Exagamglogene Autotemcel (Exa cell) zur Therapie der transfusionsabhängigen β-Thalassemie

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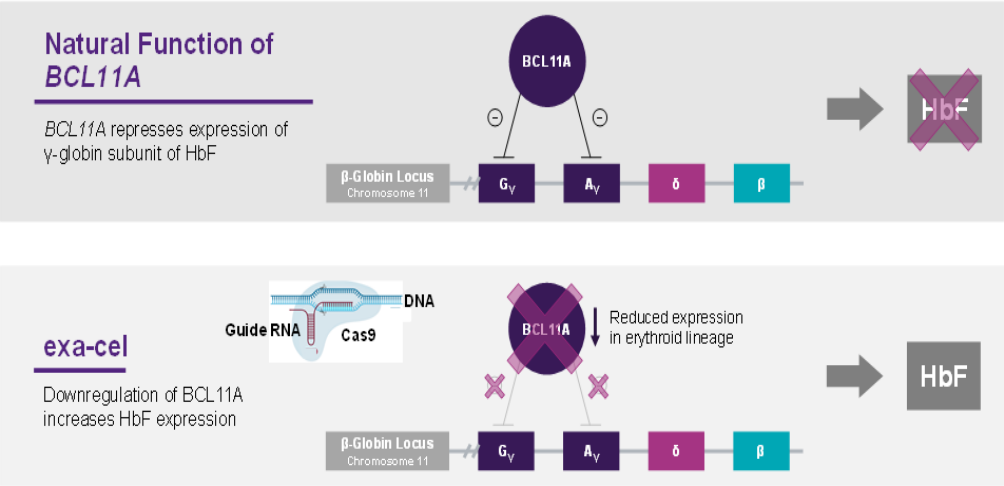
Wirkmechanismus von Exa-cel (geneditierte CD34+ Stammzellen)

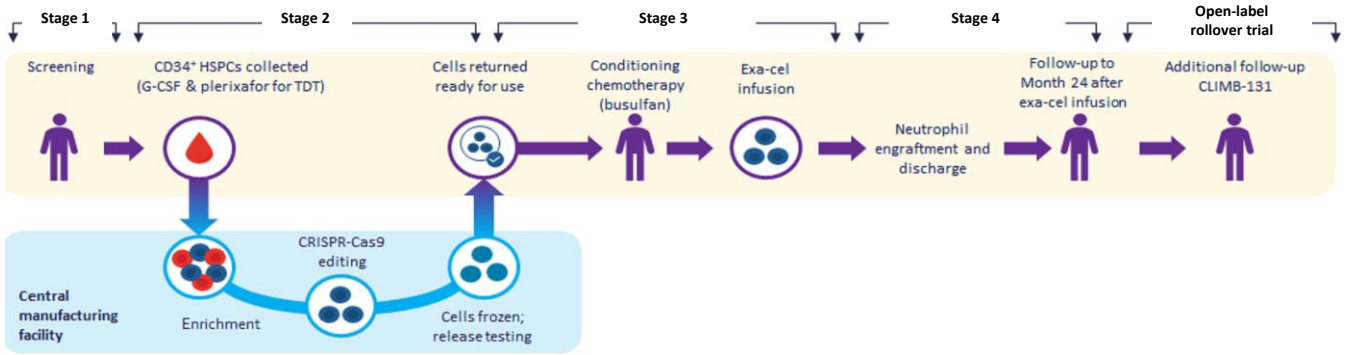


- **Exa-cel** mechanism of action: **reactivation of HbF production**, which is known to result in **reduced morbidity and mortality** in patients with hemoglobinopathy and hereditary persistence of HbF[2,3]
- **Exa-cel** is produced using non-viral, *ex vivo CRISPR Cas9* editing of the erythroid-specific enhancer region of BCL11A in CD34^{+} HSPCs to **reduce erythroid-specific expression of *BCL11A*, resulting in reactivation of HbF**
- Infusion of **exa-cel increases HbF** to levels resulting in normal/near normal total Hb levels (**mean 13.1 g/dL**), **eliminating the need for RBC transfusions**[1]

***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; **Hb,** hemoglobin; **HbF,** fetal hemoglobin; **HSPC,** hematopoietic stem and progenitor cell; **RBC,** red blood cells; **RNA,** ribonucleic acid; **TDT,** transfusion dependent β-thalassemia.

1. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676. 2. Musallam, KM, et al. *Blood*. 2013;121:2199-2212. **3**. Bauer DE, et al. *Curr Opin Gene Dev*. 2015;33:62-70.

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



Study Design	• Multicenter, open-label, single-arm, Phase 3 trial of a single infusion of exa-cel (NCT03655678) • Participants who complete CLIMB THAL-111 can enroll in CLIMB-131 for 13 years of additional follow-up (NCT04208529)
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 weighted average hemoglobin ≥9g/dL
Previously Presented Pre-specified Interim Analysis (as of January 2023)	• Already published: Trial met the primary and the key secondary endpoints[1] • Demonstrated favorable benefit/risk profile of exa-cel supporting global regulatory approvals (European Union, United States, United Kingdom, Kingdom of Saudi Arabia, Bahrain)

Updated data from CLIMB THAL-111 is presented, demonstrating durable clinical benefit with the longest follow-up of >5 years

CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; **exa-cel,** exagamglogene autotemcel; **G-CSF,** granulocyte colony-stimulating factor; **HSPC,** hematopoietic stem and progenitor cell; **M24,** month 24; **RBC,** red blood cell; **TDT,** transfusion dependent β-thalassemia.

1. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676.

Patientencharakteristik

	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] Annualized 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.

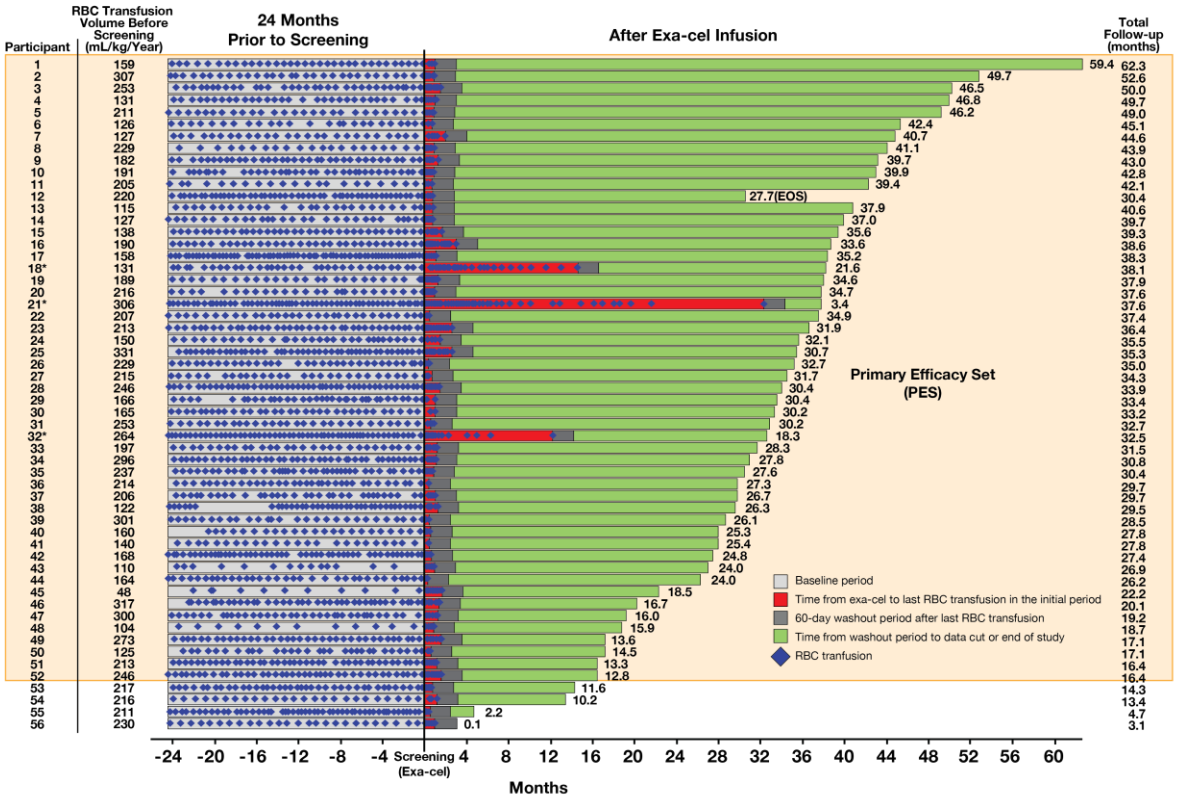
Ergebnisse

	Full Analysis Set[a] N = 56
Number of mobilization cycles, median (range)	1.0 (1, 4)
Exa-cel dose: 10^6 x $CD34^+$ 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.

Stabile Transfusionunabhängigkeit nach After Exa-cel:
bei 94.2% der Patienten für derzeit bis zu 5 Jahre



***** 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.

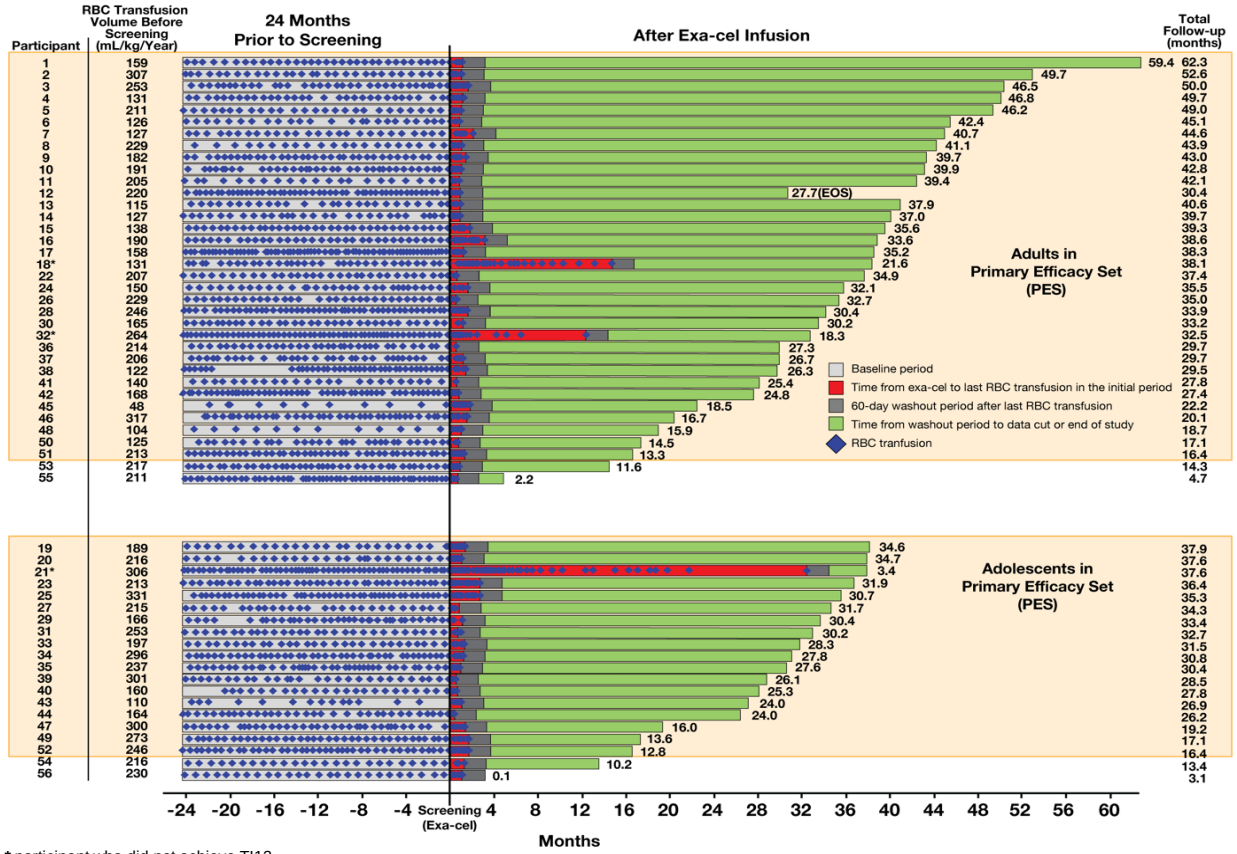
Durable transfusion independence (TI12) achieved in pivotal study CLIMB THAL-111

- 49 of 52 evaluable participants (94.2%) achieved TI12
- Mean duration of transfusion independence 31.0 months (range 12.8 to 59.4)

Three participants that did not achieve TI12 in pivotal study CLIMB THAL-111 had substantial clinical benefit in the meantime

- 2 participants stopped RBC transfusions and 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

Kein Unterschied zwischen Erwachsenen und Kindern/ Jugendlichen



***** participant who did not achieve TI12

Durable transfusion independence (TI12) achieved in both adults and adolescents in pivotal study CLIMB THAL-111

- 32 of 34 evaluable adults (94.1%) achieved TI12
- 17 of 18 evaluable adolescents (94.4%) achieved TI12

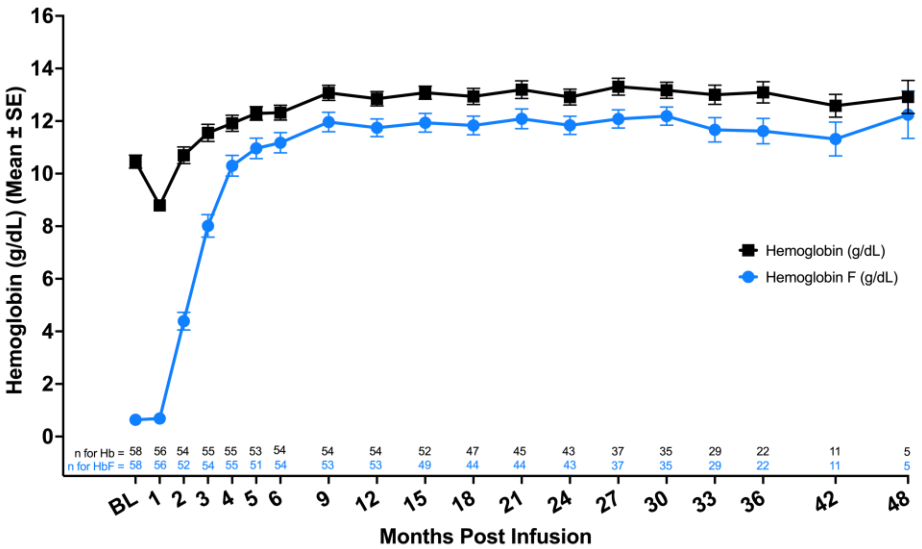
Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion (evaluable for primary & key secondary endpoints).
EOS, end of study; **exa-cel,** exagamglogene autotemcel; **RBC,** red blood cell; **TI12;** proportion of participants transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

Dauerhafter Anstieg des Gesamt Hämoglobins und des HbF auf Normalwerte bei Erwachsenen und päd. Patienten

Total Hemoglobin and Fetal Hemoglobin

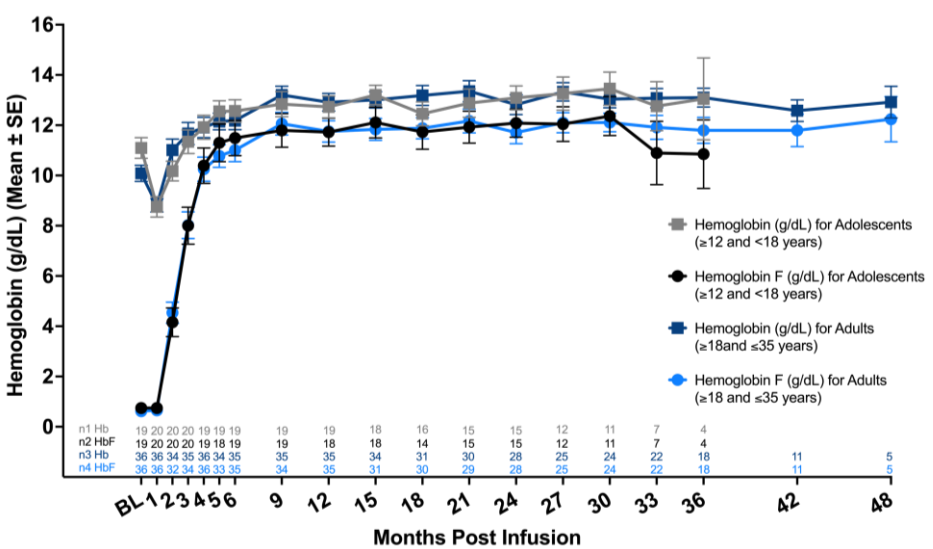
A

All Participants



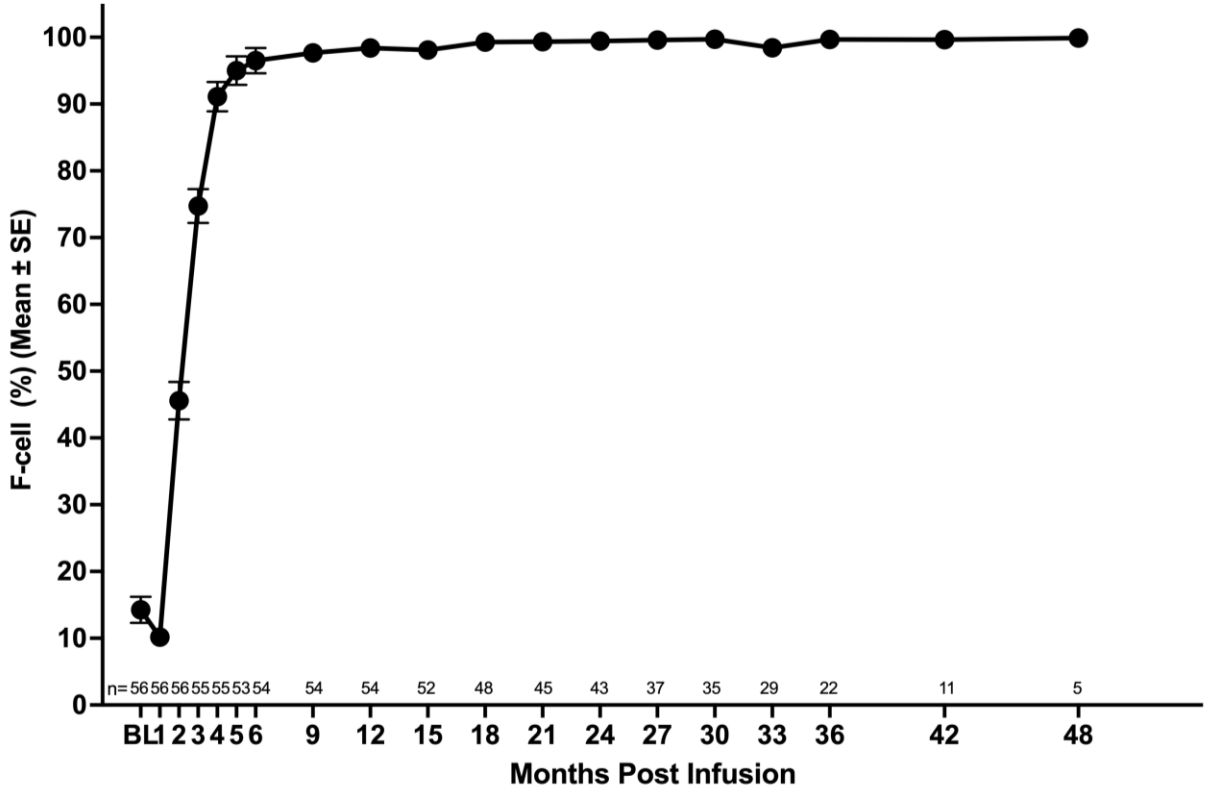
B

Adults Compared to Adolescents



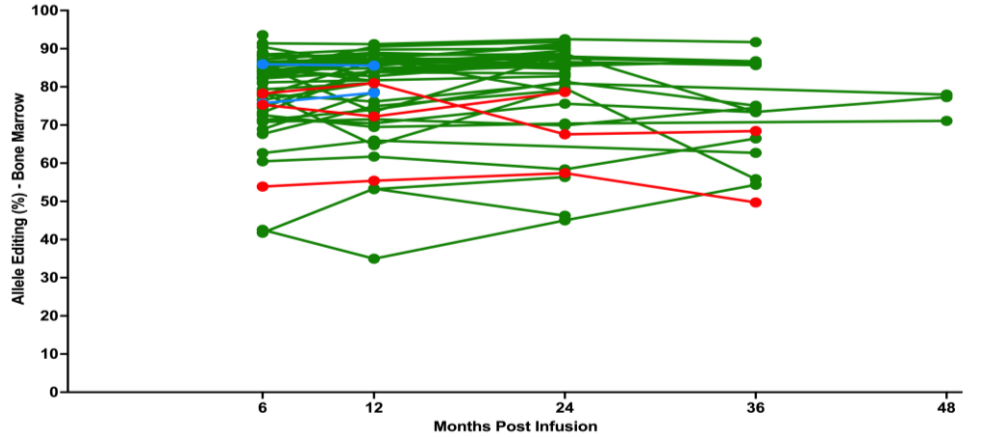
Data shown is based on the Full Analysis Set. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.
BL, baseline; **SE,** standard error.

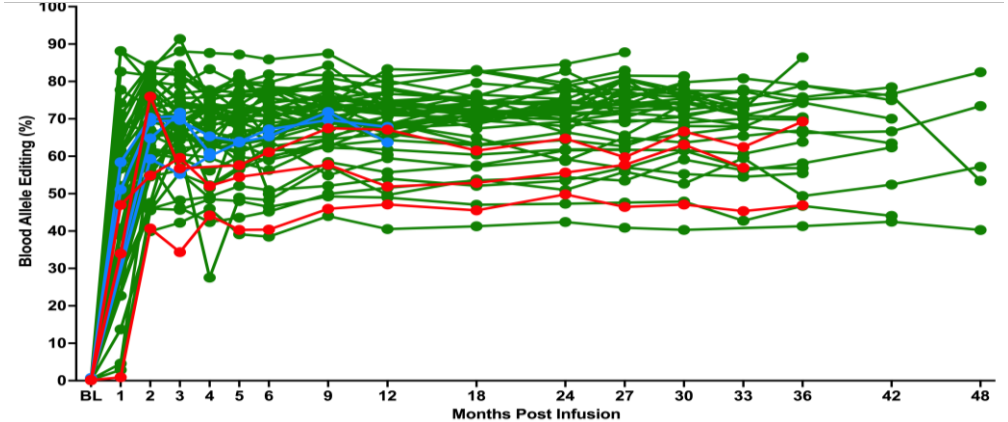
Stabiler Anteil von >99% Hb F tragenden Zellen imVerlauf



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; **HbF,** fetal hemoglobin; **SE,** standard error.

Allel Editing bleibt während der ganzen Beobachtungszeit stabil (Blut und Knochenmark): spricht für Langzeiteffekt





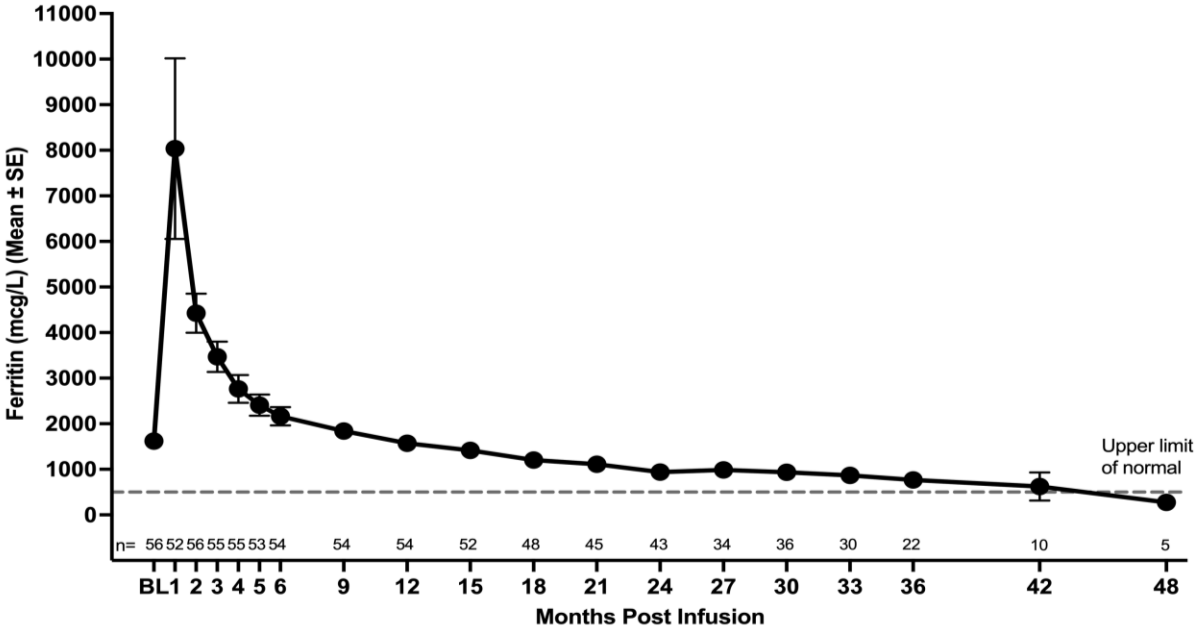
Participants NOT in Primary Efficacy Set

TI12 Not Achieved in CLIMB THAL-111

TI12 Achieved in CLIMB THAL-111

Data shown is based on the Full Analysis Set.
BL:, baseline; **exa-cel,** exagamglogene autotemcel; **TI12;** participants transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

Zusätzlicher Nutzen: Reduktion des Serum Ferritins; Chelattherapie konnte teilweise beendet werden



- **Serum ferritin**, decreased over time and **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; **SE,** standard error.

Patient Reported Outcomes: subjektive Verbesserung

- **PROs demonstrated substantial and clinically meaningful improvements in health-related quality of life**
  - Clinically meaningful improvements seen by month 6 to month 12 and sustained over time
- **Improvements seen across all instruments**
  - PRO tools specific to general well-being, HSCT, and TDT
- **Improvements seen across all domains**
  - Assessments of general health, physical, emotional, social, and functional well-being

Data shown is based on the Full Analysis Set.
exa-cel, exagamglogene autotemcel; **HSCT,** hematopoietic stem cell transplantation; **PROs,** patient reported outcomes; **TDT,** transfusion dependent β-thalassemia.

Nebenwirkungsprofil entspricht demjenigen einer autologen HSCT mit myeloablativer Busulfankonditionierung (targeted Bux, AUC 90 000)

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 AE: Preferred Term	Exa-cel N = 56
Febrile neutropenia	34 (60.7)
Headache	31 (55.4)
Stomatitis	30 (53.6)
Thrombocytopenia	25 (44.6)
Anemia	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

- **Exa-cel** is the **first approved CRISPR-Cas9** gene editing therapy
- **94.2% achieved transfusion independence** which was durable **for up to 5 years**
- 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**
- Clinically meaningful improvements in **measures of iron overload** and **quality-of-life**
- **Safety profile consistent** with **myeloablative busulfan conditioning** and **autologous HSCT; no deaths or malignancies**
- Efficacy and safety are **consistent among adolescents and adults**

Exa-cel is an alternative treatment to Allo SCT in certain patients

CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; **HbF,** fetal hemoglobin; **HSCs,** hematopoietic stem cells; **HSCT,** hematopoietic stem cell transplantation; **TDT,** transfusion dependent β-thalassemia.

Derzeitige Verfügbarkeit

- **Exa-cel hat eine Zulassung durch die EMA für:**

Transfusionsabhängige b- Thalassämie-Patienten/ Sichelzell-Patienten mit schweren Krisen >=12 Jahren ohne HLA identischen verwandten Spender

- **Derzeit auf Basis eine Einzelantrages an die betreffende Kasse.**
- **Antrag muss den Handreichungen des MDKs genügen**
- **Die ausführende Klinik muss zertifiziert und vom MDK geprüft worden sein.**
- **Voraussetzungen:**

Apherese-Einheit, GMP Labor (Kryokonservierung, Qualitätsmanagement), Einheit für Stammzelltransplantation

CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; **HbF,** fetal hemoglobin; **HSCs,** hematopoietic stem cells; **HSCT,** hematopoietic stem cell transplantation; **TDT,** transfusion dependent β-thalassemia.

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