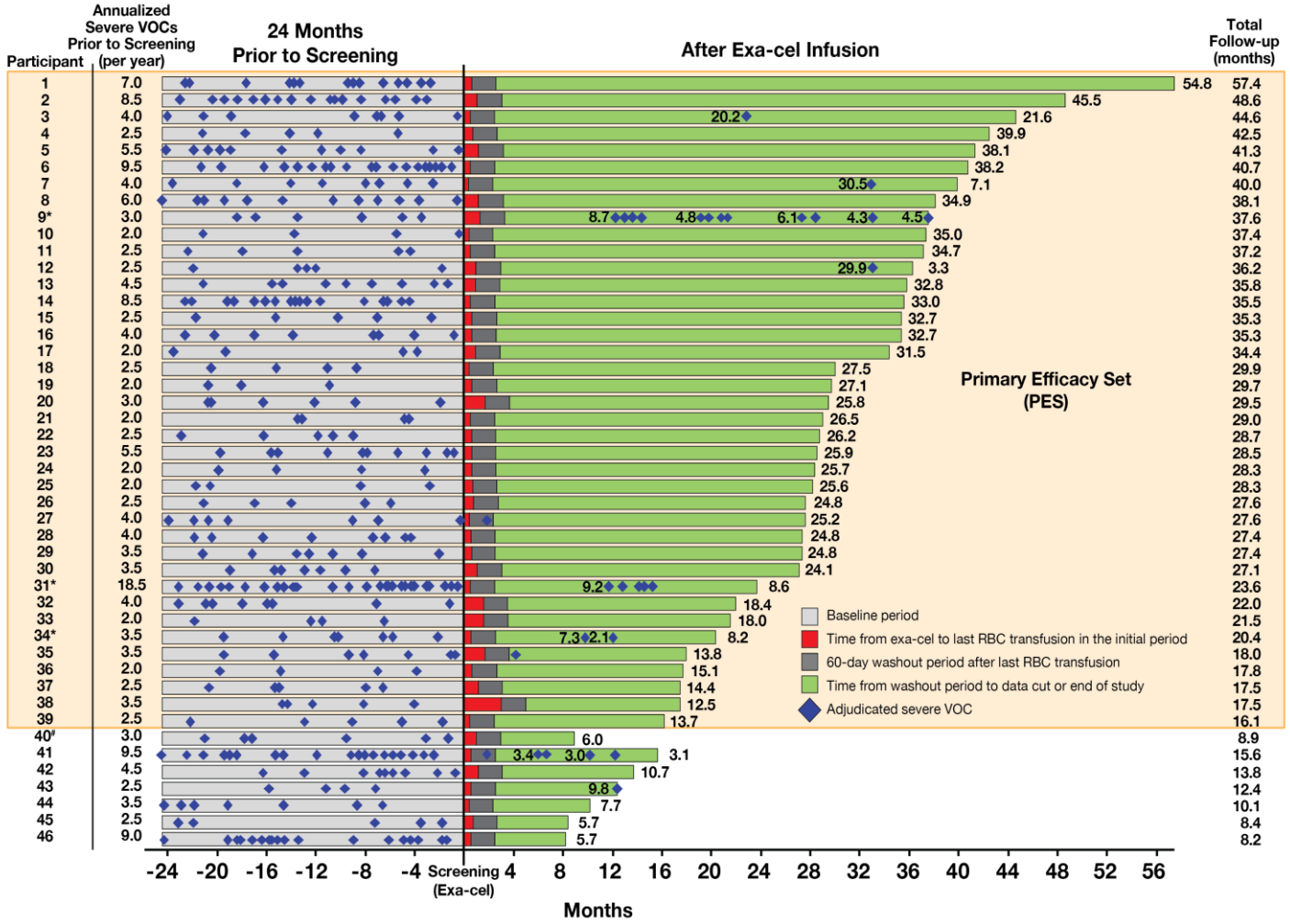
	Full Analysis Set[a] N = 46
Number of mobilization cycles, median (range)	**2.0 (1.00, 6.00)**
Exa-cel dose: 10^6 x $CD34^+$ cells/kg, mean (range)	4.7 (2.9, 14.4)
Duration (months) of follow-up after exa-cel infusion[b], mean (range)	28.2 (8.2, 57.4)
Neutrophil Engraftment[c]	
▪ Time to neutrophil engraftment (days), median (range)	**27.0 (15, 40)**
▪ Duration of neutropenia (absolute neutrophil count <500 cells/uL) (days), median (range)	17.0 (6, 30)
Platelet Engraftment[d]	
▪ Time to platelet engraftment (days), median (range)	**34.5 (23, 126)**
Time to last RBC transfusion (days), median (range)	19.5 (11, 91)
Time to hospital discharge[e] (days), median (range)	**31.5 (21, 54)**

[a] Full Analysis Set includes participants who received exa-cel infusion.
[b] Duration of follow-up include both CLIMB SCD-121 and CLIMB-131 trials.
[c] Defined as the first day of 3 consecutive measurement of absolute neutrophil count ≥500 cells/μL on 3 different days.
[d] Defined as the first day of 3 consecutive measurement of unsupported (no platelet transfusion in last 7 days) platelet count **≥50,000/μL** on 3 different days.
[e] Defined as the number of days from exa-cel infusion to hospital discharge.

Exa-cel, exagamglogene autotemcel; RBC, red blood cell.

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Severe VOC Status After Exa-cel Infusion



- **36 of 39 evaluable participants (92.3%) achieved VF12** (PES = followed for ≥16 months after exa-cel infusion)
  - 26 of 28 evaluable adults (92.9%) achieved VF12
  - **10 of 11 evaluable adolescents (90.9%) achieved VF12**

Pain events after exa-cel generally occurred in adult participants with a **history of chronic pain and/or** following an identifiable pain trigger such as:

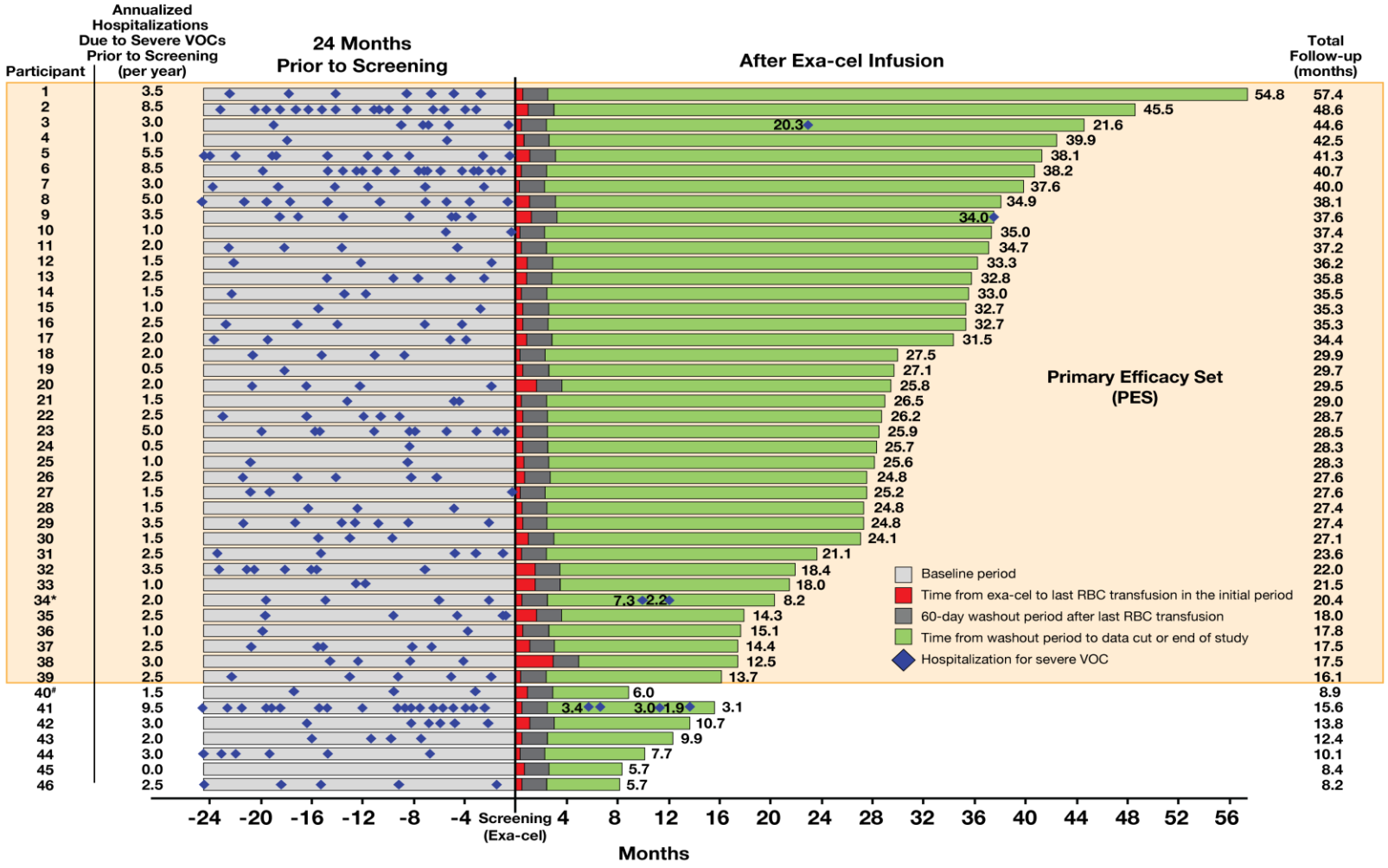
- **infection** (e.g., parvovirus B19 (recovered), influenza B, or COVID-19)
- procedure (e.g., bone marrow biopsy)
- corticosteroids

*participants who did not achieve VF12; #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.
Some subjects had VOCs after the washout period; numerical values before the VOC indicate the number of months a subject was VOC-free since the washout period/previous VOC. Data shown is based on the Full Analysis Set.

Exa-cel, exagamglogene autotemcel; PES, Primary Efficacy Set; VF12, proportion of participants free of severe VOCs for ≥12 consecutive months; RBC, red blood cell; VOC, vaso-occlusive crisis.

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Inpatient Hospitalisation Status After Exa-cel Infusion



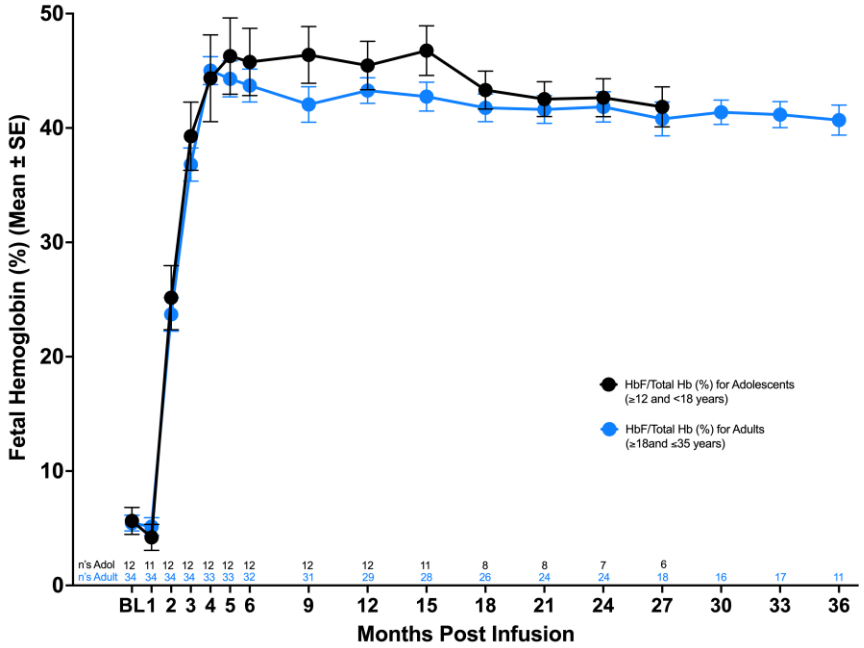
- 38 of 39 evaluable participants (97.4%) achieved HF12
- Mean duration of hospitalization-free period:
  28.2 months (range 12.5 to 54.8)

*participants who did not achieve HF12; #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.
Some had hospitalization due to VOCs after the washout period; numerical values before the hospitalization due to VOC indicate the number of months a subject was hospitalization-free since the washout period/previous hospitalization due to VOC.
Data shown is based on the Full Analysis Set.
Exa-cel, exagamglogene autotemcel; HF12, proportion of participants free from in-patient hospitalisation for severe VOCs for ≥12 consecutive months; RBC, red blood cell; VOC, vaso-occlusive crisis.

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

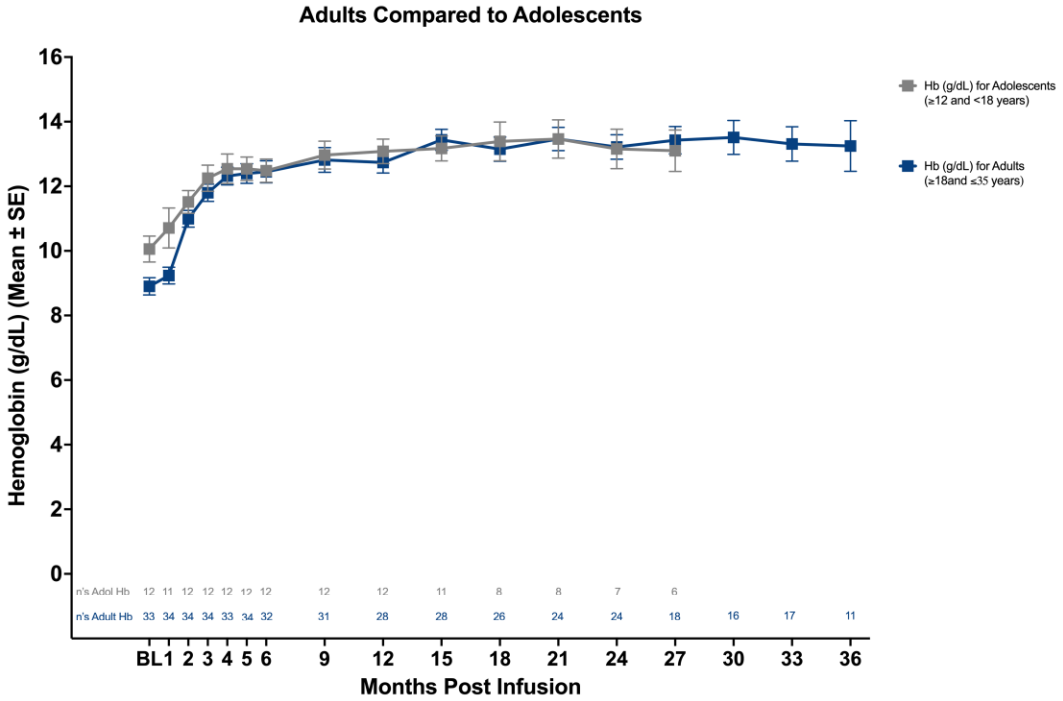
Total Hemoglobin and Fetal Hemoglobin

HbF Percentage



- **Mean (range) HbF percentage in adolescents:** 45.5 (37.7, 64.7) at month 12; 42.6 (37.6, 51.1) at month 24
- **Mean (range) HbF percentage in adults:** 43.3 (31.3, 59.1) at month 12; 41.8 (26.9, 53.0) at month 24

Total Hb



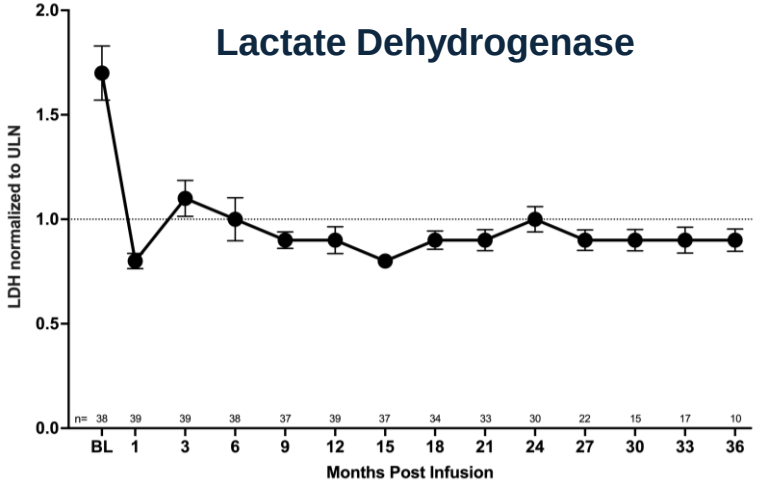
- **Mean (range) Hb (g/dL) in adolescents:** 13.1 (11.2, 15.7) at month 12; 13.2 (12.0, 16.5) at month 24
- **Mean (range) Hb (g/dL) in adults:** 12.7 (9.3, 15.7) at month 12; 13.2 (10.5, 17.3) at month 24

Data shown is based on the Full Analysis Set. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.
BL, baseline; Hb, hemoglobin; HbF, fetal hemoglobin; SE, standard error.

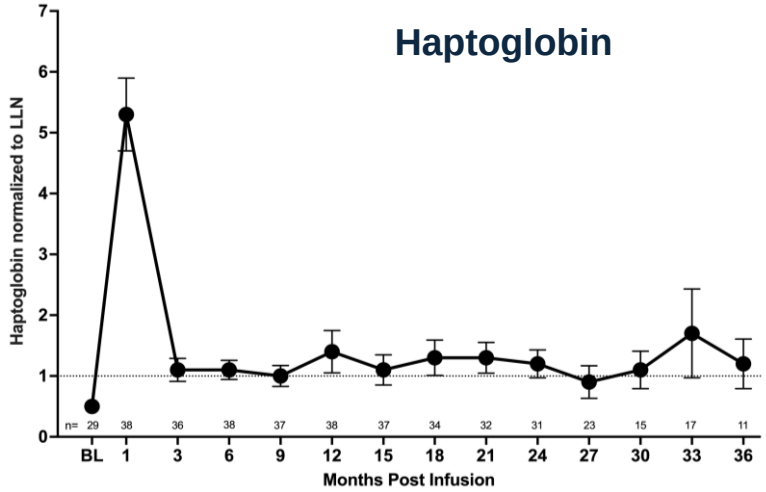
As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Markers of Hemolysis

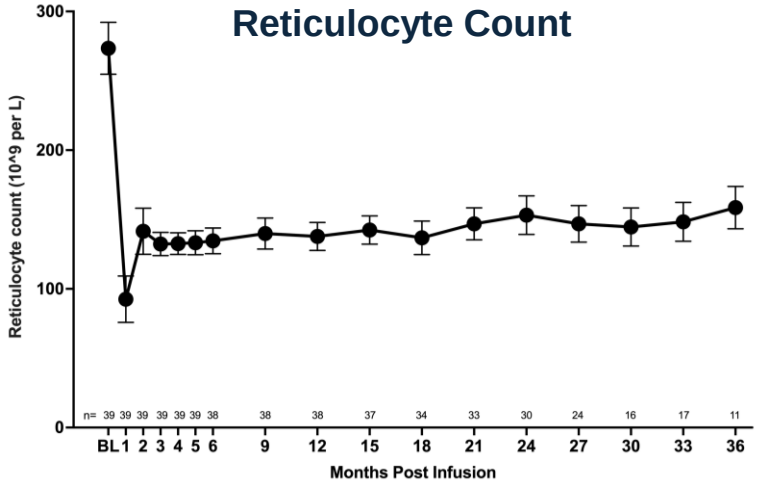
Lactate Dehydrogenase



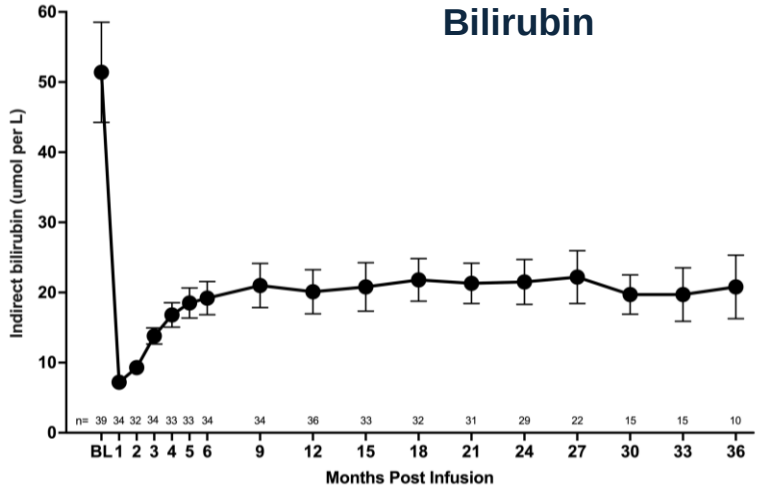
Haptoglobin



Reticulocyte Count



Bilirubin



Figures depict data for all timepoints where at least 5 participants have completed the specified visit.
BL, baseline; L, liter; LDH, lactate dehydrogenase; LLN, lower limit of normal; ULN, upper limit of normal.

As presented by Frangoul H, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Summary of Adverse Events

Post Exa-cel Adverse Events: Overview	Exa-cel N = 46 (FAS)
Participants with	
Any AEs, n (%)	46 (100.0)
AEs related to exa-cel, n (%)[a]	13 (28.3)
AEs related to busulfan, n (%)[a]	46 (100.0)
AEs Grade 3/4, n (%)	46 (100.0)
SAEs, n (%)	22 (47.8)
SAEs related to exa-cel, n (%)[a]	0
AEs leading to death, n (%)[b]	1 (2.2)
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets.
[a] includes related and possibly related AEs.
[b] One death, from respiratory failure due to COVID-19 infection, was not considered to be related to exa-cel.

Common Adverse Events: Preferred Term	Exa-cel N = 46 (FAS)
Nausea	32 (69.6)
Stomatitis	29 (63.0)
Vomiting	27 (58.7)
Febrile neutropenia	25 (54.3)
Headache	25 (54.3)
Abdominal pain	24 (52.2)
Pruritus	23 (50.0)

Table includes common adverse events occurring in ≥50% of participants.

Most adverse events occurred in the first 6 months with rates decreasing over time; safety is consistent in adolescents and adults

AE, adverse event; exa-cel, exagamglogene autotemcel; FAS, full analysis set; SAE, serious adverse event.

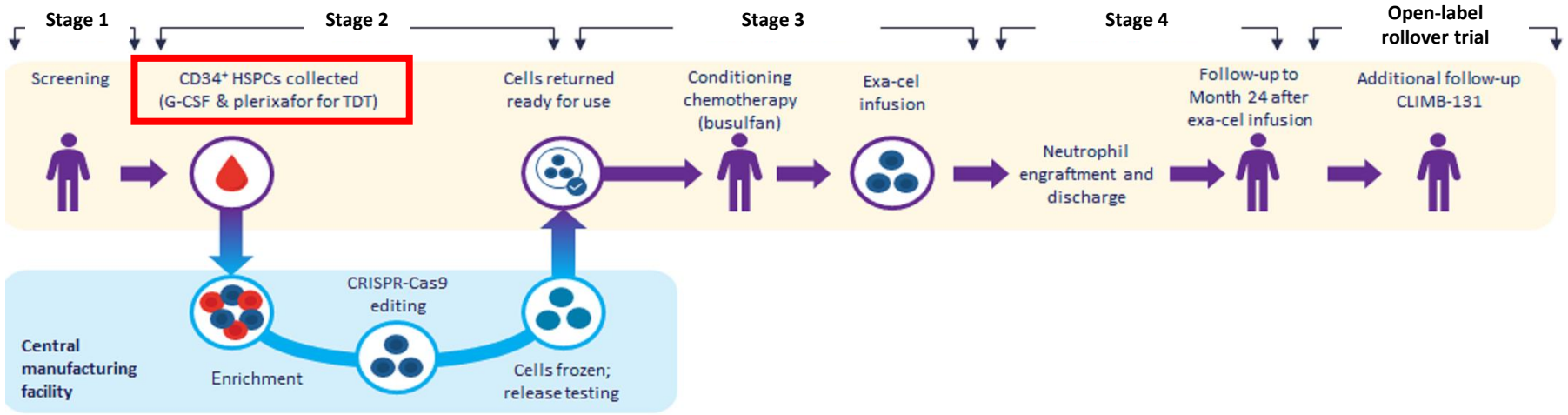
Conclusions

- **92.3% (36/39) achieved the primary endpoint and were free from VOC for ≥12 consecutive months** (VF12) (**mean duration of VOC-free period 27.9 months**, with the longest follow-up of 4.8 years (range 12.5 to 54.8) (PES))
- **97.4% (38/39) achieved secondary endpoint and were ≥12 consecutive months free from hospitalisation for VOC** (HF12) (mean duration of hospitalisation-free period 28.2 months (range 12.5 to 54.8) (PES))
- **Durable increases in mean HbF to ~40% with pancellular distribution resulted in total hemoglobin levels at normal or near normal levels**
- **Stable allelic editing in bone marrow and peripheral blood**, demonstrating durable editing of long-term HSCs
- **Clinically meaningful and durable improvements in hemolysis measures and quality-of-life assessments**
- There were no SAEs related to exa-cel; Safety profile is consistent with myeloablative busulfan conditioning and autologous HSCT (FAS)

Exa-cel, exagamglogene autotemcel; FAS, full analysis set; HbF, foetal haemoglobin; HF12, proportion of participants free from in-patient hospitalisation for severe VOCs for ≥12 consecutive months; HSCs, haematopoietic stem cells; HSCT, haematopoietic stem cell transplantation; PES, primary efficacy set; SAE, serious adverse event; SCD, sickle cell disease; VF12, proportion of participants free of severe VOCs for ≥12 consecutive months; VOC, vaso-occlusive crises.

As presented by Locatelli F, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Pivotal Phase 3 Trial of Exa-cel in Participants With TDT



Study Design	• Global, multicenter, open-label, single-arm, 2-year Phase 3 trial of a single infusion of exa-cel (NCT03655678)
Participants	• Dosing completed with **56 participants** dosed (as of data cutoff: March 2024) • **12 to 35 years of age with TDT, including β^0/β^0 genotypes, defined as a history of ≥100 mL/kg/year or ≥10 units/year of packed RBC transfusions in the previous 2 years**
Primary Efficacy Endpoint	• Proportion of participants transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL
Analyses	• **Full Analysis Set: participants who received exa-cel infusion.** • **Primary Efficacy Set:** participants who were **followed for ≥16 months after exa-cel infusion** (evaluable for primary & key secondary endpoints).

Participants who complete CLIMB THAL-111 could enrol in CLIMB-131 for 13 years of additional follow-up

Primary endpoint: assessed starting 60 days after last RBC transfusion for post-transplant support or TDT disease management.
CRISPR/Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; exa-cel, exagamglogene autotemcel; G-CSF, granulocyte colony-stimulating factor; HSPC, haematopoietic stem and progenitor cell; RBC, red blood cell; TDT, transfusion dependent β-thalassemia.

As presented by Locatelli F, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Demographics and Baseline Clinical Characteristics

	Full Analysis Set[a] N = 56	Primary Efficacy Set[b] N = 52
Age at screening, years, mean (SD)	21.2 (6.5)	21.5 (6.7)
≥12 and <18 years, n (%)	20 (35.7)	18 (34.6)
≥18 and ≤35 years, n (%)	**36 (64.3)**	**34 (65.4)**
Sex, n (%)		
Male	31 (55.4)	27 (51.9)
Female	25 (44.6)	25 (48.1)
Genotype, n (%)		
β^0/β^0	**22 (39.3)**	**19 (36.5)**
β^0/β^0-like (β^0/IVS-I-110; IVS-I-110/IVS-I-110)	13 (23.2)	12 (23.1)
Non-β^0/β^0-like	21 (37.5)	21 (40.4)
Historical RBC transfusions per year,[c] units, mean (range)	**37.0 (11, 71)**	**36.3 (11, 71)**

[a] Full Analysis Set includes participants who received exa-cel infusion.
[b] Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion (evaluable for primary & key secondary endpoints).
[c] Annualised over 2 years before signing of the informed consent form or latest screening for participants who underwent rescreening in CLIMB THAL-111.

Exa-cel, exagamglogene autotemcel; RBC, red blood cell; SD, standard deviation.

As presented by Locatelli F, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Treatment and Engraftment Results

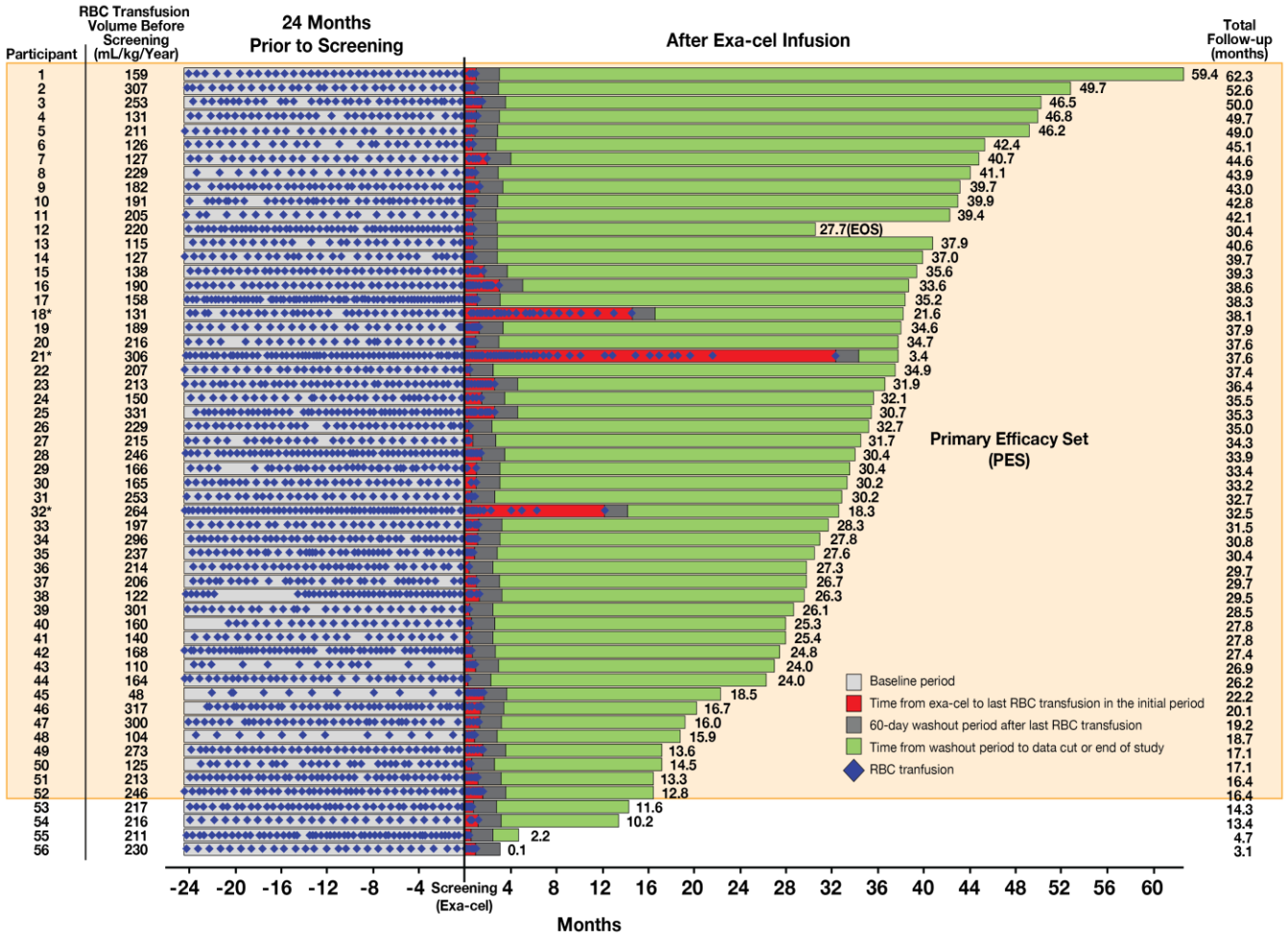
	Full Analysis Set[a] N = 56
Number of mobilisation cycles, median (range)	**1.0 (1, 4)**
Exa-cel dose: x 10^6 $CD34^+$ cells/kg, mean (range)	8.4 (3.0, 19.7)
Duration (months) of follow-up after exa-cel infusion,[b] mean (range)	32.3 (3.1, 62.3)
Neutrophil Engraftment[c]	
Time to neutrophil engraftment (days), median (range)	**29.0 (12, 56)**
Duration of neutropenia (absolute neutrophil count <500 cells/uL) (days), median (range)	20.5 (4, 48)
Platelet Engraftment[d]	
Time to platelet engraftment (days), median (range)	**43.5 (20, 200)**
Time to hospital discharge[e] (days), median (range)	**39.0 (23, 110)**

[a] Full Analysis Set includes participants who received exa-cel infusion.
[b] Duration of follow-up includes both CLIMB THAL-111 and CLIMB-131 trials.
[c] Defined as the first day of 3 consecutive measurement of absolute neutrophil count ≥500 cells/μL on 3 different days.
[d] Defined as the first day of 3 consecutive measurement of unsupported (no platelet transfusion in last 7 days) platelet count **≥20,000/μL** on 3 different days.
[e] Defined as the number of days from exa-cel infusion to hospital discharge following neutrophil engraftment.

Exa-cel, exagamglogene autotemcel.

As presented by Locatelli F, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Transfusion Status After Exa-cel Infusion



49 of 52 evaluable participants **(94.2%) achieved TI12** (PES). Mean duration of transfusion independence was 31.0 months (range 12.8 to 59.4)
- 32 of 34 evaluable **adults (94.1%) achieved TI12**
- 17 of 18 evaluable adolescents (94.4%) achieved TI12

All participants who achieved transfusion independence (TI12) remained transfusion independent through follow-up

Three participants that did not achieve TI12:

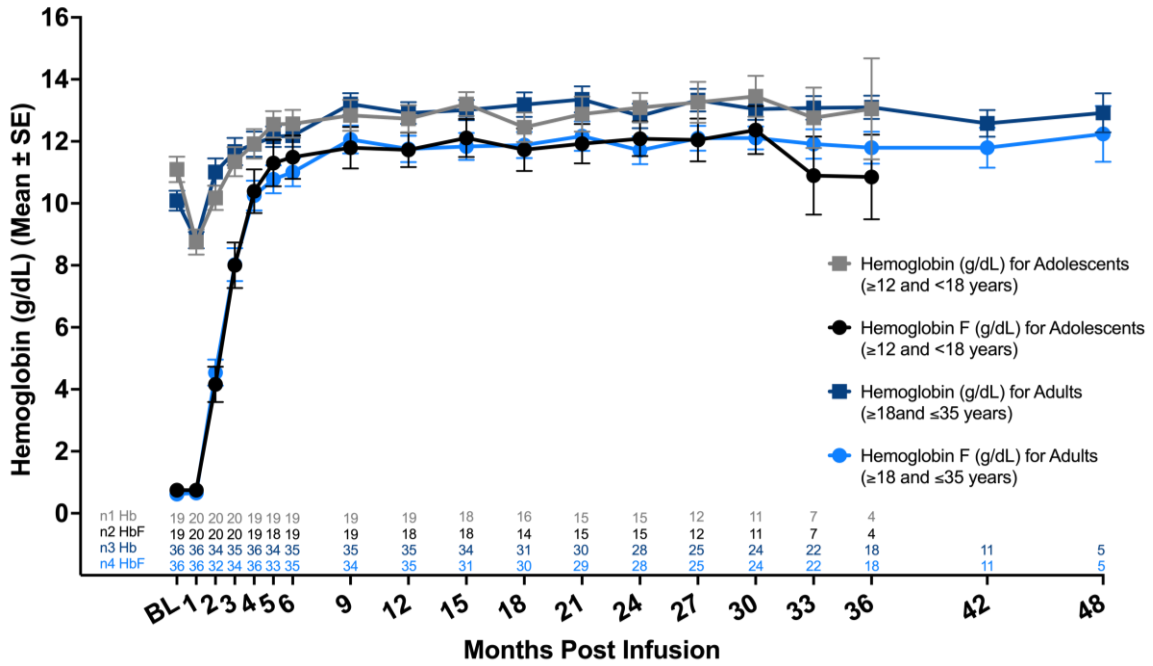
- 2 participants stopped RBC transfusions and subsequently achieved TI12 in CLIMB-131: transfusion independence duration of 21.6 and 14.3 months
- 1 participant stopped RBC transfusions and went 10.6 months without a transfusion before a transient episode of anemia (related to a viral gastroenteritis); participant has been transfusion free for 3.4 months since this event

* Participant who did not achieve TI12.
Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion (evaluable for primary & key secondary endpoints).

EOS, end of study; exa-cel, exagamglogene autotemcel; RBC, red blood cell; TI12; proportion of participants transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

Total Hemoglobin and Fetal Hemoglobin

Adults Compared to Adolescents



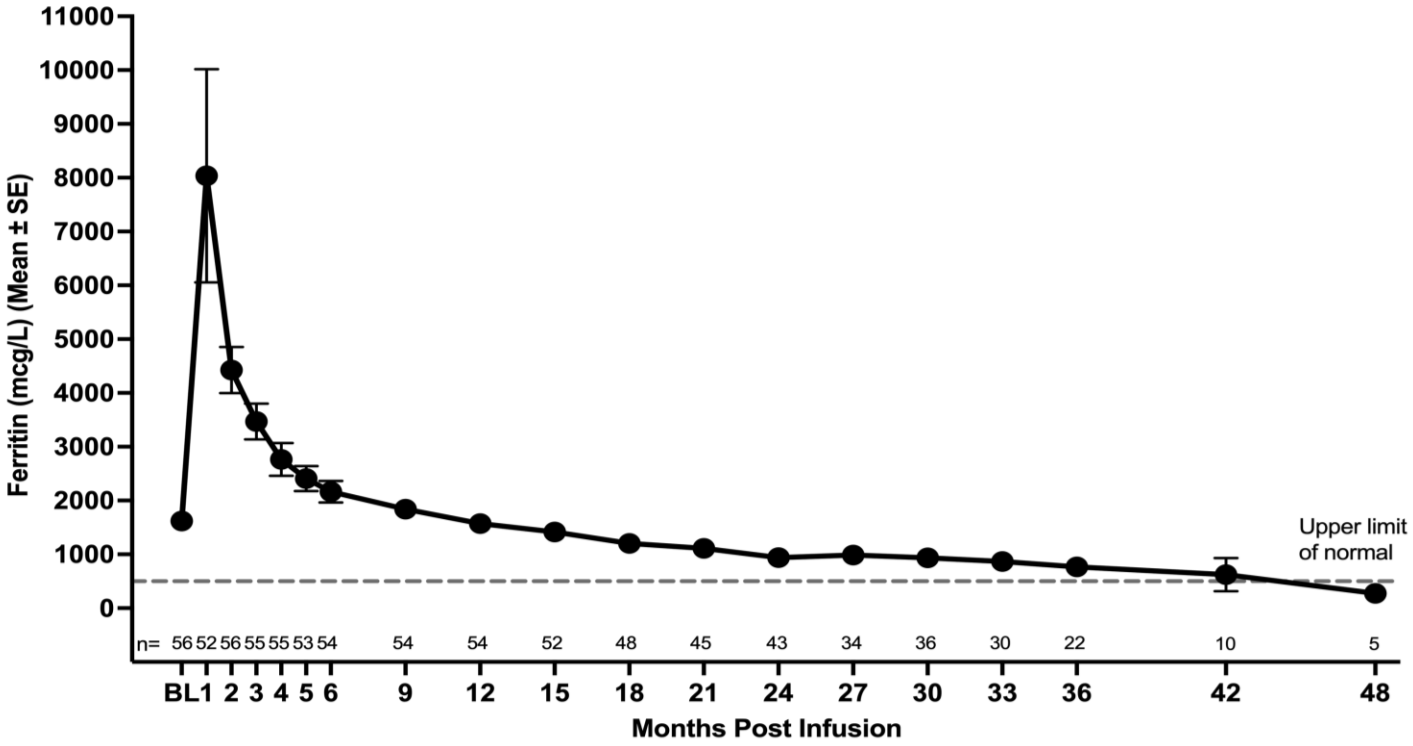
Data shown is based on the Full Analysis Set. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

BL, baseline; Hb, hemoglobin; HbF, fetal hemoglobin; SE, standard error.

As presented by Locatelli F, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Serum Ferritin Following Exa-cel Infusion

Serum Ferritin



- Serum ferritin, a measure of iron stored in tissues, decreased over time and reached below baseline by month 24
- **All 56 participants resumed iron removal therapy after exa-cel**, as expected given the pre-existing TDT related iron overload present at baseline
- **To date, 41.1% (23 of 56 participants) have been able to stop iron removal therapy**

Data shown is based on the Full Analysis Set. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

BL, baseline; exa-cel, exagamglogene autotemcel; TDT, transfusion dependent β-thalassemia; SE, standard error.

As presented by Locatelli F, et al. Presented at 29th Annual European Hematology Association; 16 June 2024.

Summary of Reported Adverse Events

Post-exa-cel AE Overview	Exa-cel N = 56
Participants with	
Any AEs, n (%)	56 (100.0)
AEs related to exa-cel, n (%)[a]	16 (28.6)
AEs related to busulfan, n (%)[a]	55 (98.2)
AEs Grade 3/4, n (%)	50 (89.3)
SAEs, n (%)	19 (33.9)
SAEs related to exa-cel, n (%)[a,b]	2 (3.6)
AEs leading to death, n (%)	0
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets.
[a] Includes related and possibly related AEs (or SAEs).
[b] SAEs previously reported in 2 participants and fully resolved. One participant had SAEs starting peri-engraftment and in context of HLH (HLH, acute respiratory distress syndrome, and headache were related to exa-cel; idiopathic pneumonia syndrome was related to exa-cel and busulfan). One participant had SAEs of delayed neutrophil engraftment and thrombocytopenia both related to exa-cel and busulfan (neutrophil engraftment achieved on Day 56 without use of backups cells).

Common Adverse Events: Preferred Term	Exa-cel N = 56
Febrile neutropenia	34 (60.7)
Headache	31 (55.4)
Stomatitis	30 (53.6)
Thrombocytopenia	25 (44.6)
Anaemia	25 (44.6)
Nausea	24 (42.9)
Mucosal inflammation	23 (41.1)
Vomiting	23 (41.1)

Table includes common AEs occurring in ≥40% of participants.

7 (12.5%) participants had VOD events
- All events were related to busulfan conditioning
- All events resolved after defibrotide treatment without any participant receiving ventilatory support or dialysis

Most adverse events occurred in the first 6 months with rates decreasing over time; safety is consistent in adolescents and adults

Data shown is based on the Full Analysis Set.
AE, adverse event; exa-cel, exagamglogene autotemcel; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; SAE, serious adverse event; VOD, venoocclusive liver disease.

Conclusions

- **94.2% (49/52) achieved the primary endpoint and were transfusion independent for ≥ 12 consecutive months** (TI12) (PES). Mean duration of transfusion independence was 31.0 months, with the longest follow-up up to 5 years (range 12.8 to 59.4)
- **Durable increases in total hemoglobin to normal or near normal levels**
- **Stable allelic editing in bone marrow and peripheral blood**, demonstrates durable editing of long-term HSCs thus-far
- **Clinically meaningful improvements in measures of iron overload and quality-of-life were observed**
- Serious adverse reactions attributed to exa-cel occurred in 2 patients with TDT, all resolved (FAS)
- Safety profile is consistent with myeloablative busulfan conditioning and autologous HSCT

Exa-cel, exagamglogene autotemcel; FAS, full analysis set; HSCs, hematopoietic stem cells; HSCT, hematopoietic stem cell transplantation; PES, primary efficacy set; SAE, serious adverse event; TDT, transfusion dependent β-thalassemia.

THERAPEUTIC INDICATIONS

Transfusion-dependent β-thalassemia (TDT)

CASGEVY is indicated for the treatment of transfusion dependent β-thalassemia in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Sickle cell disease (SCD)

CASGEVY is indicated for the treatment of severe sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

CASGEVY summary of product characteristics. Vertex Pharmaceuticals (Ireland) Limited. February 2024.

CONTRAINDICATIONS AND SPECIAL POPULATIONS

Contraindications to **mobilisation** and **myeloablative conditioning** agents must be considered.

CASGEVY should not be used in patients with active **HIV-1**, **HIV-2**, **HBV**, or **HCV**.

Treatment with CASGEVY is not recommended in patients who have received a **prior allogeneic** or **autologous** HSC transplant.

CASGEVY has not been studied in patients **> 35 years** of age.

CASGEVY has not been studied in patients with **renal impairment** (defined as eGFR < 60 mL/min/1.73 m^2) or **hepatic impairment**.

The safety and efficacy of CASGEVY in patients **< 12 years** of age has not been established.

eGFR, estimated glomerular filtration rate.

CASGEVY summary of product characteristics. Vertex Pharmaceuticals (Ireland) Limited. February 2024.

PREPARATION FOR APHERESIS AND CONDITIONING

SCD

- Prior to apheresis it is recommended that **SCD** patients receive RBC exchange or simple transfusion(s) with a goal of maintaining hemoglobin S (HbS) levels **< 30%** of total Hb while keeping total Hb concentration **≤ 11 g/dL**.
- It is recommended that patients receive RBC exchange or simple transfusion(s) for at least the **8 weeks prior to** the **initiation of myeloablative conditioning** with a goal of maintaining HbS levels **< 30%** of total Hb while keeping total Hb concentration **≤ 11 g/dL**.
- Disease modifying therapies (e.g., **hydroxyurea/hydroxycarbamide**, ~~**crizanlizumab**~~, ~~**voxelotor**~~) must be **discontinued 8 weeks before** the planned **start of mobilisation and conditioning**.
- **Iron chelation therapy** must be stopped at least **7 days prior** to myeloablative conditioning.

TDT

- Prior to the apheresis procedure it is recommended that **TDT** patients receive RBC transfusion(s) with a goal to maintain total hemoglobin (Hb) concentration **≥ 11 g/dL**.
- It is recommended that **TDT** patients maintain total Hb concentration ≥ 11 g/dL for **60 days prior** to **myeloablative conditioning**.
- **Iron chelation therapy** must be stopped at least **7 days prior** to myeloablative conditioning.

CASGEVY summary of product characteristics. Vertex Pharmaceuticals (Ireland) Limited. February 2024.

CELL COLLECTION

- A total collection target of at least **20 × 10^6 $CD34^+$ cells/kg** is recommended for product manufacture.

- In addition, at least **2 × 10^6 $CD34^+$ cells/kg** are required to be collected for a back-up collection of unmodified rescue cells, which may be needed for rescue treatment following:
  Compromise of CASGEVY after initiation of myeloablative conditioning and before CASGEVY infusion;
  Neutrophil engraftment failure;
  Loss of engraftment after infusion with CASGEVY.

CASGEVY summary of product characteristics. Vertex Pharmaceuticals (Ireland) Limited. February 2024.