HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Exagamglogene autotemcel

(Exa-cel, Casgevy®)

Health Technology Assessment

Final report

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Health Technology Assessment

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List of Abbreviations

AEs ..... adverse events
ASCT..... Autologous stem cell transplant
ASH..... Amercian Society of Hematology
AT..... Austria
ATMP..... advanced therapy medicinal product
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaft
BMT ..... Bone Marrow Transplantation
BMTS ..... Bone Marrow Transplantation Subscale
CADTH ..... Canadian Agency for Drugs and Technologies in Health
CBC..... complete blood count
CRISPR ..... Clustered Regularly Interspaced Short Palindromic Repeats
DCEA..... distributional cost-effectiveness analysis
DGKJ ..... German Society for Paediatrics and Adolescent Medicine
DNA..... Deoxyribonucleic acid
EMA ..... European Medicines Agency/Europäischen Arzneimittelagentur
ERA..... Environmental Risk Assessment
EUnetHTA ..... European Network for Health Technology Assessment
EQ VAS..... EuroQol Visual Analogue Scale
evLY..... equal-value life years
Exa-cel..... Exagamglogene autotemcel
FACT-G..... Functional Assessment of Cancer Therapy–General
G-CSF ..... granulocyte-colony stimulating factor/Granulozyten-Kolonie-stimulierende Faktor
GPOH ..... Guideline of the Society for Paediatric Oncology and Haematology
Hb..... haemoglobin
HbA..... adult haemoglobin
HBB..... beta globin gene
HbF ..... fetal haemoglobin/fetalem Hämoglobin
HbS..... Haemoglobin S, sickle haemoglobin/Sichelzellhämoglobin
HbSC..... haemoglobin SC disease
HDT..... health technology developer
HLA ..... human leukocyte antigen/Humanes Leukozyten-Antigen
HSC..... haematopoietic stem cells
HSCT ..... haematopoietic stem cell transplantation
HSPC ..... haematopoietic stem and progenitor cells/hämatopoetische Stamm- und Vorläufer-zellen
HPLC..... high-performance liquid chromatography
INATHA..... International HTA Database (INAHTA)
ICER ..... Institute for Clinical and Economic Review
IEF ..... isoelectric focusing
IQWiG..... Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
kg..... kilogram/Kilogramm
mcg..... microgram

MIT ..... Massachusetts Institue of Technology
mg..... milligram
MRI ..... magnetic resonance imaging
NHS..... National Health Service
NICE..... National Institute for Health and Care Excellence
PCR..... polymerase chain reaction
QALY ..... quality-adjusted life years
QoL ..... quality of life
PRIME ..... Priority Medicines Scheme
PICo ..... Problem, Interest, Context
PROs ..... patient reported outcomes
RBC..... red blood cell
SAE..... severe adverse event
SCD..... sickle cell disease/Sichelzellkrankheit
SCT ..... stem cell transplantation
SoC ..... standard of care
STIKO..... Ständige Impfkommission
TDT ..... transfusion-dependent β-thalassemia/transfusionsabhängige β -Thalassämie
TIF ..... Thalassaemia International Federation
TRM..... Transplant-related mortality
UE ..... unerwünschtes Ereignis
VAS ..... visual analogue scale
VOCs..... vaso-occlusive crises/vaso-okklusive Krisen
VOD ..... veno-occlusive disease
WBC..... white blood cell

Zusammenfassung

Überblick über das neue Arzneimittel

bedingte Marktzulassung Feb 2024

1. CRISPR/Cas9 Gentherapie

2 Indikationen: transfusionsabhängigen β-Thalassämie (TDT) & schwere From der Sichelzellkrankheit (SCD)

Exagamglogene autotemcel (Exa-cel, Casgevy®) ist die erste CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-basierte Therapie, die am 9. Februar 2024 von der Europäischen Arzneimittelagentur (European Medicines Agency, EMA) eine bedingte Marktzulassung erhielt. Das von Vertex Pharmaceuticals vertriebene Medikament ist als "Advanced Therapy Medicinal Product" (ATMP) klassifiziert und hat für zwei Indikationen den Status eines Orphan Drugs erhalten. Die Zulassung umfasst die Behandlung der transfusionsabhängigen β-Thalassämie (transfusion-dependent β-thalassemia, TDT) und der schweren Form der Sichelzellkrankheit (sickle cell disease, SCD) bei Patient*innen ab zwölf Jahren, die grundsätzlich für eine hämatopoetische Stammzelltransplantation geeignet wären, jedoch keinen Humanes Leukozyten-Antigen (HLA)-kompatiblen verwandten Spender zur Verfügung haben. Bei SCD müssen zusätzlich rezidivierende vaso-okklusive Krisen vorliegen.

komplexer Herstellungsprozess: Stammzellgewinnung & Modifikation

Die Therapie basiert auf einem komplexen Herstellungs- und Behandlungsprozess. Zunächst werden patient*inneneigene CD34+ hämatopoetische Stamm- und Vorläuferzellen (hematopoietic stem and progenitor cells, HSPCs) durch Mobilisierung und Apherese gewonnen. Für die Herstellung von Exa-cel wird eine Sammlung von mindestens 20 Millionen ($20 \times 10^{\wedge}6$) CD34+-Zellen pro Kilogramm (kg) Körpergewicht angestrebt. Zusätzlich müssen mindestens 2 Millionen ($2 \times 10^{\wedge}6$) CD34+-Zellen pro kg als unmodifizierte „Rescue-Zellen“ gesammelt werden. Die gewonnenen Zellen werden mittels der CRISPR-Cas9-Technologie genetisch modifiziert, indem die erythroidspezifische Enhancer-Region des BCL11A-Gens editiert wird. Dies führt zu einer erhöhten γ-Globin-Expression und einer gesteigerten Produktion von fetalem Hämoglobin (HbF) in den Erythrozyten. Die modifizierten Zellen werden dann nach myeloablativer Konditionierung als einmalige Infusion verabreicht, wobei die empfohlene Mindestdosis 3 Millionen ($3 \times 10^{\wedge}6$) CD34+-Zellen pro kg Körpergewicht beträgt.

aufwendige Vor- & Nachbehandlung

Die Behandlung erfordert eine umfassende Vorbereitung und Nachsorge. Bei Patient*innen mit TDT muss der Hämoglobinwert vor der Mobilisierung auf mindestens 11 g/dl eingestellt werden. Es wird empfohlen, bei Patient*innen mit schwerer SCD mindestens acht Wochen vor Behandlungsbeginn einen Erythrozytenaustausch durchzuführen oder einfache Transfusionen zu verabreichen, um den Anteil an Sichelzellhämoglobin (HbS) auf unter 30% zu senken. Krankheitsmodifizierende Therapien müssen acht Wochen vor Behandlungsbeginn abgesetzt werden. Die myeloablative Konditionierung erfolgt über vier Tage mit Busulfan, wobei die Plasmaspiegel engmaschig überwacht werden müssen.

Transfusionsabhängige β-Thalassämie (TDT)

Indikation und therapeutisches Management

TDT:

Krankheitsbild &

Die β-Thalassämie ist eine erbliche Hämoglobinopathie, die durch eine reduzierte oder fehlende Produktion von Beta-Globin-Ketten gekennzeichnet ist, was auf Mutationen im HBB-Gen zurückzuführen ist. Der Schweregrad der Erkrankung korreliert direkt mit dem verbleibenden Anteil der Beta-Globin-

Produktion. Patient*innen mit TDT haben eine minimale bis vollständig fehlende Produktion von Beta-Globin-Ketten und folglich wenig bis kein adultes Hämoglobin (HbA). Die Erkrankung manifestiert sich meist im Säuglingsalter, üblicherweise zwischen dem sechsten und zwölften Lebensmonat, wenn der physiologische Übergang von fetalem zu adultem Hämoglobin erfolgt.

Komplikationen

Ohne adäquate Behandlung entwickeln Patient*innen schwerwiegende Komplikationen. Klinische Manifestationen umfassen schwere Anämie, Komplikationen der Hämolyse und extramedulläre Blutbildung. Zu den charakteristischen Symptomen gehören Blässe, Ikterus, Wachstumsstörungen und eine ausgeprägte Hepatosplenomegalie. Die extramedulläre Blutbildung führt häufig zu Skelettveränderungen, insbesondere im Gesichtsbereich. Regelmäßige Transfusionen sind erforderlich, die jedoch eine Eisenüberladung verursachen können, was zu Schädigungen von Organen wie Herz, Leber und endokrinen Drüsen führt. Kardiale Komplikationen stellen die häufigste Todesursache dar.

Inzidenz, Prävalenz und geschätzte Zahl der Patient*innen in Österreich

Österreich (AT):

gesamt 60-79 TDT Patient*innen (Pat.)

Exa-cel → ~15 Pat.

Die geschätzte Gesamtzahl der TDT-Patient*innen (einschließlich Einheimische und Menschen mit Migrationshintergrund) liegt bei 60 bis 79 in Österreich. Laut klinischen Expert*innen und dem Hersteller könnten in den nächsten drei Jahren etwa 15 TDT-Patient*innen für eine Behandlung mit Exa-cel in Frage kommen, davon drei bis vier Patient*innen im Alter von zwölf bis 17 Jahren.

Standardtherapie (SoC) und alternative Behandlungsmöglichkeiten bei TDT

Standardtherapie (SoC) in AT: Erythrozytenkonzentraten & Eisenchelattherapie

Die Standardtherapie (SoC) für TDT in Österreich umfasst die Verabreichung von Erythrozytenkonzentraten und eine Eisenchelattherapie. Zusätzlich stehen laut Leitlinien kausale (autologe Stammzelltransplantation, Hydroxyurea, Luspatercept) und symptomatische Behandlungsoptionen (Chelattherapie und Management von Sekundärerkrankungen) zur Verfügung, die meist lebenslang erforderlich sind.

Klinische Wirksamkeit und Sicherheit

einarmige Phase 2/3 Studie

Die Wirksamkeit und Sicherheit von Exa-cel bei TDT Patient*innen wurden in einer offenen, einarmigen Phase 2/3 Studie untersucht (CTX001-111).

TDT Studie:

91% transfusionsunabhängig

In der CTX001-111-Studie wurden 52 Patient*innen im Alter von zwölf bis 35 Jahren mit Transfusionsabhängigkeit eingeschlossen. Das Durchschnittsalter betrug 21,1 Jahre, und die Geschlechterverteilung war nahezu ausgeglichen. Die Patient*innen benötigten vor Therapiebeginn im Median 35 Transfusionen pro Jahr. Von den 52 eingeschlossenen Patient*innen wiesen 35 eine ausreichende Nachbeobachtungszeit (16 Monate) für die Analyse des primären Endpunkts auf. 91% der Patient*innen (32 von 35) erreichten den primären Endpunkt der Transfusionsunabhängigkeit, definiert als ein Hämoglobinwert von mindestens 9 g/dl über zwölf aufeinanderfolgende Monate ohne Transfusionen. Die durchschnittliche Dauer der Transfusionsunabhängigkeit betrug 22,5 Monate (Bereich: 13,3 bis 45,1 Monate).

Verbesserung der Lebensqualität (QoL)

Die Lebensqualität der Patient*innen verbesserte sich signifikant, mit einem Anstieg des EuroQol Visual Analogue Scale (EQ VAS) Scores um durchschnittlich 10,2 Punkte nach 24 Monaten sowie Verbesserungen im Functional Assessment of Cancer Therapy–General (FACT-G) Score um 10,3 Punkte und im Bone Marrow Transplantation (BMT) Score um 6,8 Punkte.

Das Sicherheitsprofil zeigte, dass alle Patient*innen mindestens ein unerwünschtes Ereignis (UE) erfuhren, meist mit einer Schwere von Grad 1 oder 2. Nebenwirkungen (Grad 3 oder 4) traten bei etwa 95% der Patient*innen auf und waren hauptsächlich auf die Busulfan-Konditionierung zurückzuführen. Schwerwiegende Nebenwirkungen (SUE) traten dabei bei 17 Patient*innen (32,7 %) auf, davon bei zwei Patient*innen (3,8 %) im Zusammenhang mit Exa-cel und bei 9 Patient*innen (17,3 %) im Zusammenhang mit der Busulfan-Konditionierung. Die meisten UE und SuE wurden innerhalb der ersten sechs Monate nach der Konditionierung und Infusion von Exa-cel beobachtet, und die Häufigkeit von (S)UE ging danach zurück.

Sicherheitsprofil → häufige Nebenwirkungen:

Stomatitis (40%), febrile Neutropenie (54%) und Thrombozytopenie (35%)

Sichelzellkrankheit (SCD)

Indikation und therapeutisches Management

Die SCD ist eine vererbte Hämoglobinopathie, die auf einer Punktmutation im Beta-Globin-Gen basiert, welches das HbS hervorbringt. Diese Erkrankung tritt auf, wenn HbS im homozygoten Zustand oder als heterozygote Kombination mit anderen spezifischen Beta-Globin-Genvarianten wie Hb C, Hb D, Hb E oder in Verbindung mit β-Thalassämie vorliegt.

SCD:

Krankheitsbild &

Die wichtigsten akuten Manifestationen bei SCD umfassen Infektionen, Anämie und vaskuläre Verschlüsse (vasookklusive Ereignisse), die oft lebensbedrohlich sein können. Zudem ist bekannt, dass Infektionen eine der Hauptursachen für Morbidität und Mortalität darstellen und durch verschiedene Mechanismen wie Hyposplenismus oder Asplenie begünstigt werden. Chronische hämolytische Anämie, aplastische Krisen und splenische Sequestrationskrisen tragen zur Krankheitslast bei und können ebenfalls akut lebensbedrohlich sein. Weitere typische Symptome umfassen pulmonale Komplikationen, wie das akute Thoraxsyndrom und pulmonale Hypertonie, sowie neurologische Komplikationen, einschließlich Schlaganfälle und Krampfanfälle.

Komplikationen

Inzidenz, Prävalenz und geschätzte Zahl der Patient*innen in Österreich

Die geschätzte Gesamtzahl der SCD-Patient*innen (einschließlich Einheimische und Menschen mit Migrationshintergrund) liegt bei etwa 132. Laut klinischen Expert*innen und dem Hersteller könnten in den nächsten drei Jahren etwa 15 SCD-Patient*innen für eine Behandlung mit Exa-cel in Frage kommen, davon neun bis zwölf Patient*innen im Alter von 12 bis 17 Jahren.

AT:
gesamt 132 SCD Pat.

Exa-cel → ~15 Pat.

SoC und alternative Behandlungsmöglichkeiten bei SCD

Die SoC bei SCD in Österreich besteht aus der oralen Verabreichung von Hydroxyurea. Leitliniengemäß stehen weitere Therapieoptionen zur Verfügung: Bluttransfusionen, Phlebotomie (Aderlass), Stammzelltransplantation.

SoC in AT:
Hydroxyurea

Klinische Wirksamkeit und Sicherheit

Die Wirksamkeit und Sicherheit von Exa-cel bei SCD Patient*innen wurden in einer offenen, einarmigen Phase 2/3 Studie untersucht (CTX001-111).

einarmige Phase 2/3 Studie

In der CTX001-121-Studie wurden 44 Patient*innen mit SCD behandelt, von denen 30 für die primäre Wirksamkeitsanalyse geeignet waren. Das Durchschnittsalter betrug 22,1 Jahre, und die Geschlechterverteilung war nahezu ausgeglichen. Vor Therapiebeginn hatten die Patient*innen im Median 4,1 schwere vaso-okklusive Krisen (VOC) pro Jahr. Nach der Behandlung waren 97% der Patient*innen (29 von 30) für mindestens zwölf Monate frei von schweren VOCs, und keine der Patient*innen musste aufgrund von Krisen

97% keine vaso-okklusive Krisen (VOCs)

hospitalisiert werden. Die mittlere krisenfreie Zeit betrug 22,4 Monate (Bereich: 14,8 bis 45,5 Monaten).

Sicherheitsprofil → häufige Nebenwirkungen:

Stomatitis (55%), febrile Neutropenie (48%) und Appetitlosigkeit (41%)

Das Sicherheitsprofil in der SCD-Studie war ähnlich wie in der TDT-Studie (CTX001-111). Alle Patient*innen erlebten mindestens ein UE, wobei die meisten Ereignisse von Grad 1 oder 2 waren. Nebenwirkungen (Grad 3 oder 4) traten ebenfalls bei etwa 95% der Patient*innen auf, primär bedingt durch die Busulfan-Konditionierung. Schwerwiegende Nebenwirkungen (SUE) traten dabei bei 20 Patient*innen (45,5 %) auf, von denen keines mit Exa-cel in Verbindung gebracht wurde und bei vier Patient*innen (9,1%) ein möglicher Zusammenhang mit Busulfan nicht ausgeschlossen werden konnte. Die meisten UE und SUE wurden innerhalb der ersten sechs Monate nach der Konditionierung und Infusion von Exa-cel beobachtet, und die Häufigkeit von (S)UE ging danach zurück.

Methodische Einschränkungen und Heterogenität der Studienpopulationen

begrenzte Aussagekraft aufgrund diverser Limitationen

Beide Studien (CTX001-121 & CTX001-111) zu Exa-cel deuten auf eine Wirksamkeit hin, dennoch sind die Ergebnisse aufgrund des einarmigen Studiendesigns und der geringen Stichprobengröße nur begrenzt verallgemeinerbar. Die beobachteten unerwünschten Ereignisse entsprachen zwar den bekannten Nebenwirkungen der Busulfan-Konditionierung. Dennoch sind klinische Langzeitdaten über mindestens fünf Jahre erforderlich, insbesondere zur Bewertung potenzieller Off-Target-Effekte der Genomeditierung sowie des Risikos maligner Entartungen.

fehlende Langzeitdaten

Limitationen der TDT-Studie (CTX001-111)

TDT: heterogene Population & Unklarheiten bezügl. der Interimsanalysen

Die Studienpopulation zeigte eine ausgeprägte Heterogenität. Der mediane jährliche Transfusionsbedarf der Patient*innen bei Studienbeginn variierte erheblich (196,8 ± 63,0 ml/kg), was auf unterschiedliche Schweregrade der Erkrankung hindeutet. Solche Unterschiede in der Krankheitslast können die Interpretation der Wirksamkeit beeinträchtigen. Ein weiterer kritischer Punkt betrifft die Durchführung der Interimsanalysen: Neben der vordefinierten dritten Interimsanalyse (16. Januar 2023) wurden zusätzliche, nicht vorab spezifizierte Datenpunkte (16. April 2023 und 18. September 2023) ausgewertet, was das Risiko für Multiplizitätsprobleme erhöht.

Limitationen der SCD-Studie (CTX001-121)

SCD: subjektive Endpunkte & heterogene Population

Die Studienpopulation wies eine deutliche Heterogenität auf, besonders hinsichtlich der Häufigkeit schwerer VOCs pro Jahr (4,1 ± 3,0). Ein zusätzliches methodisches Problem stellen die VOCs als subjektiver Endpunkt dar. Da deren Definition zwischen verschiedenen Studien variieren kann, besteht Unsicherheit darüber, ob alle VOC-Ereignisse zu Studienbeginn konsistent erfasst wurden. Diese Variabilität könnte zu Verzerrungen hinsichtlich der tatsächlichen Häufigkeit der Krisen und der Interpretation der Wirksamkeit in der heterogenen Studienpopulation geführt haben.

Organisatorische, ethische und soziale Aspekte

hohe Anforderungen an Infrastruktur

Die Implementierung von Exa-cel stellt erhebliche Anforderungen an das Gesundheitssystem. Die Behandlung erfordert eine hochspezialisierte Infrastruktur und ein erfahrenes, multidisziplinäres Team. Patient*innen müssen für etwa fünf bis sechs Wochen stationär aufgenommen werden, während die Kapazitäten der Transplantationszentren bereits ausgelastet sind.

Lücken in Erwachsenenversorgung (derzeit in onkolog. Abteilungen)

Eine besondere Herausforderung ist die Versorgung erwachsener Patient*innen, da spezialisierte Abteilungen für Hämoglobinopathien bisher nur in der Pädiatrie existieren. Erwachsene Patient*innen werden derzeit in onkologischen Abteilungen mitbetreut. An der Medizinischen Universität Wien wurde bislang keine autologe Stammzelltransplantation bei erwachsenen Patient*innen mit SCD oder TDT – aufgrund von Komorbiditäten und mangelnder Therapietreue - durchgeführt. Die Planung der Behandlungskapazitäten muss sicherstellen, dass andere Patient*innen dadurch nicht benachteiligt werden.

intensive Vorbereitungen & Aufklärung der Patient*innen und Angenhörigen notwendig

Die Therapie erfordert eine intensive Aufklärung und Vorbereitung der Patient*innen und ihrer Angehörigen. Die Belastungen durch die Vorbehandlungen und die Risiken der Therapie müssen umfassend erläutert werden. Eine zusätzliche Herausforderung stellt die Transition von der pädiatrischen zur erwachsenenmedizinischen Versorgung dar. In der Vergangenheit haben Lücken in der Übergangsversorgung zu schwerwiegenden Komplikationen bis hin zu Todesfällen geführt.

vulnerable Patient*innengruppe

Ethische Herausforderungen ergeben sich aus verschiedenen Faktoren. Die betroffenen Patient*innen gehören häufig zu vulnerablen Bevölkerungsgruppen, oft mit Migrationshintergrund und sozioökonomischen Benachteiligungen. Viele erreichen Österreich in einem schlechten Gesundheitszustand, insbesondere unbegleitete Minderjährige, die während der Flucht keine adäquate Behandlung erhielten. Sprachbarrieren und eingeschränkte Kenntnisse des Gesundheitssystems können den Zugang zur Therapie zusätzlich erschweren.

eingeschränkte Autonomie → durch regelmäßige Krankenhaus (KH)-Aufenthalte

Die Autonomie der Patient*innen ist durch die derzeitige Standardtherapie stark eingeschränkt, da regelmäßige Krankenhausaufenthalte für Transfusionen und eine lebenslange Medikamenteneinnahme erforderlich sind. Die Gentherapie könnte diese Einschränkungen erheblich reduzieren. Dennoch ist für die Durchführung der Therapie ein sehr guter Allgemeinzustand und eine hohe Therapietreue erforderlich. Die begrenzte Evidenz zur Langzeitwirksamkeit und -sicherheit muss in der Entscheidungsfindung berücksichtigt werden.

Kosten-Effektivität

Hersteller stellt kein gesundheitsökonomisches Modell zur Verfügung

bei derzeitigem Preis laut int. Modelle nicht kosteneffektiv

UK-Analyse empfiehlt geregelter Zugang mit begleitender Datenerhebung

Der Hersteller legte zum Zeitpunkt der Erstellung des HTA-Berichts kein gesundheitsökonomisches Modell für Österreich vor. Stattdessen wurden veröffentlichte pharmakoökonomische Analysen herangezogen, insbesondere ein US-amerikanisches Modell des Institute for Clinical and Economic Review (ICER). Die Basis-Analyse ergab, dass Exa-cel bei einem Preis von 1,7 Millionen Euro für Patient*innen mit SCD nicht kosteneffektiv ist im Vergleich zur Standardtherapie, wobei die Kosteneffektivität stark von den Annahmen zur Langzeitwirkung und den Komplikationsraten der Therapie abhängt. Das National Institute for Clinical Excellence (NICE) im Vereinigten Königreich kam zu dem Schluss, dass Exa-cel zwar potenziell hohe Gesundheitsgewinne bietet, die langfristige Sicherheit und Kosteneffektivität jedoch unsicher sind, weshalb die Anwendung von Exa-cel in Form eines Managed-Access-Programms empfohlen wurde, im Rahmen dessen zusätzliche Daten erhoben werden.

Behandlungskosten und Budgetfolgen

hohe Behandlungskosten à € 1,9 Mio/Patient*in (Herstellerpreis versch. EU Länder)

Die Behandlungskosten von Exa-cel sind erheblich und umfassen sowohl den Preis des Medikaments selbst als auch die begleitenden medizinischen Kosten wie Krankenhausaufenthalte, vorbereitende Maßnahmen und die Behandlung potenzieller Nebenwirkungen. Der Herstellerpreis von Exa-cel liegt in mehreren EU-Ländern, darunter Frankreich und Luxemburg, bei etwa 1,9 Millionen Euro.

AT 3-Jahres Budgetfolgenanalyse:

€ 15,7 Mio./Jahr (davon 97% Medikamentenkosten)

3 Jahre: Gesamtkosten für alle Pat. inkl. Exa-cel € 60,6 Mio. versus Standard of Care € 14 Mio.

Mangels Herstellerdaten wurde für die österreichischen Patient*innenpopulationen für SCD und TDT eine eigene Budgetfolgenanalyse durchgeführt. Dafür wird bei der SCD in Jahr 1 mit 132 Patient*innen und in Jahr 3 mit 160 Patient*innen pro Jahr gerechnet, bei der TDT mit 70 im ersten Jahr und 84 im 3. Jahr. Basierend auf Schätzungen klinischer Experten und Studiendaten wird davon ausgegangen, dass über drei Jahre 30 Patient*innen für Exa-cel geeignet sind, wovon tatsächlich 24 (12 bei TDT und 12 bei SCD) behandelt werden. Die jährlichen Budgetfolgen für das Arzneimittel und begleitenden Maßnahmen vor, während und nach der Behandlung betragen €15,7 Mio. (€47 Mio. über drei Jahre), davon 97% Medikamentenkosten. Die Gesamtbehandlungskosten aller Patient*innen über drei Jahre würden sich neben den bestehenden Therapien mit Exa-cel auf €60,6 Mio. (TDT: €31,7 Mio.; SCD: €28,9 Mio.) belaufen – im Vergleich zu €14 Mio. (TDT: €8,6 Mio.; SCD: €5,4 Mio.) mit den bestehenden Therapien ohne Exa-cel. Die größte Unsicherheit der Analyse betrifft die tatsächliche Anzahl der durchgeführten Exa-cel-Behandlungen, da diese den stärksten Einfluss auf die Budgetfolgen hat.

Entwicklungskosten und öffentliche Beiträge

Entwicklung: öffentlich-private Zusammenarbeit

Die Entwicklung von Exa-cel resultierte aus einer Zusammenarbeit zwischen Vertex Pharmaceuticals, CRISPR Therapeutics und akademischen Institutionen wie dem Broad Institute an der Harvard University. Diese Zusammenarbeit nutzte sowohl öffentliche als auch private Finanzierung. Die Technologie der CRISPR-Cas9-Gentherapie basiert auf grundlegenden wissenschaftlichen Entdeckungen, die überwiegend in öffentlichen Einrichtungen durchgeführt wurden, etwa an der Osaka University und der University of California. Während die öffentlichen Entwicklungsbeiträge dokumentiert sind, hat Vertex Pharmaceuticals die gesamten Entwicklungskosten für Exa-cel nicht offengelegt, was die Transparenz der finanziellen Aufwendungen für dieses Medikament einschränkt.

Schlussfolgerung

potentiell kurativ, aber viele Unsicherheiten

Exa-cel stellt einen potenziellen Fortschritt in der Behandlung genetischer Blutkrankheiten im Vergleich zur SoC dar und könnte Patient*innen mit TDT und SCD eine kurative Option bieten. Die Therapie zeigt Hinweise auf eine Reduzierung des Transfusionsbedarfs (TDT) und der Häufigkeit schmerzhafter VOCs (SCD), was auf eine mögliche Verbesserung der Lebensqualität hinweist. Angesichts der begrenzten Langzeitdaten zur Sicherheit sowie der erheblichen Behandlungskosten ist eine kritische Betrachtung erforderlich. Die finanziellen Anforderungen und die notwendigen strukturellen Anpassungen im Gesundheitssystem bedürfen sorgfältiger Planung, um einen bedarfsgerechten und nachhaltigen Zugang zu dieser Therapie zu gewährleisten.

Executive Summary

Overview of the New Medicinal Product

Exagamglogene autotemcel (exa-cel, Casgevy®) received conditional marketing authorization from the European Medicines Agency (EMA) on February 9, 2024, as the first CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based gene therapy. It is classified as an Advanced Therapy Medicinal Product (ATMP) and has orphan drug status for two indications. It is approved for treating transfusion-dependent β-thalassemia (TDT) and severe sickle cell disease (SCD) in patients aged twelve years or older who are eligible for hematopoietic stem cell transplantation but lack a human leukocyte antigen (HLA)-matched related donor. For the SCD indication, additionally, recurrent vaso-occlusive crises (VOCs) must be present.

first CRISPR therapy: conditional marketing authorisation (MA) Feb 2024

Disease Description and Standard of Care (Soc)

TDT and SCD are inherited blood disorders. TDT requires regular blood transfusions and leads to iron overload and organ damage. SCD causes painful VOCs and organ complications. In Austria, the carrier rate for both conditions is approximately 0.2% in the native population, with an estimated number of 60-79 patients with TDT and 132 with SCD including both indigenous and migrant individuals.

inherited blood disorders: transfusion-dependent β-thalassemia (TDT) & severe sickle cell disease (SCD)

The current standard of care (SoC) for TDT in Austria consists of erythrocyte concentrates and iron chelation therapy. Guidelines recommend additional treatment options: causal treatments (autologous stem cell transplantation, hydroxyurea, luspatercept) and symptomatic therapies (chelation therapy and management of secondary conditions), which typically require lifelong administration. For SCD, the SoC in Austria comprises oral administration of hydroxyurea. Guidelines suggest additional treatment options including blood transfusions, phlebotomies, stem cell transplantation, and gene therapy/gene editing.

Standard of Care (SoC) in Austria (AT):

TDT → erythrocyte concentrates and iron chelation therapy

SCD → hydroxyurea

Clinical Effectiveness and Safety

Two single-arm Phase 2/3 studies demonstrated Casgevy's® efficacy. In the TDT study (CTX001-111; n=35), 91% of patients achieved transfusion independence. In the SCD study (CTX001-121; n=30), 97% of patients remained free from severe VOCs for at least twelve months. All patients experienced adverse events, mostly related to the conditioning regimen, with most being grade 1 or 2 in severity. One death occurred in the SCD study due to COVID-19, deemed unrelated to treatment.

clinical studies: high response rates

Both studies face limitations from their single-arm, open-label designs and small sample sizes, limiting external validity and relative effectiveness assessment. Additionally, the demanding treatment process, involving prolonged hospitalisations and Busulfan conditioning, poses real-world challenges for patient compliance and accessibility, underscoring the need for comprehensive long-term safety monitoring.

several limitations: single-arm, open-label, small sample sizes, external validity

organisational and Ethical Aspectsspecialised centres and patient information required the patient belong to a vulnerable group

Treatment requires specialised centres and experienced medical teams. Patients need five to six weeks of hospitalisation. In Austria, three centers are designated for treatment. Challenges include appropriate information of patients to enable informed decisions, transition from pediatric to adult care and addressing health inequalities, as affected populations often have migration backgrounds and face socioeconomic disadvantages.

Economic Aspects

high costs: €1.9 M per treatment (based on EU countries), at this price not considered cost-effective

The treatment costs are substantial, with a price of approximately €1.9 million in European countries (*without any confidential price discounts*). International cost-effectiveness analyses concluded that incremental cost-effectiveness ratios exceed accepted reference values. The UK's NICE recommended exa-cel with managed access agreements due to uncertainty about long-term effectiveness and cost-effectiveness.

Austria (3 years of treatment)→ exa-cel €60,6 M versus €14 M standard of care

In Austria, with 132-160 SCD and 70-84 TDT patients annually, we assumed that 24 patients (12 with TDT and 12 with SCD) would receive exa-cel over three years. The annual budget impact for drug acquisition and additional costs is €15.7 million (€47 million/three years), with total treatment costs of existing therapies and exa-cal of €60.6 million (SCD: €28.9 million; TDT: €31.7 million) compared to €14 million (TDT: €8.6 million; SCD: €5.4 million) without exa-cel. The main uncertainty is the actual number of treatments, as this most significantly impacts the budget.

Development Costs and Public Contributions

collaboration between manufacturer and academic institutions

The development of exa-cel resulted from a collaboration between Vertex Pharmaceuticals, CRISPR Therapeutics, and academic institutions. While basic CRISPR research was largely publicly funded,Vertex Pharmaceuticals

Conclusion

promising but uncertain long-term effects

In conclusion, while exa-cel shows promising clinical efficacy for both TDT and SCD, challenges remain regarding long-term effectiveness and safety data, high treatment costs, and ensuring needs-based access to therapy. Careful patient selection and comprehensive follow-up will be essential for successful implementation in clinical practice.

1 Overview of the new medicinal product

1.1 INN, product name, ATC code, Pharmacologic class, Manufacturer/Marketing authorisation holder & Data exclusivity

International Nonproprietary Names (INN)	Exagamglogene autotemcel CTX001, exa-cel
Proprietary name	Casgevy®
ATC code	B06AX05
Pharmacologic class	Gene editing therapy is classified as an advanced therapy medicinal product (ATMP) by the European Medicines Agency (EMA) [1].
Manufacturer / Marketing authorisation holder	The marketing authorisation holder of Casgevy® is Vertex Pharmaceuticals (Ireland) Limited [1].
Data exclusivity	Orphan market exclusivity for the "treatment of β-thalassaemia intermedia and major" (based on designation EU/3/19/2210) began on 12 February 2024, granting ten years of exclusivity. This orphan market exclusivity will expire on 12 February 2034 [2]. Orphan market exclusivity for the "treatment of sickle cell disease" (based on designation EU/3/19/2242) also began on 12 February 2024, with ten years of exclusivity. It will expire on 12 February 2034 [2].

1.2 EMA approval status/Date of marketing authorisation/Expected approval date/Authorisation details

European Medicines Agency (EMA)-Zulassung

Exagamglogene autotemcel (exa-cel, Casgevy®) received EMA approval, with the marketing authorisation granted on 9 February 2024 [3].

zusätzliche Überwachung, bedingte Marktzulassung, PRIME

The medicine is under additional monitoring, received conditional marketing authorisation, and was included in the EMA Priority Medicines (PRIME) scheme during its development [3].

2019: Orphan-Status für β-Thalassämie

2020: Orphan-Status für SCD

On 17 October 2019, the European Commission granted orphan designation to Vertex Pharmaceuticals Limited for autologous CD34+ hematopoietic stem cells with a “Clustered Regularly Interspaced Short Palindromic Repeats” (CRISPR)-edited erythroid enhancer region of the BCL11A gene (CTX001) for the treatment of transfusion-dependent β-thalassaemia (TDT) intermedia and major. On 9 January 2020, orphan designation was granted for autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene (CTX001) for the treatment of sickle cell disease (SCD) [4].

EMA Zulassungen: transfusionsabhängige β -Thalassämie (TDT) &

Exa-cel is indicated for the treatment of TDT in patients twelve 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 [5].

schwere Form der SCD

Exa-cel is indicated for the treatment of severe SCD in patients twelve years of age and older with recurrent vaso-occlusive crises (VOCs) for whom HSC transplantation is appropriate, and an HLA-matched related HSC donor is not available [5].

1.3 Posology and method of administration

autorisierte Zentren und erfahrene Ärzte notwendig

Exa-cel must be administered in an authorised treatment centre by a physician experienced in HSC transplantation and treating patients with β-haemoglobinopathies, who is also trained in administering and managing patients treated with exa-cel. Before starting mobilisation, apheresis, and myeloablative conditioning, it must be confirmed that haematopoietic stem cell transplantation (HSCT) is appropriate for the patient [5].

1.3.1 Posology

einmalige Anwendung

Exa-cel is intended for autologous use. Treatment consists of a single dose containing a dispersion for infusion of viable CD34+ cells in one or more vials. The minimum recommended dose of exa-cel is 3×10^6 CD34+ cells per kilogram (kg) of body weight [5].

1.3.2 Mobilisation and apheresis

Mobilisierung von Stammzellen und Apherese

Before exa-cel can be manufactured, patients must undergo CD34+ haematopoietic stem and progenitor cell (HSPC) mobilisation, followed by apheresis to isolate the CD34+ cells. A total collection target of at least 20 × 10 ^ 6 CD34+ cells per kg is recommended for exa-cel manufacture. The collected cells should be sent for product manufacturing even if the total collection target is not reached [5].

weitere Mobilisierungs- und Apheresezyklen können notwendig sein

In addition, at least 2×10^6 CD34+ cells per kg must be collected for backup unmodified rescue cells. A third day of cell collection can be used to obtain backup rescue cells if needed. Suppose the minimum dose of exa-cel is not met after the initial product manufacturing. In that case, the patient will need to undergo additional cycles of mobilisation and apheresis to obtain more cells for further product manufacture. Each mobilisation and apheresis cycle must be separated by at least 14 days [5].

unveränderte Zellen werden als Reserve für Rescue-Therapie entnommen

The backup collection of $\geq 2 \times 10^6$ CD34+ cells per kg of unmodified rescue cells must be collected from the patient and cryopreserved before myeloablative conditioning and infusion with exa-cel. The unmodified cells may be needed for rescue treatment under any of the following conditions: compromise of exa-cel after the initiation of myeloablative conditioning and before exa-cel infusion; neutrophil engraftment failure; or loss of engraftment after infusion with exa-cel [5].

Mobilisation and apheresis in study patients with transfusion-dependent β-thalassemia (Study 111)

Mobilisierung und Apherese bei TDT: Erythrozytentransfusionen

To maintain a total haemoglobin (Hb) concentration of ≥11 grams per decilitre (g/dl), trial patients underwent red blood cell (RBC) transfusions before mobilisation and apheresis. They continued receiving transfusions until the initiation of myeloablative conditioning [5].

Granulozyten-Kolonie-stimulierende Faktor (G-CSF) + Plerixafor zur Mobilisierung

To mobilise stem cells for apheresis, patients in study 111 received granulocyte-colony stimulating factor (G-CSF). Patients with an intact spleen received a planned dose of 5 micrograms (mcg)/kg G-CSF approximately every twelve hours via intravenous or subcutaneous injection for five to six days. Splenectomised patients received a planned dose of 5 mcg/kg G-CSF once daily for five to six days. If there was no increase in white blood cell (WBC) or peripheral blood CD34+ counts, the dose for splenectomised patients was increased to every twelve hours [5].

Apherese bis zu drei Tage für Zellgewinnung

After four days of G-CSF administration, all patients received plerixafor at a planned dose of 0.24 milligrams (mg) per kg, administered via subcutaneous injection approximately four to six hours prior to each planned apheresis. Apheresis was performed for up to three consecutive days to achieve the target collection of cells for manufacturing and the unmodified rescue CD34+ cells [5].

Mobilisation and apheresis in study patients with SCD (Study 121)

Mobilisierung und Apherese bei SCD: Erythrozytenaustausch/einfache Transfusionen

Before the planned start of mobilisation, study patients underwent RBC exchange or simple transfusions for at least eight weeks. They continued receiving transfusions or RBC exchanges until the initiation of myeloablative conditioning. Haemoglobin S (HbS, sickle haemoglobin) levels were maintained at less than 30% of total Hb while keeping the total Hb concentration at or below 11 g/dl [5].

Plerixafor zur Mobilisierung von Stammzellen

To mobilise stem cells for apheresis, patients in the study 121 received plerixafor at a planned dose of 0.24 mg per kg via subcutaneous injection approximately two to three hours before each planned apheresis. Patients underwent apheresis for up to three consecutive days to achieve the target collection of cells for manufacturing exa-cel and the unmodified rescue CD34+ cells. G-CSF must not be administered for mobilisation in patients [5].

krankheitsmodifizierende Therapien müssen abgesetzt werden

Disease-modifying therapies, including hydroxyurea/hydroxycarbamide, crizanlizumab or voxelotor, must be discontinued eight weeks before the planned start of mobilisation and conditioning in patients with TDT and SCD [5, 6].. Of note,the marketing authorisation of crizanlizumab (Adakveo®) has been revoked by the EMA in August 2023 [7]; in September 2024, the EMA recommended the suspension of Voxelotor (Oxbryta®) due to safety reasons [8].

1.3.3 Pre-treatment conditioning

vollständige myeloablative Konditionierung

Before the administration of exa-cel, full myeloablative conditioning must be completed in patients with TDT and SCD. Conditioning must not be initiated until the complete set of vials constituting the total dose of exa-cel has been received at the authorised treatment centre and the availability of the backup collection of unmodified CD34+ cells is confirmed [5].

Pre-treatment conditioning in study patients with TDT (Study 111) and SCD (Study 121)

Busulfan zur myeloablativen Konditionierung

All trial patients (Study 111 and Study 121) received complete myeloablative conditioning with Busulfan before exa-cel treatment. Busulfan was administered for four consecutive days intravenously via a central venous catheter at a planned starting dose of 3.2 mg/kg per day once daily or 0.8 mg/kg every six hours. Busulfan plasma levels were measured by serial blood sampling, and the dose was adjusted to maintain exposure to the target range [5].

Prophylaxe gegen Krampfanfälle und VOD

in AT nur als symptomatische Behandlung

Before initiating Busulfan conditioning, all study patients (Study 111 and Study 121) received anti-seizure prophylaxis with agents other than phenytoin[1]. Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome was administered to the trial patients according to institutional guidelines [5]. Clinical experts have indicated that VOD prophylaxis in Austria would be administered only in the case of signs and symptoms of VOD, using defibrotide therapy for 21 days [6].

Therapie vor der myeloablativen Konditionierung (TDT & SCD)

In patients with TDT, it is recommended to maintain total Hb concentration ≥11 g/dl for 60 days before myeloablative conditioning. In patients with SCD, it is recommended that patients receive RBC exchange or simple transfusion(s) for at least eight weeks before initiating myeloablative conditioning to maintain HbS levels <30% of total Hb while keeping total Hb concentration ≤11 g/dl [5].

Absetzen krankheitsmodifizierender Therapien vor Konditionierung

Verfügbarkeit von Exa-cel muss vorab bestätigt werden

At the initiation of RBC exchanges or simple transfusions, disease-modifying therapies (including hydroxyurea/hydroxycarbamide, crizanlizumab or voxelotor[2]) have to be discontinued in patients with TDT and SCD. Iron chelation therapy must be stopped at least seven days before myeloablative conditioning. Prophylaxis for seizures and hepatic VOD/hepatic sinusoidal obstruction syndrome should be considered according to institutional guidelines. Before starting the myeloablative conditioning regimen, the availability of the complete set of vials constituting the dose of exa-cel and unmodified rescue cells must be confirmed [5].

1.3.4 Pre-medication

Prämedikation zur Reduktion von Infusionsreaktionen

According to the exa-cel Product Information, premedication with paracetamol and diphenhydramine, or equivalent medicinal products, is recommended to be administered according to institutional guidelines before the

[1] Phenytoin was not used for anti-seizure prophylaxis because of its induction of cytochrome P450 and resultant increased clearance of Busulfan.

[2] Of note, in September 2024, the EMA recommended the suspension of Voxelotor (Oxbryta®) due to safety reasons.

infusion of exa-cel to reduce the possibility of an infusion reaction in patients with TDT and SCD [5].

1.3.5 Administration protocol

Verabreichung nach 2-7 Tagen

After completing the myeloablative conditioning regimen, a minimum of 48 hours must elapse before exa-cel infusion. Exa-cel must be administered a maximum of seven days after the last dose of myeloablative conditioning. Before thawing (exa-cel is stored in the vapour phase of liquid nitrogen at ≤ -135 °C) and administration of exa-cel, it must be confirmed that the patient's identity matches the unique patient information on the exa-cel vial(s) and accompanying documentation. Additionally, the total number of vials must be verified against the patient-specific information on the lot information sheet [5].

Identitätsprüfung vor Exa-cel-Verabreichung

Verabreichung via zentralem Venenkatheter

Exa-cel is administered as an intravenous bolus via a central venous catheter. The total volume of Casgevy administered within one hour must not exceed 2.6 ml per kg. Infusions with exa-cel must be completed as soon as possible and no more than 20 minutes after thawing [5].

1.3.6 Patient monitoring and management after exa-cel administration

Standardverfahren → Patient*innen-Monitoring

After administering exa-cel, standard patient monitoring and management procedures for HSC transplantation must be implemented. This includes monitoring complete blood counts and evaluating transfusion requirements. Blood products must be irradiated within the first three months after exa-cel infusion. It may be necessary to restart iron chelation following exa-cel infusion. Non-myelosuppressive iron chelators should be avoided for at least three months, and myelosuppressive iron chelators should be avoided for at least six months after exa-cel administration. If suitable, phlebotomy can be used as an alternative to iron chelation [5].

Blutprodukte: Bestrahlung in den ersten 3 Monaten notwendig

1.4 Requirements for companion diagnostics and monitoring during exa-cel treatment

begleitende Maßnahmen

During exa-cel treatment, the following monitoring procedures are required:

Überwachung von Überempfindlichkeits-reaktionen, Neutrophilen-Engraftment, Thrombozyten-Engraftment und Infektionssymptomen

- Monitoring for hypersensitivity reactions should take place during and after exa-cel infusion. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptoms should be measured before the start of the infusion and approximately every 30 minutes from when the first vial of exa-cel is infused until two hours after the last vial of exa-cel is infused.
- Monitoring of neutrophil engraftment failure (absolute neutrophil counts and infections) should be conducted after exa-cel infusion.
- Delayed platelet engraftment (bleeding) should be monitored after exa-cel infusion.

- Clinical laboratory assessments are required after exa-cel infusion.
- Standard procedures for patient monitoring and management after HSCT, including monitoring of complete blood counts and transfusion needs, should be applied after exa-cel infusion.
- Monitoring for signs and symptoms of infections (risk of transmission of an infectious agent) is relevant after exa-cel infusion [5].

2 Indication and therapeutic management

2.1 Description of the disease

2.1.1 Transfusion-dependent β-thalassemia (TDT)

Thalassämien: erbliche Hämoglobinopathien

β-thalassemia is an inherited haemoglobinopathy caused by a reduced production of beta chains and accumulation of excess alpha chains. The severity of the disease correlates with the amount of normal beta globin production. Terminology has shifted from using the "major, intermedia, minor" categorisation to referring to the disorder as transfusion-dependent or non-transfusion-dependent [9]. However, since the previously used terms are still present in the guidelines applied in Austria, these are also used in this report.

TDT ehemals "Thalassaemia major": regelmäßige Transfusionen notwendig

Patients with TDT (previously "beta thalassemia major") require regular transfusions due to severe anaemia and/or significant complications of extramedullary hematopoiesis. Patients with TDT have minimal to no beta globin chain production and consequently little to no adult haemoglobin (Hb A). After birth, when the fetal haemoglobin (HbF) to Hb A transition occurs, symptoms typically manifest during late infancy, approximately between six and twelve months of age. Depending on the aggressiveness of therapy and other mitigating factors, presentations of the disease can be remarkably heterogeneous [9].

Clinical manifestations

Clinical manifestations of TDT are related to anemia, complications of hemolysis and extramedullary hematopoiesis [9]:

klinische Manifestationen: Anämie, Blässe, Gedeihstörung, Hepatosplenomegalie, Skelettveränderungen

- **Anaemia:** Infants with severe anaemia who receive no treatment present with pallor, jaundice, dark urine from hemolysis, irritability, and abdominal swelling from hepatosplenomegaly, which may be followed by high-output heart failure, failure to thrive, and infection. The Hb level can be as low as 3-4 g/dl. There is typically pronounced hypochromia and microcytosis, abnormal RBC morphology, an increased RBC count, and laboratory evidence of non-immune hemolysis. When sites of extramedullary hematopoiesis expand, skeletal abnormalities of the face and long bones, hepatosplenomegaly, and kidney enlargement develop. Splenomegaly due to hemolysis may be exacerbated by extramedullary hematopoiesis and liver disease from iron overload. Late symptoms of iron overload can affect the heart, liver, endocrine organs, and others. These patients require chronic transfusions [9].

Patient*innen anfälliger für Infektionen

Patients with TDT, if not optimally transfused, are under constant erythropoietic stress. Thus, they are more susceptible to infections, drugs, or nutritional deficiencies that interfere with RBC production [9].

Komplikationen der Hämolyse

- **Complications of hemolysis:** In patients with TDT, bilirubin (pigment) gallstones and biliary tract inflammation can occur as a complication of chronic haemolytic anaemia. Hepatosplenomegaly may be caused by chronic hemolysis, extramedullary hematopoiesis in the liver and spleen, and hepatic iron deposition. In the past, viral hepatitis acquired from transfusions also occurred. In patients with TDT

who do not receive iron chelation therapy, hepatomegaly typically develops within the first few years of life. The risk of hepatocellular cancer may be increased. Splenomegaly is a common symptom in patients with TDT, leading to early satiety, shortened survival of transfused RBCs, or progressive worsening of anaemia [9].

Komplikationen der extramedullären Blutbildung & Eisenüberladung

- **Complications of extramedullary hematopoiesis:** When ineffective erythropoiesis occurs in patients with thalassemia, erythropoiesis can develop extramedullary. Complications of extramedullary hematopoiesis include skeletal changes (such as facial deformities, alterations in body habitus, osteopenia/osteoporosis, bony masses, and bone pain), iron overload (which can cause toxicity in the liver, heart, endocrine organs, and other tissues), and growth impairment. Common findings of iron overload are endocrine and metabolic abnormalities, including hypogonadism (most commonly reported), hypothyroidism, insulin resistance and growth impairment [9].

häufig treten kardiale Komplikationen auf

Cardiac complications are common in patients with TDT; heart failure and arrhythmias can be fatal. The causes of cardiac complications are multifactorial and include anaemia, cardiac iron deposition, diabetes, vascular dysfunction due to oxidative stress, pulmonary arterial hypertension, high cardiac output related to chronic tissue hypoxia and increased pulmonary vascular resistance, vitamin D deficiency, and others. Iron accumulation plays the most significant role in the prevailing view and can cause myocardial fibrosis and necrosis [9].

meisten Patient*innen haben beeinträchtigte Lungenfunktionen

Most patients with TDT have mild pulmonary function abnormalities, including restrictive and small airway obstructive defects, hyperinflation, decreased maximal oxygen uptake, and abnormal anaerobic thresholds, but symptoms are relatively infrequent. The mechanism of these pulmonary function abnormalities is poorly understood since they do not appear to correlate with iron burden, severity of anaemia, or degree of hemolysis, and transfusions do not correct them. After splenectomy, profound thrombocytosis increases the patient´s risk for pulmonary vascular obstruction. Adult patients with TDT may develop pulmonary hypertension, which might be caused by prior splenectomy, older age, chronic hemolysis with decreased nitric oxide availability, cardiac iron overload, platelet activation, and smoking [9].

Thrombosen, Ulcus cruris

Further clinical manifestations include thrombosis and leg ulcers. Additionally, there is a question of whether patients with thalassemia who survive into adulthood have an increased risk of cancer [9].

Diagnostic evaluation

Diagnosestellung: (Familien-)anamnese + Laborwerte

The diagnostic evaluation of thalassemia depends on the personal and family history and available laboratory results. Evaluating the family history of thalassemia can help determine the type and severity of the condition. A family history of SCD, trait, or other haemoglobinopathies can suggest compound syndromes or may indicate anaemia without a specific diagnosis. Since both parents may be asymptomatic carriers, a negative family history does not eliminate the possibility of thalassemia. Disease onset in infancy (six to twelve months) suggests TDT; diagnosis later in life suggests that patients may have a milder form [9].

First, the family or clinician may be contacted with positive results from prenatal testing or a newborn screening[3] test. Initial testing includes a complete blood count (CBC), a review of the blood smear and iron studies (to evaluate for iron deficiency and iron overload). Hb analysis and/or genetic testing are recommended in suitable patients to confirm the diagnosis. Iron deficiency is the primary condition in the differential diagnosis of thalassemias [9].

Pränataldiagnostik, Neugeborenenscreening, Blutbild

Prognosis and natural course of the disease

The prognosis for patients with TDT has dramatically improved over the past decades with the introduction of non-invasive methods (to measure liver and cardiac iron accumulation before the appearance of clinical symptoms), improved iron chelators, and a decreased risk of infection with RBC transfusions. After 2000, these developments led to a significant decrease in cardiac mortality, which was previously reported to cause 71% of deaths in TDT patients. The prognosis of the disease continues to improve as access to both RBC transfusions and iron chelation increases. However, life expectancy remains reduced in low-resource settings, with more than half of individuals dying before the age of 30, compared to more than half living to the age of 60 in high-resource settings [10].

Prognose und Verlauf: abhängig vom Zugang zu medizinischer Versorgung

2.1.2 Sickle-cell disease (SCD)

SCD occurs when Hb S is present in the homozygous state or compound heterozygosity with specific other beta globin gene (HBB) variants (Hb C, D, or E) or with β-thalassemia. Hb S results from a particular point mutation in the gene HBB, which encodes Hb beta chains [11].

Sichelzellkrankheit: erbliche Hämoglobinopathie

Clinical manifestations

The major acute manifestations of SCD are related to infection, anemia, and vasoocclusion; many of these complications are potentially life-threatening [12].

klinische Manifestationen

- **Infection:** is a major cause of morbidity and mortality for children and adults with SCD caused by mechanisms including functional hyposplenism or asplenism, altered humoral and cellular immunity, reduced tissue perfusion, presence of an indwelling catheter, splinting, and hypoventilation. Common sites of infection include bacteremia, meningitis, and pulmonary infections, which may present with fever and leukocytosis and, in some cases, with focal findings including fever, headache, meningismus, and/or seizures in meningitis or fever, chest pain, cough, wheezing, and/or hypoxemia [12].

  Infektionen sind Hauptursache für Morbidität und Mortalität

- **Anaemia:** SCD leads to chronic, compensated hemolytic anaemia that may include episodes of acute declines in the Hb level. Other contributing factors to chronic anaemia are an inappropriately low serum erythropoietin concentration and/or folate or iron deficiency. An aplastic crisis can cause an acute drop in the Hb level, a splenic sequestration crisis, and a hyperhemolytic crisis, all of which are potentially life-threatening [12].

  chronisch hämolytische Anämie

[3] Of note, currently, diagnostic evaluation of thalassemia is not included in Austrian newborn screening program.

Milzsequestration: potentiell lebensbedrohlich

- **Splenic sequestration crisis:** is a potentially life-threatening complication of SCD and is characterized by an acute drop in Hb level. This occurs when RBCs are captured and pool within the spleen. Consecutively, a large percentage of the total blood volume can become sequestered in the spleen, leading to hypovolemic shock and death. Splenic sequestration has been reported to affect as many as 30% of young children with SCD and can be the presenting symptom in up to 20% of patients overall. Patients with splenic sequestration crisis present with a rapidly enlarging spleen and a marked decrease in Hb level despite persistent reticulocytosis. The mortality rate is as high as 10-15%, and patients often die before transfusions can be administered [12].

Gefäßverschlüsse führen zu Schmerzen

- **Vaso-occlusive pain:** Sickled RBCs have a marked reduction in deformability and other effects, including increased adhesion to vascular endothelial cells, resulting in an inflammatory state and activation of hemostatic mechanisms. All of these changes lead to vascular obstruction and vaso-occlusion with pain as one of the major consequences. Patients may have intermittent episodes of acute pain, which sometimes is accompanied by underlying chronic pain [12].

vasookklusive Krisen (früher: "Sichelzellkrisen") können zeitgleich mit lebensbedrohlichen Komplikationen auftreten

Acute painful episodes (previously called "sickle cell crisis") are one of the most common types of vaso-occlusive events in SCD. However, there is significant variability in the severity and frequency of acute painful episodes, vaso-occlusive pain in SCD is intense. Pain can occur at the same time (and therefore mask) other potentially life-threatening complications of SCD. Most pain episodes are managed by children, adolescents, and adults at home [12].

neurologische Komplikationen, z.B. Insult, Krämpfe

- **Neurologic complications:** SCD is associated with several cerebrovascular and other neurologic complications, including stroke and transient ischemic attack, seizures and posterior reversible encephalopathy [12].

zahlreiche pulmologische Komplikationen möglich

- **Pulmonary complications:** Pulmonary complications occurring in patients with SCD include acute chest syndrome, asthma, sleep-disordered breathing, nocturnal hypoxemia and pulmonary hypertension [12].

Niere häufig betroffen

- **Kidney infarction or medication toxicity**: Involvement of the kidney occurs commonly in patients with SCD; up to one-fifth of patients develop chronic kidney disease. Therefore, unnecessary exposure to nephrotoxic medication should be avoided [12].

Daktylitis typisches Symptom bei Kindern

- **Skeletal complications** are frequent in SCD, including dactylitis (typically in infants and younger children), osteoporosis, avascular necrosis and osteomyelitis [12].

kardiale Komplikationen führen oft zum Tod

- **Cardiac complications** are a common and often unrecognized cause of morbidity and mortality in SCD, representing a major cause of death in adult patients. Cardiomyopathy and heart failure, myocardial infarction, dysrhythmia, and sudden death can occur [12].

psychosoziale Aspekte

- **Psychosocial issues:** Although most individuals with SCD are well-adjusted, the stress of living with a chronic medical condition may contribute to low self-esteem, social isolation, poor relationships, and withdrawal from normal daily activities [12].

Priapismus, Thromboembolien

- Further acute manifestations of SCD include complications that are related to **priapism**, **venous thromboembolism** or correlate with pregnancy [12].

- The **major chronic manifestations** of SCD are caused by chronic organ ischemia and infarction and include chronic pain, anemia, with transfusional iron overload, neurologic deficits or seizure disorder, pulmonary conditions including pulmonary hypertension, impaired kidney function and hypertension, osteoporosis and complications of bone infarction, cardiomyopathy with diastolic dysfunction and heart failure, liver injury and pigmented gallstones, delayed puberty and reduced growth, chronic leg ulcers, proliferative retinopathy and psychosocial stress [12].

zahlreiche chronische Manifestationen

Diagnostic evaluation

Pränataldiagnostik, Neugeborenenscreening, (Familien-)anamnese

The diagnosis of sickle cell disorders can take place in several settings, such as prenatal testing, newborn screening (selective screening of infants of high-risk parents or universal testing of newborns), diagnosis of symptomatic individuals and testing of relatives [13].

Neugeborenenscreening auch in AT geplant

Of note, in contrast to Germany, SCD is currently not included in the Austrian newborn screening program. According to expert information, currently, efforts are being made to include screening for SCD in the Austrian newborn screening programme.

verschiedene Diagnoseverfahren möglich

Diagnosis of a sickle cell disorder is generally made via high-performance liquid chromatography (HPLC), isoelectric focusing (IEF), or gel electrophoresis techniques; polymerase chain reaction (PCR) or Deoxyribonucleic acid (DNA) sequencing may also be used. For children and adults, the combination of HPLC and IEF allows for a definitive diagnosis of SCD [13].

Prognosis and natural course of the disease

Lebenserwartung reduziert

Prognose bei guter medizinischer Versorgung verbessert, dennoch chronische Erkrankung

Survival of patients with SCD is reduced compared to those without SCD. Due to the institution of comprehensive care that includes newborn screening, immunizations, antibiotics, hydroxyurea, and more rapid prevention and treatment of disease complications, the prognosis for SCD has been steadily improving. In regions where comprehensive care is available, the disease has shifted from being a fatal paediatric illness to proceed as a chronic disease that is often associated with progressive deterioration in the quality of life (QoL) and organ function [14].

2.2 Incidence, prevalence and estimated number of patients in Austria

AT: 0,2% Träger in einheim. Bevölkerung geschätzte Gesamtpopulation: 60-79 bei TDT und 132 bei SCD

In Austria, in 2020, the carrier rate of β-thalassaemia and SCD in the indigenous population was 0.2% [15]. The number of accepted migrants from regions with a high prevalence of thalassemia and a low prevalence of SCD was 311,000, while the number of accepted migrants from areas with a high prevalence of SCD was 14,000. The estimated patient population, including both

indigenous and migrant individuals, was 60-79 for β-thalassemia syndromes and 132 for SCD[4] [15].

AT → geringe Anzahl an geeigneten Patient*innen

According to estimates from clinical experts, a total of 30 patients could potentially be eligible for exa-cel treatment in Austria over the next three years. The manufacturer estimates a number of 15 patients with TDT and 15 patients with SCD who could be eligible for exa-cel. From a paediatric perspective, there are currently only three to four patients with TDT and nine to twelve patients with SCD who are eligible for treatment with exa-cel [6].

2.3 National and international treatment guidelines

For Austria, no specific guidelines are available for treating thalassemia and SCD.

Leitlinien zur Behandlung der Thalassämie

Internationally, the following guidelines are available for the treatment of thalassemia:

- AWMF-Leitlinie 025/017 "Thalassämien". S1-Leitlinie der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) und Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ) [16].
- Onkopedia Guideline "Beta Thalassämie" [17].
- Guidelines for the Management of Transfusion-Dependent Thalassaemia (4th edition, Version 2.0, 2021) by the Thalassaemia International Federation (TIF) [18].

Leitlinien zur Behandlung der SCD

International guidelines for the treatment of SCD:

- American Society of Hematology (ASH) 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults [19].
- AWMF-Leitlinie 025/016 „Sichelzellkrankheit". S2k-Leitlinie der Gesellschaft für Pädiatrische Onkologie und Hämatologie und der Deutschen Gesellschaft für Kinder- und Jugendmedizin [20].
- Onkopedia Guideline "Sichelzellkrankheiten" [21].

2.3.1 Treatment guidelines[5] for patients with TDT

Paediatric patients

Guidelines für pädiatrische Patien*innen

In Austria, for the **treatment of children with TDT**, the S1 Guideline of the Society for Paediatric Oncology and Haematology (GPOH) and the German Society for Paediatrics and Adolescent Medicine (DGKJ) is applied [16].

[4] Information on the number of patients, where access to an updated registry is not available are derived from information provided by national experts, either during Thalassaemia Interntional Federation (TIF) visits or during the TIF European Symposium for Thalassemia and Sickle Cell Disease (December 2020).

[5] In the guidelines cited herein, the former terms "thalassaemia major, intermedia and minor" are used instead of "transfusion-dependent thalassaemia" or "non-transfusion-dependent thalassaemia".

Curative treatment options

- Haematopoietic SCT

  Stammzelltransplantation

  If an **HLA-identical related donor** (sibling) is available, this treatment is chosen for patients with thalassaemia major. Less than 25% of patients have an HLA-identical stem cell donor in the family. In experienced centres, HSCT with an HLA-identical, unrelated donor is also an accepted indication. For this, high-resolution molecular typing for both HLA class I and HLA class II alleles is required. Due to the increasing risk of transplant-related morbidity and mortality (which increases with age), transplantation should be **performed in early childhood** if possible. At this point, most patients do not yet have organ damage caused by chronic iron overload [16].

- Gene therapy

  Gentherapie

  The most essential gene therapy approach currently is exa-cel, which works by silencing the BCL11A gene in hematopoietic stem cells. Long-term studies on the efficiency of erythropoiesis are of great importance in ruling out the possibility that the phenotype of TDT does not eventually develop. Busulfan-based conditioning is required for all currently investigated gene therapy approaches, which causes the corresponding side effect profile (including VOD of the liver) [16].

Symptomatic treatment

- Transfusion therapy

  Transfusionstherapien

  The symptomatic treatment of thalassaemia major includes **regular transfusion therapy in combination with chelation therapy** to prevent a threatening iron overload of the organism. Organ damage occurring during the course of the disease and/or endocrine organs requires appropriate disease- and organ-specific treatment. The indication for the start of transfusion treatment is a repeated drop of Hb below eight g/dl. The beginning of a regular transfusion programme may be indicated in the case of typical clinical symptoms and constant values above this Hb level. The recommended baseline Hb level for permanent extensive suppression of endogenous erythropoiesis is erythropoiesis is 9.5-10 g/dl. A transfusion interval of three (to four) weeks is generally recommended. An extended blood group determination and genotyping may be helpful or necessary to reduce the risk of alloimmunisation [16].

- Chelation therapy

  Eisenchelatoren

  The start of iron elimination therapy is indicated if the serum ferritin concentration is repeatedly >1000 μg/l in the regular determination and/or the liver iron content in the magnetic resonance imaging (MRI) reaches 4.5 mg/g dry weight (value depends on method). These values are reached after ten to 15 transfusions depending on the transfusion volume. For primary therapy, deferasirox and deferoxamine are recommended, depending on the patient's age. For secondary therapy, deferiprone is available [16].

- Luspatercept[6]

Luspatercept

Luspatercept was authorised in 2020 to treat adult patients with TDT. The approval was based on results of the BELIEVE trial, showing long-term response with a reduction of the transfusion burden by >33% in about one-third of patients. The most severe side effects were thromboembolic events in 3.6% of the β-thalassaemia patients treated with luspatercept (0.9% with placebo). All events were reported in patients who had undergone splenectomy and had at least one further risk factor. Therefore, before using the drug, especially in splenectomised patients, a detailed evaluation of haemostaseological underlying diseases and, if necessary, a thrombophilia screening to exclude further risk factors is strongly recommended. Trials investigating luspatercept in paediatric patients are ongoing (NCT04143724) [16].

Adult patients

TDT bei Erwachsenen: Onkopedia-Leitlinie

For the treatment of **TDT in adult patients** in Austria, the Onkopedia guideline [17] is applied, with the following treatment options recommended:

Patients with thalassemia major or intermedia should be presented to a haematologist experienced in the care of patients with β-thalassemia at the latest after diagnosis for consultation and determination of the therapeutic procedure [17].

Causal therapeutic options

- Allogeneic SCT

Stammzelltransplantation

Transplantation with haematopoietic stem cells from an **HLA-identical family donor** is currently the treatment of choice for patients with TDT, with most patients undergoing transplantation during childhood. Adult patients often already have significant organ damage, which increases the rate of complications, including transplant-associated mortality. In patients without a related donor, an HLA-identical donor can be a suitable treatment option, though strict donor selection is necessary to minimise transplant-associated complications. Transplantation from HLA-haploidentical donors is possible but is currently still classified as experimental and not generally recommended. When deciding for or against SCT, especially from a non-related, HLA-identical donor with the associated risks, developments in drug therapy (such as iron chelation) and the resulting improvements in the long-term prognosis of patients with thalassaemia major regarding morbidity and mortality, must be considered. Nevertheless, SCT from a non-related HLA-identical donor, and possibly from an HLA-haploidentical donor, remains an important treatment option, particularly for patients who cannot receive long-term transfusion therapy due to severe alloimmunisation [17].

- Gene therapy

Gentherapie

In the long term, using gene therapy approaches, curative treatment of thalassaemia major is also possible. The most important alternative gene therapy approach is silencing the BCL11A gene in hematopoietic stem cells. BCL11A is the most critical suppressor of HbF synthesis in adult erythropoiesis, and initial positive results have been demonstrated for this

[6] Although luspatercept is not authorised for the treatment of children with TDT, the guideline cited herein refers to it in chapter "Symptomatic treatment of thalassaemia major".

form of gene therapy. Long-term studies on the efficiency of erythropoiesis are of great importance to ensure that the phenotype of thalassemia intermedia does not eventually develop. All currently investigated gene therapy approaches require the patient's conditioning, which is presently Busulfan-based. This also determines the corresponding side effect profile, including the occurrence of VOD of the liver in individual patients [17].

- Hydroxycarbamide

  Hydroxycarbamide

  Hydroxycarbamide is an orally administered **cytostatic drug that induces the formation of HbF** and increases the proportion of primary HbF-producing cells. To date, it was the only drug that increased the Hb content in a significant proportion of patients with thalassaemia intermedia. There is a lack of randomised studies on hydroxycarbamide, so its use must be carefully considered in each case [17].

- Luspatercept

  Luspatercept

  Luspatercept is a recombinant fusion protein, leading to an increase in the effectiveness of erythropoiesis. As mentioned above, luspatercept was approved for treating adult patients with TDT in 2020. The approval was based on the randomised, double-blind, placebo-controlled BELIEVE study results described earlier in – Paediatric patients [17].

Symptomatic treatment

- Transfusion therapy

  Bluttransfusionen

  Transfusion of **erythrocyte concentrates** for thalassemia major or intermedia aims to correct the anaemia and its consequences and suppress the patient´s ineffective erythropoiesis. In patients with TDT, transfusion therapy starts in infancy. A baseline Hb level of 9.5-10 g/dl and a post-transfusion Hb level of 13-13.5 g/dl should be reached with transfusion therapy. It is recommended to conduct transfusion therapy in intervals of three weeks (max. four weeks) with a transfusion volume of twelve to 15 ml/kg of body weight or a transfusion interval of two weeks with a lower transfusion volume. Significantly longer transfusion intervals should be avoided [17].

- Chelation therapy

  Eisenchelatoren

  Chelation therapy is used to reduce total body iron to a level that minimizes the risk of complications from secondary hemochromatosis. In contrast, the side effects of chelation therapy should be avoided. The aim is to achieve a liver iron level of <5 mg/g (MRI-based). Deferoxamine, administered subcutaneously, and the oral chelating agent deferasirox are approved for the primary treatment of patients with TDT. The oral chelating agent deferiprone is also available as a secondary therapy. Some patients develop severe iron overload despite chelation therapy, usually due to a lack of compliance. Intensified iron elimination treatment by a combination of chelating agents is necessary for these patients to achieve a rapid and sustained reduction in iron overload [17].

2.3.2 Guidelines for the treatment of patients with SCD

Paediatric patients

Leitlinie für Kinder mit SCD

In Austria, the S2k Guideline of the GPOH and the DGKJ [16] are used to treat **children with SCD**; the following options are recommended:

- Basic measures

Basismaßnahmen

Basic measures include patient education (patients and carers should be informed about possible complications of SCD), information about strategies to avoid complications of SCD, infection prophylaxis, vaccinations, routine diagnostics (patients with SCD should be referred to a specialist centre at least once a year) [20].

- Hydroxycarbamide

Hydroxycarbamid empfohlen

Hydroxycarbamide is approved for the prevention of recurrent, painful VODs, including acute chest syndrome, in adults, adolescents, and children over two years of age with symptomatic SCD. It can prevent complications of SCD and reduce mortality by **increasing the HbF level** and reducing the neutrophil count. Although the response to hydroxycarbamide cannot be reliably predicted, its effectiveness in reducing the frequency of pain events and episodes of acute chest syndrome is well documented. Any patient with SCD who has experienced painful VODs (even mild ones) or acute chest syndrome should be treated with hydroxycarbamide. Treatment should be initiated as early as possible. The side effect profile of hydroxycarbamide in children does not differ significantly from that in adults; in particular, no negative influence on growth and development has been demonstrated. Side effects include (dose-dependent) myelosuppression and immunosuppression with the risk of opportunistic infections, azoospermia and skin changes. It is unclear to what extent hydroxycarbamide affects fertility. Adolescents and women of childbearing potential should be aware of the need for safe anticonception. Due to the risk of azoospermia, post-pubertal patients should be made mindful of the option to cryopreservation of sperm [20].

- Transfusion therapy

Transfusionstherapien: wichtige Therapieoption

The **transfusion of RBC concentrates** is an important element in the treatment of patients with SCD. Transfusions are necessary for the treatment of certain acute complications but can also be part of a long-term therapy concept. However, only a few indications are supported by valid study data. Transfusions are associated with potentially serious side effects, particularly due to the risk of alloimmunisation, haemosiderosis and the transmission of infections. They should, therefore, only be used with caution and a clear indication. Transfusions positively affect both the vaso-occlusive and the haemolytic-vasculopathy components of the disease [20].

- Allogeneic SCT

allogene SZT: etablierte Therapie

The only curative therapy currently available for patients with SCD is HSCT, providing an established treatment method for this patient group for over 30 years. Data from a registry study showed that **HSCT of HLA-identical siblings** offers excellent long-term survival in patients with SCD. If no HLA-identical sibling donor is available, transplantation from a 10/10 HLA-identical unrelated donor should be considered as an alternative option. It is recommended that haploidentical SCT should only be carried out as part of a study and in experienced centres. Since

the indication for allogeneic SCT in SCD is also an indication for treatment with hydroxycarbamide and treatment with hydroxycarbamide probably has a favourable effect on the outcome of SCT, all patients should be treated with hydroxycarbamide during the preparation period for SCT. Before HSCT is performed, the patient should be informed about the possibility of fertility-preserving measures [20].

- Gene therapy

  In 2017, the first successful gene therapy (betibeglogene autotemcel/Zynteglo®) was reported in a patient with SCD. Various studies with different techniques and vectors are ongoing and show promising results [20].

  Gentherapie

- Psychosocial care

  Psychosocial care is a standard part of treatment in paediatric oncology and haematology; in recent years, a variety of care concepts have been developed for these patients and their relatives [20].

  psychosoziale Betreuung

Adult patients

For the treatment of **adult patients with SCD** in Austria, the Onkopedia guideline [21] is applied, recommending the following:

SCD bei Erwachsenen: Onkopedia-Leitlinie

- Basic measures

  These include the best possible **educational and vocational training**, doing sports, avoiding excess weight, covering the increased fluid requirement and avoiding smoking. Before starting a family, it is strongly recommended that the partner be tested for other Hb abnormalities to be able to offer genetic counselling and possibly prenatal diagnostics [21].

  Basismaßnahmen

- Infection prophylaxis and vaccinations

  All **vaccinations** recommended by the STIKO (Standing Committee on Vaccination) should be carried out; annual flu vaccination should also be administered. For sickle cell patients who have received a sequential vaccination for pneumococcal prophylaxis (PCV13 + PPSV23) in the past, vaccination with PCV20 is recommended at least 6 years after the PPSV23 vaccination. PCV20 is authorised from > 18 years of age [21].

  Infektionsprophylaxe + Impfungen

- Hydroxycarbamide

  In patients with SCD, **hydroxyurea reduces pain crises** and acute thorax syndrome in about 70% of cases and also has a positive effect on kidney function. Side effects include myelosuppression, possible azoospermia (cryopreservation recommended for post-pubertal patients), hypomagnesemia, skin and nail alterations, possible increase in Hb to values above ten g/dl with an increase in viscosity and potential need for phlebotomy. No teratogenic or oncogenic effect was observed at the recommended dosage [21].

  Hydroxycarbamid

- Blood transfusions

  Alloimmunizations, even after only a few transfusions, frequently occurs in sickle cell patients (20% to 80%) due to the significant differences in the distribution of blood group characteristics among different ethnic groups. If possible, the antigen systems RhD, rhesus mosaic, K,k, Kp(a), Kp(b), Fy(a), Fy(b), Jk(a), Jk(b), M, N, S, s, Lu(a), Lu(b), Le(a), Le(b) should be typed using conventional serological methods before the first administration. Transfusions should **only** be given **when strictly indicated**. Neither the chronically low Hb levels in homozygous sickle cell patients (6-8 g/dl) nor pain crises are an indication for transfusion.

  Bluttransfusionen: strenge Indikationsstellung, Gefahr der Alloimmunisierung

Acute indications for transfusion therapy include symptomatic anaemia, acute apoplexy, acute chest syndrome, multi-organ failure, severe sepsis, mesenteric/Girdle syndrome and acute intrahepatic cholestasis. Long-term indications include primary or secondary stroke prevention, recurrent acute chest syndrome despite hydroxyurea treatment, repeated pain crises despite hydroxyurea (or in case of intolerance), intractable leg ulcers, recurrent intrahepatic cholestasis, progressive end-organ damage (cardiac, pulmonary, renal), and particular indications such as pregnancy with complications [21].

- Phlebotomies

Phlebotomien

More than 90% of all adult patients with HbSC (haemoglobin SC disease; a typical phenotype in SCD patients) have Hb values >10 g/dL (often exceeding 12 g/dL), resulting in increased blood viscosity, which can lead to frequent pain crises, vertigo, and/or hearing loss or deafness. In patients with these manifestations and an Hb >11 g/dl, phlebotomy is recommended to reduce the Hb to <10 g/dl. All sickle cell patients **with pain crises** whose Hb is >10 g/dl should undergo phlebotomy to reduce viscosity. This also includes HbSS or HbSβ thalassaemia patients receiving hydroxyurea, in whom the Hb level can rise to values >10 g/dl and lead to the symptoms mentioned above [21].

Therapieoptionen:

Further therapeutic approaches

- Allogenic SCT

Stammzelltransplantation

SCT with a high-resolution **HLA-identical family donor** is still the only established curative therapeutic approach and should be considered regardless of age. Particularly after the age of 14 to 15, undesirable side effects, such as transplant-associated mortality and the incidence of chronic graft-versus-host disease, increase. As already mentioned in the paediatric treatment plan, the transplantation results with an unrelated donor do not correspond to those of a family donor and should, therefore, be critically scrutinised. As an HLA-identical sibling donor or an unrelated donor can only be found for a few patients (<20%), haploidentical transplantation (parents, siblings and biological children) has been increasingly investigated in recent years. This procedure can achieve considerable success when performed by experienced transplant teams in designated centres [21].

- New drug approaches

The marketing authorisations for crizanlizumab (Adakveo®) and for Voxelotor (Oxbryta®) were revoked and suspended by the EMA, respectively. Pyruvat kinase activators are currently under clinical investigation. [21].

- Gene therapy and gene editing therapy

Pyruvatkinase-Aktivatoren derzeit in klinischer Prüfung

gentherapeutische Ansätze

Until recently, several gene therapy approaches were being trialled in Europe. Viral-based gene therapy, which uses a lentiviral vector to introduce a functional β-globin gene into the stem cells, was withdrawn from the European market. CRISPR/Cas9-based gene editing disinhibits the blockade of gamma chain transcription through a targeted knock-out (BCL-11a) and thus increases HbF production. This therapy was recently approved by the EMA and will be available in selected German centres from mid-January 2025 [21].

2.4 Current standard of care (SoC) and expected role of the new medicinal product within the established treatment pathway

2.4.1 SoC for TDT

SoC für TDT in AT: Erythrozytenkonzentrate und Eisenchelattherapie

alternative Behandlungsmöglichkeiten laut Leitlinien

According to expert information, the current SoC for treating TDT in Austria consists of administering **erythrocyte concentrates and chelation therapy** [6].

According to guidelines [16, 17, 20, 21], alternative treatment options for TDT include autologous stem cell transplantation (ASCT), hydroxyurea, and luspatercept (Reblozyl®) as causal treatments, as well as the administration of erythrocyte concentrates, chelation therapy, and the management of secondary conditions (e.g., cardiopulmonary diseases, endocrinopathies, osteopenia-osteoporosis syndrome, thromboembolic events) as symptomatic treatments, with a necessity for lifelong administration.

A detailed description of the respective treatment options can be found in chapter 2.3.1.

2.4.2 SoC for SCD

SoC für SCD in AT: Hydroxyurea

in Österreich (AT): Austauschtranfusionen vor Exa-cel als Standard of Care (SoC)

alternative Behandlungsmöglichkeiten laut Leitlinien

According to information from clinical experts in Austria, the SoC for treating SCD is the **oral administration of hydroxyurea** [6].

According to expert opinion, Austria's standard of care (SoC) would include exchange transfusions for six months before exa-cel administration to optimise organ function [6].

Guidelines [16, 17, 20, 21] recommend the administration of hydroxyurea, blood transfusions, phlebotomies, SCT, and gene therapy/gene editing.

A detailed description of the respective treatment options can be found in chapter 2.3.2.

2.4.3 Expected role of the new medicinal product

Exa-cel: potentielle Heilung bei TDT and SCD

Within the established treatment pathway, the expected role of exa-cel is to provide a **potentially** curative treatment option for patients aged twelve years or older with:

- TDT for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available.
- Severe SCD with recurrent VOCs for whom transplantation is appropriate and an HLA-matched related HSC donor is not available.

2.4.5 Early Access or Named Patient Programme

kein Early Access or Named Patient Programme

According to the manufacturer, the Early Access or Named Patient Programme is currently not planned [22].

2.5 Organizational, ethical and social aspects of new therapy

2.5.1 Method

strukturiertes Herangehen nach dem EUnetHTA CoreModel®

To structure the information on these non-clinical domains, we used the European Network for HTA (EUnetHTA) approach, called core model®. The model uses structured questions to address different organizational, ethical and social aspects.

Quellen:

The data sources used to answer the questions are

Interviews mit führenden Kliniker*nnen
Schriftliche Befragung von Patient*innen
Literatur

- Interviews with three leading clinical experts (for questions see Table A - 5 in appendix)
- Questionnaires with open-ended questions filled out by nine people with lived experience (seven patients, two carers; 67% females; around half each suffer from severe Thalassemia and SCD; for questions see Table A - 4 in the appendix)
- Literature retrieved from the systematic search (see chapter 3.2.1)

The information from these three data sources has been clustered into the different categories within the organisational, ethical and social domains of the EUnetHTA core model® and narratively summarised. The raw data are available on request from the authors.

2.5.2 Organisational aspects

Health delivery process and management

hoch-spezialisierte Behandlung mit Vor- und Nachbereitung in Zentren

Transplantationszentren arbeiten bereits jetzt an ihren Grenzen

Hospitalisierung zur Vorbereitung

Apherese auch ambulant

The technology requires several highly specialised preparatory interventions and treatments, close monitoring after the treatment and less frequent but regular long-term monitoring (see chapte 1.3). The entire procedure must occur in transplantation centres with currently limited capacities. Highly skilled clinical experts who have knowledge of the mobilisation procedures to harvest stem cells and of stem cell transplantation itself need to be in place. In contrast to allogeneic stem cell transplantation, collecting stem cells for gene therapy is expected to take longer (requires more apheresis cycles) because more stem cells may be required for gene editing. Some procedures involve logistical challenges, such as determining the Busulfan blood level, which is currently done in Zürich for the St. Anna Children's Hospital. The preparatory interventions predominately require hospital inpatient admission, while some (e.g., apheresis) can be done in the hospital outpatient setting.

Clinical experts estimate the patient's hospital stay for the entire procedure to be five to six weeks. Close and efficient communication between the patients and the health care professionals is needed during all phases. The patient should be capable of speaking German. If this is not the case, language support needs to be in place at any time during the procedures.

Dauer des Aufenthalts während Behandlung: 5-6 Wochen

ggf. Sprachhunterstützung notwendig

The intervention, therefore, needs to be planned carefully in advance so that all the required staff, including auxiliary services such as language interpreters, infrastructure and capacities, are available. It needs to be clarified in advance who is responsible for the case (case-management) to coordinate all services properly. Centres in which the intervention can take place need to be defined in advance. This includes information for potential referrers and patients.

Fall-Management zur Koordinierung

According to expert information, this kind of therapy for congenital blood diseases has so far not been intended for adults and specialised departments for stem cell transplantation do not exist in adult care but adults are treated in hematology departments. So far, these patients have run alongside oncology departments. In the Viennese General Hospital, the largest teaching hospital in Austria, no adult has ever undergone transplantation with autologous stem cells in the respective indications. If adults receive the intervention in the future, capacity must be provided so that other patients do not suffer undue disadvantages. For the costs beyond the gene therapy itself a reimbursement mechanism may have to be established within the hospital financing system (LKF). Finally, training has to be provided for staff in adult care.

bislang spezialsierte Versorgung bei Hämoglobinopathien nur für Kinder, Erwachsene werden in onkologischen Kliniken mitversorgt

Kapazitätsplanung und Abgeltung abseits der Gentherapie-Kosten

Patients or their carers, in the case of minors, need to be informed in detail and understand the consequences of this intervention (e.g., extended hospital stay, very burdensome interventions that lead to temporarily very low quality of life, and monitoring after the intervention) so that they can make an informed decision.

Patient*innen und deren Angehörige brauchen Aufklärung zu den Konsequenzen und Belastungen der Intervention

Patients may need to transition from paediatric to adult health care during the monitoring phase. Appropriate transition and coordination between the health care staff from paediatrics to adult care need to be in place. Gaps between paediatrics and adult care have been significant barriers to therapies so far and even led to the death of patients after the close monitoring and treatment by the paediatrics team had stopped due to the transition into adulthood. According to clinical experts, there is often a misconception among healthcare professionals that the treatment of severe SCD is exclusive to paediatrics, as affected children would not survive until adulthood.

Versorgung von Patient*innen in der Transitionsphase oft mangelhaft im Langzeit-Monitoring

The short follow-up of patients in the clinical studies and the uncertainties for long-term benefits and risks (e.g., secondary myeloid dysplasias) require ongoing data collection in treated patients. Clinical experts are negotiating with international registry operators to feed in their data. However, post-launch evidence generation requires highly compliant patients who attend their regular monitoring appointments.

Datendokumentation aufgrund der kurzen Nachbeobachtungszeiten unabdingbar

Patient*innen müssen aber „compliant" sein und zur Nachsorge kommen

Culture

kulturell bedingte Zurückhaltung

Sorge wegen Neben- und Folgewirkungen

hohe Erwartungen und hohe Nachfrage

Sorge, dass Ablehnungen notwendig

Both clinical experts and patient representatives state that some patients may be hesitant towards the new technology. According to the clinical experts, some have had bad experiences with medical 'experiments' 20 years ago; others are worried about severe side effects such as adverse impacts on fertility or increased long-term cancer risks (see chapter 2.4.3). A considerable proportion of respondents were not aware of the new technology and its characteristics. Others, who may have heard about the new technology, may have high expectations and demand the new therapy without being aware of the consequences of the treatment, the uncertainties of the evidence, or the eligibility criteria. Some clinicians have expressed concern that the demand from patients who are not eligible for treatment could be high and that it can be stressful to make decisions or refuse treatment.

2.5.3 Ethical and social aspects

Benefit-harm balance

Nutzen-Risiko Abwägung

Gentherapien (basiernd auf viralen Vektoren) sind mit Umweltrisken assoziiert

für exa-cel nicht zutreffend

jedoch zu Genediting bislang keine Langzeit-Erfahrungen

According to the EUnetHTA core model which we used for systematically addressing the ethical aspects, benefit-risk assessment needs to be an integral of the ethical assessment. The expected direct benefits and harms related to exa-cel are presented in chapter 3.2. Regarding potential further and indirect harms, it needs to be noted that exa-cel is a gene therapy. All gene therapies require specific safety attention because of potential risks for unintended persons, animals, plants, microorganisms and the environment at large, subsumed under the term 'environmental risks'. Regulations exist on how to address the environmental risks of gene therapies via the so-called Environmental Risk Assessment (ERA) [23]. Most environmental risks are described in connection with viral vector-based gene therapies, such as the risk of viral vector shedding. Exa-cel is not based on virus vectors but on human gene editing technology (CRISPR/cas9); therefore, many of the potential risks associated with other approved gene therapies do not apply. According to the EPAR, the result of the ERA for exa-cel was that both the manufacturing process and the clinical use provide a negligible risk for the environment and for third parties [8]. However, it needs to be noted that it is the first gene editing gene therapy ever approved, with no long-term experience and potential unintended consequences.

Patients' perspective on experiences of living with the conditions, symptoms and burden of disease

Erfahrungsberichte von Patient*innen mit TDT: Müdigkeit und Erschöpfung (vor der nächsten Transfusion)

People with lived experience with TDT who answered the questionnaire described the most common symptoms as tiredness and exhaustion, especially closer to the date of blood transfusion. After the transfusion, patients said it takes a few days to feel better again. The second commonly described symptom, in particular by patients with SCD, is pain, which can be very severe, e.g., in the spine, extremities or pelvis, as well as headaches. Cold temperatures can trigger pain crises. Frequently, patients mention mental health problems (e.g., depression, mood swings). According to clinical experts, adolescents with severe symptoms are at high risk for suicide.

Further less often mentioned symptoms are long-term impairments of joints, polyneuropathy, osteoporosis, impaired wound healing, dizziness, and hormonal problems (e.g., one patient describes she cannot menstruate). In an acute crisis, a patient describes that he/she cannot speak. Further, patients mention the yellowing of eyes (caused by bilirubin released when the red blood cells die, which occurs faster in patients with SCD) and sepsis caused by the Portacath that patients have been implanted to allow permanent access to the veins.

Patient*innen mit SCD: Schmerzen an Wirbelsäule, in Extremitäten oder Becken infolge Depressionen und Stimmungsschwankungen zahlreiche Symptome und Beeinträchtigungen

Patients must undergo regular blood transfusions, which can occur once a month or more frequently. The transfusion requires a hospital stay for one to two days, including further examinations (e.g., blood test). Many patients have had to undergo transfusion from a very young age onwards. In addition, patients need to take regular oral medication (iron chelation). Patients unanimously emphasised the significant benefits of oral iron chelation, which previously had to be applied as a subcutaneous infusion for several hours five to seven times a week [24]. Both diseases are related to reduced life expectancy, particularly in severe forms and if not treated adequately [25].

regelmäßige Transfusionen bedingen Spitalsaufenthalte

orale Eisenchelatoren brachten großen Nutzen

Most patients who responded are employed; however, they describe challenges. Patients depend on understanding employers who accept the person's need for regular hospital stays. A full-time job is often impossible, and the employee may need extra breaks. Some respondents are worried about losing their jobs and feeling guilty for their regular absences. Patients mention the extra burden of planning and coordinating work and therapies/hospital stays.

verständnisvolle Arbeitgeber wegen Krankenhausaufenthalten oder häufigen Pausen bei Berufstätigkeit notwendig

Patients describe that combining work, family and caring duties is challenging. Female patients, in particular, stress the limitations the disease brings for childcare responsibilities and the burden for their partners. Some patients struggle with not being able to meet expectations from friends or family members regarding joining activities (e.g., sports activities). Some respondents feel isolated, for example, because others may misinterpret their yellow eyes as having an infectious disease. Many respondents expressed hesitancy to speak openly about the disease with friends or colleagues because of fear of stigmatisation and discrimination. Respondents' general worries were the lack of sufficient blood donors, co-morbidities in old age, and whether they could be handled.

beruflich und private Belastungen für Patient*innen:

Familie, Kinderbetreuung, Freund*innen, Freizeit und Sport sind beeinträchtigt

Sorgen zur Zukunft

Caregivers or family members describe frequent worries about the health state of the patient, in particular, if the patient has severe pain crises. Living with a family member with the disease requires understanding, flexibility and taking on more household or caring responsibilities. Partners or children of patients need to be well informed about the disease because they may need to take active action in case of a crisis. Family members find it stressful not being able to talk openly about the disease with others.

Angehörige brauchen Verständnis für Schmerzkrisen, Haushaltsführung etc.

Expectations and wishes regarding the new therapy

Patients most frequently expressed expectations for a new therapy that it would increase their quality of life and enable them to live a normal life by reducing pain crises, reducing or eliminating hospital stays for transfusion, and improving mental health. Another expectation is that with a new therapy, it is no longer necessary to take regular medication or to reduce the frequency of drug intake.

Erwartung an neue Therapie: Steigerung der Lebensqualität, Verringerung von Schmerz und Transfusionen

Erwartung an Heilung, Therapie nur, wenn Organe und Fertilität intakt bleiben und weniger risikoreich wie allogene SCT

Patients wish to have a therapy that cures the diseases. Still, they also expressed that they would not accept severe side effects that damage organs or impair fertility because they tolerate the current treatment and mostly manage the disease well. The new therapy would have to be less risky than an allogeneic stem cell transplantation.

Social group aspect

SCD-Betroffene sind vornehmlich afrikanischer Herkunft, TDT in Ost- und Süd-Ost Asien

verschärft globale Ungleichheit durch Mangel an Zugang zur Therapie

SCD and TDT are global health concerns. Since SCD predominantly occurs in people of African and African-Caribbean descent, the highest prevalence of SCD is in Africa. TDT prevalence is highest in East Asia and South East Asia [25, 26]. Representatives from high-prevalence countries stress that the availability of the new gene therapy brings with it a responsibility for international collaboration to avoid an increase in global health inequality by limiting access to therapy to high-income countries while the majority of eligible patients live in low and middle-income countries. Strategies on a global level are needed to ensure equitable distribution and access [27].

Zugangsbarrieren in Österreich: Sprache, Aufenthaltstitel, Kenntnis des Gesundheitssystems

Within Austria, barriers for access in eligible patients may be due to language, lack of familiarity with the health care system, that patients have no permanent residence or only access healthcare in case of acute crisis without permanent monitoring.

Autonomy, Justice and Equity

SCD und TDT Patient*innen gehören zu vulnerablen Bevölkerungsgruppen: Migrant*innen aus sozio-ökonomisch deprivierten Verhältnissen

Patients eligible for treatment with the new therapy belong to a vulnerable group. In Austria, most if not all of them have a migration or refugee biography. Many belong to a disadvantaged socio-economic group with limited knowledge of the national language. Many arrive in a very poor health state, especially if they are unaccompanied minors without access to treatment during the flight. Some of them have to be hospitalised for a longer time period or require treatment over many months to improve their health state. Another reason for the poor health state is that access to current SoC is often restricted in the countries of origin. For example, they have to pay for the blood products privately.

Selbstbestimmung der Patient*innen ist durch Spitalsaufenthalte, lebenslange Medikamentierung etc. beschränkt

Patients' autonomy is additionally restricted by the current therapies, which require frequent hospital admission for transfusion in the case of TDT, two to four hospital admissions per year for patients with SCD and taking lifelong medication. If patients with TDT are abroad longer (e.g., on holidays), they need to organise access to transfusion, and an appropriate donor must be available. There can be adverse reactions if the blood product is not genetically matched, which is often the case in countries with less advanced health care systems. Patient autonomy likely increases if the new therapy successfully reduces the number of blood transfusions or the need for other regular treatments.

Patients must be extensively informed to guarantee patient autonomy when applying the new treatment with exa-cel. To support informed decisions, patient information needs to include details on the procedures and treatments before, during and after the intervention, the duration of those procedures, the potential risks and benefits of the treatment and all additional procedures. They need to be aware of the need for several weeks of hospital stay and of the vulnerability after the intervention because of immunodeficiencies of up to one year with increased susceptibility to infectious diseases. The magnitude of the entire treatment package – one of the clinical experts compared it with heart surgery – needs to be communicated. Furthermore, patients must be aware that they can only undergo the procedure if they are in a very good health state, thus being compliant with ongoing therapies with the current SoC. Additionally, patients need to be informed about the uncertainties arising from the limited evidence available to date regarding benefits and harms, including potential long-term cancer risks. An important aspect regarding autonomy is that a considerable proportion of the eligible patients will be minors, with parents having to make decisions on their behalf.

informierte Entscheidungen und Aufklärung der Patient*innen zu den Belastungen der Vorbehandlungen und zu Risken (Immundekte) bis zu einem Jahr nach der Gentherapie sind unerlässlich

zudem Unsicherheiten aufgrund der kurzen Nachbeobachtung

Bedeutung von „Compliance"

Regarding justice and equity, access to the new therapy may be limited because patients cannot or do not access the current SoC. This may be due to a lack of knowledge on the condition and the health consequences of inadequate treatment, language barriers, lack of knowledge on how to access care and where to find specialists or lack of health insurance coverage in the case of undocumented migrants. Since a good health state is a pre-condition for the treatment with exa-cel, poor treatment with the current alternatives results in disqualification for the new treatment.

Verteilungsgerechtigkeit: schlechter allgemeiner Gesundheitszustand, Sprachbarrieren, Unwissenheit tragen zu ungleichem Zugang bei

Inequity and injustice can occur in different and sometimes subtle forms and can affect patient autonomy in multiple ways. A recent US study found that the rate of postpartum sterilisation is significantly higher in American women with sickle cell disease than in those without after controlling for other factors [28]. Although the exact reasons are unknown, it cannot be ruled out that direct or indirect coercion might play a role in the argument to reduce pregnancy complications. However, pregnancy complications in women with SCD may be controlled if women have access to specialised SCD care. Furthermore, access to contraception might influence the decision about sterilisation. The heightened sensitivity to potential coercion is fuelled by observations of racism against people with SCD. For example, sickle cell crises are sometimes disbelieved and interpreted as drug-seeking behaviour among staff in accident and emergency departments in the US. This kind of data analysis is unavailable for Austria and cannot be directly transferred from the US context. Yet, anecdotal evidence for misinterpreting severe pain and the need for opiates by healthcare staff has also been provided by clinical experts in Austria. Overall, these data draw attention to potential discrimination resulting from racism.

weiteres Beispiel für Ungleichheit und Ungleichbehandlung:

SCD Frauen (in USA) haben deutlich häufiger postpartale Sterilisationen, ggf. durch Nötigung

Diskriminierung von SCD Betroffenen

Limitations

The limitation of this chapter is that the number of people with lived experience and clinical experts involved is limited and is not a representative sample. In particular, voices from children or adolescents or carers of very young children with the disease are missing. It is, therefore, highly likely that we have missed some relevant aspects.

Limitationen: kein representative Gruppe von betroffenen Pts.

2.6 Registries and documentation of application

Indikationsregister dokumentieren jegliche Interventionen in definierten Patientengruppen

Disease-specific registries contain data on patients with a specific clinical indication. In contrast to epidemiological registries, no data on the prevalence or incidence are collected, and in contrast to product-specific registries on medicinal products, indication registries are open to any intervention in the respective patient group. Inclusion in a disease-specific registry usually takes place during routine care [29]. Available indication registries are:

Registries for Beta Thalassaemia and Sickle cell disease

Register zu Beta Thalassämie und Sichelzellanämie:

Register für Seltene Anämien der (deutschen) Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)

GPOH-Registry of Rare Anaemia (Register für Seltene Anämien) of the German Society of Paediatric Oncology and Haematology (https://www.gpoh.de/studienportal/haematologische_studien_und_register/register_fuer_seltene_anaemien) is a multi-centre, retro- and prospective, non-interventional, clinical and epidemiological registry aiming at

- Documenting the epidemiology, type and complications of rare anaemias and improving the care of affected patients by advising doctors who treat patients with rare anaemias and by adapting treatment guidelines based on the results of the registry evaluation, and
- Identification of the causes of rare and as yet unexplained anaemias with the help of specialised and individual step-by-step diagnostics, as well as the establishment of a biobank with samples from patients with rare anaemias and provision of the data for scientific evaluation and as a decision-making aid for health policy decisions

  The Registry - based on a detailed study protocol (https://www.gpoh.de/sites/gpoh/kinderkrebsinfo/kinderblutkrankheiten/content/e94267/e109792/e137555/e223089/download223207/Registerprotokoll_SelteneAnmien_Version2.0.pdf) - is kept by University of Heidelberg, was initiated in 2020 and collects data on demographics, course the disease and therapeutic interventions and is meant to be open-ended for long term data. The German Childhood Cancer Foundation funds the GPOH-Registry.

RADeep, die Europäische Epidemiologische Plattform für seltene Anämiekrankheiten (Europa)

RADeep, the Rare Anaemia Disorders European Epidemiological Platform (https://www.radeepnetwork.eu/), is an initiative conceived in the core of ERN-EuroBloodNet as an umbrella for both new and already existing European patients' registries in rare anaemia disorders (RAD). The intentions of RADeep are

- To ensure interoperability within European structures fostering research,
- To allow mapping at the European level of the diagnosis methods, demography, survival rate, main clinical features and treatments of RAD patients in order
- To improve access to specialised and adequate health care and
- To facilitate research and development of new treatments, thus
- To increase the knowledge and promote best practices across the EU.

RADeep overs the following RADs: Pyruvate Kinase Deficiency (PKD), Sickle Cell Disease (SCD), and Thalassaemia major and intermedia (THAL). A total of 129 centres from 15 European countries are included. Austria is not

participating. https://www.radeepnetwork.eu/radeep-network/radeep-european-mapping/

RADeep is co-financed by public funds and through EuroBloodNet Association by private funds from pharmaceutical companies (Bristol Myers Squibb, Novartis AG, Agios Pharmaceuticals Inc.) to facilitate data gathering and processing of data for disease-specific outcomes.

ERH, the European Haemoglobinopathy Registry (https://www.sicklecellsociety.org/resource/european-haemoglobinopathy-registry/), is a multi-centre registry of patients with haemoglobinopathies (sickle cell and thalassaemia patients), being developed at Central Middlesex Hospital (CMH, London), collaborators are hospitals involved in the treatment of SCD. EHR intends to monitor the clinical care provided for patients with disorders more effectively and determine the effectiveness of health care services provided. EHR is a national charity in the UK.

ERH, das Europäische Register für Hämoglobinopathie (UK)

Registry for Beta Thalassaemia only

TIF, Thalassaemia International Federation (https://thalassaemia.org.cy/de/), aims to address the needs of thalassaemia patients and families. The Federation currently represents 242 members from 67 countries. The overall proportion of industry-related funding is 48%.

TIF, Internationale Thalassämie Vereinigung (weltweit)

Neither Austria nor Germany is participating in HER or TIF.

In Austria, a recent report [29] identified a patient registry for patients with inherited haemoglobinopathies and rare inherited anaemias. The registry was intended to document and characterize patients and evaluate possible predictive factors for disease progression. However, whether this registry (at the Medical University of Vienna) is active or inactive, is not apparent.

Register an MUW, allerdings ob aktiv nicht ersichtlich

3 Relative clinical effectiveness and safety assessment

3.1 Research question and scope

The following research question will be answered:

In patients aged ≥12 years

- with TDT for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available, and/or
- with SCD with recurrent VOCs for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available.

Is exa-cel, in comparison to standard of care (SoC), more effective and safe concerning

- TDT: Change from baseline in PROs (EQ VAS, FACT-G, BMTS), proportion of subjects achieving transfusion independence for at least 12 consecutive months, duration of transfusion independence and mortality, (S)AE and assessment of neutrophil and platelet engraftment, and/or
- SCD: Change from baseline in PROs (ASCQ-Me, EQ-VAS, Bone Marrow Transplantation Subscale, Pain Numeric Rating System), freedom from severe vaso-occlusive crises for at least 12 consecutive months, freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months, duration of time free from severe vaso-occlusive crises and mortality, (S)AE and assessment of neutrophil and platelet engraftment.

The scope of this assessment is presented according to the PICO-scheme in the following Table 3-1.

Fragestellung:

vergleichende Wirksamkeit von Exa-cel vs. SoC in TDT und SCS Patient*innen ≥12 Jahre in patient*innen- und systemrelevanten Endpunkten

Table 3-1: Assessment scope including the PICO questions

Description of PICO elements	PICO
P	**TDT**: Patients aged ≥12 years with TDT for whom HSC transplantation is appropriate and a HLA-matched related HSC donor is not available. **SCD**: Patients aged ≥12 years with SCD with recurrent VOCs for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available.
I	Treatment consists of a single dose containing a dispersion for infusion of viable CD34+ cells in one or more vials. The minimum recommended dose of exa-cel is 3×10^6 CD34+ cells/kg of body weight, administered as an intravenous bolus via a central venous catheter.
C[a]	**TDT** ■ Stem cell transplantation (SCT) ■ Hydroxycarbamide (hydroxyurea) ■ Luspatercept (Reblozyl®) ■ **Erythrocyte concentrates, chelation therapy**, treatment of secondary diseases (cardiopulmonary diseases, endocrinopathies, osteopenia-osteoporosis syndrome, thromboembolic events) **SCD** ■ **Hydroxycarbamide (hydroxyurea)** ■ **Simple transfusions and exchange transfusions** ■ Phlebotomies ■ Stem cell transplantation (SCT)
O	**TDT** **Efficacy** ■ Change from baseline in PROs (EQ VAS, FACT-G, BMTS) ■ Proportion of subjects achieving transfusion independence for at least 12 consecutive months ■ Duration of transfusion independence ■ PROs from patient questionnaire/interview (AIHTA) ■ Average Hb level of at least 9 g per deciliter without red-cell transfusion for at least 6 months ■ Total and fetal haemoglobin concentrations ■ Reduction in red-cell transfusions ■ Percentage of alleles with intended genetic modification in peripheral blood and bone marrow cells ■ Change in iron-overload measures ■ Measures of ineffective erythropoiesis **Safety** ■ Mortality ■ AEs ■ Assessments of neutrophil and platelet engraftment ■ Clinical laboratory assessments: CBC with differential, serum chemistry, urinalysis, infectious pathogens testing, immunological testing, hemolysis testing, iron studies, coagulation, dyserythropoiesis testing, other blood tests (% edited cells, CD34+ cell count, globin assessment, genotyping of HBB and alpha loci, serum pregnancy test if applicable). ■ Clinical evaluation of vital signs: blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry; subject weight (kg) and height (cm). ■ Electrocardiograms ■ Physical examinations: examination of general appearance, head, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen (including spleen size), lymph nodes, extremities, vascular and neurological systems and Karnofsky performance status. **SCD** **Efficacy** ■ Change from baseline in PROs (ASCQ-Me, EQ VAS, Bone Marrow Transplantation Subscale, Pain Numeric Rating System) ■ Freedom from severe vaso-occlusive crises for at least 12 consecutive months ■ Freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months ■ Duration of time free from severe vaso-occlusive crises

Description of PICO elements	PICO
	■ PROs from patient questionnaire/interview (AIHTA) ■ Freedom from severe vaso-occlusive crises for at least 9 consecutive months ■ Total and fetal Hb concentrations ■ Percentage of red cells with fetal haemoglobin ■ Percentage of alleles with intended genetic modification in the nucleated peripheral blood cells and CD34+ cells of the bone marrow ■ Change in hemolysis markers (absolute reticulocyte count and indirect bilirubin, lactate dehydrogenase, and haptoglobin levels **Safety** ■ Mortality ■ AEs ■ Assessment of neutrophil and platelet engraftment ■ Clinical laboratory assessments: CBC with differential, serum chemistry, urinalysis, infectious disease marker testing, immunological testing, hemolysis testing, coagulation, other tests (at screening only: genotyping of HBB and alpha loci, haemoglobin fractionation, allelic editing blood, allelic editing bone marrow aspirate, HbF distribution, F-cells, CD34+ cell count, inflammatory and endothelial activation markers, pregnancy test if applicable). ■ Physical examination and vital signs: blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry; subject weight (kg) and height (cm). ■ Electrocardiograms ■ Physical examinations includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat; respiratory; cardiovascular; lymph nodes; abdomen (including spleen); skin; musculoskeletal; neurological systems, and Karnofsky performance status.
a: Austria's Standard of Care (SoC) is printed in **bold**.	
PICO: population-intervention-comparator-outcome	

3.2 Methods

Criteria for selecting studies for the assessment

Einschlusskriterien

The following study designs were considered for inclusion/exclusion:

- Inclusion criteria: Double-blinded, randomised, placebo-controlled or single-arm studies (before-after case series).
- Exclusion criteria: Phase I clinical studies, case studies.

3.2.1 Information retrieval

Suche in 4 Datenbanken

A systematic literature search was conducted between 26th and 30th September 2024 in the following four databases:

- Medline via Ovid
- Embase.com
- The Cochrane Library
- International HTA Database (INAHTA)

systematische Suche: 147 Treffer (nach Deduplizierung)

The systematic search was limited to articles published in English or German and in Medline and Embase to only randomised controlled trials (RCTs) or non-randomised studies of interventions (NRSIs) conducted in humans. Publication type filters (to exclude e.g. conference abstracts, comments, editorials) were not implemented. After deduplication, overall 147 citations were included. The specific search strategy employed can be found in the Appendix. (Table A - 1, Search strategies).

Suche nach laufenden Studien ergab 10 Treffer

Furthermore, on 17 September 2024, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted, resulting in 10 potential relevant hits (ongoing trials not included in the evidence base).

Kontakt zu Hersteller: keine zusätzliche Evidenz

Additionally, the health technology developer (HTD) was contacted as of 30th September 2024 for a submission dossier. The HTD provided the two pivotal trials, two abstracts and the EPAR. No additional clinical evidence was identified.

Involvierung von 9 Patient*innen und 3 Klinikern

Finally, expert input was included:

- Five TDT patients and four SCD patients were involved and responded to 12 questions on PRO.
- Three clinicians, experts in stem cell transplantations were interviewed on course of the disease, standard of care and on exa-cel.

3.2.2 Selection of relevant studies

Overall 147 hits were identified. No additional citations were found through handsearching. The references were screened by two independent researchers (EM, CW), and a third researcher (ER) was involved to resolve disagreements. The selection process is displayed in Figure 3-1.

verblindete Auswahl

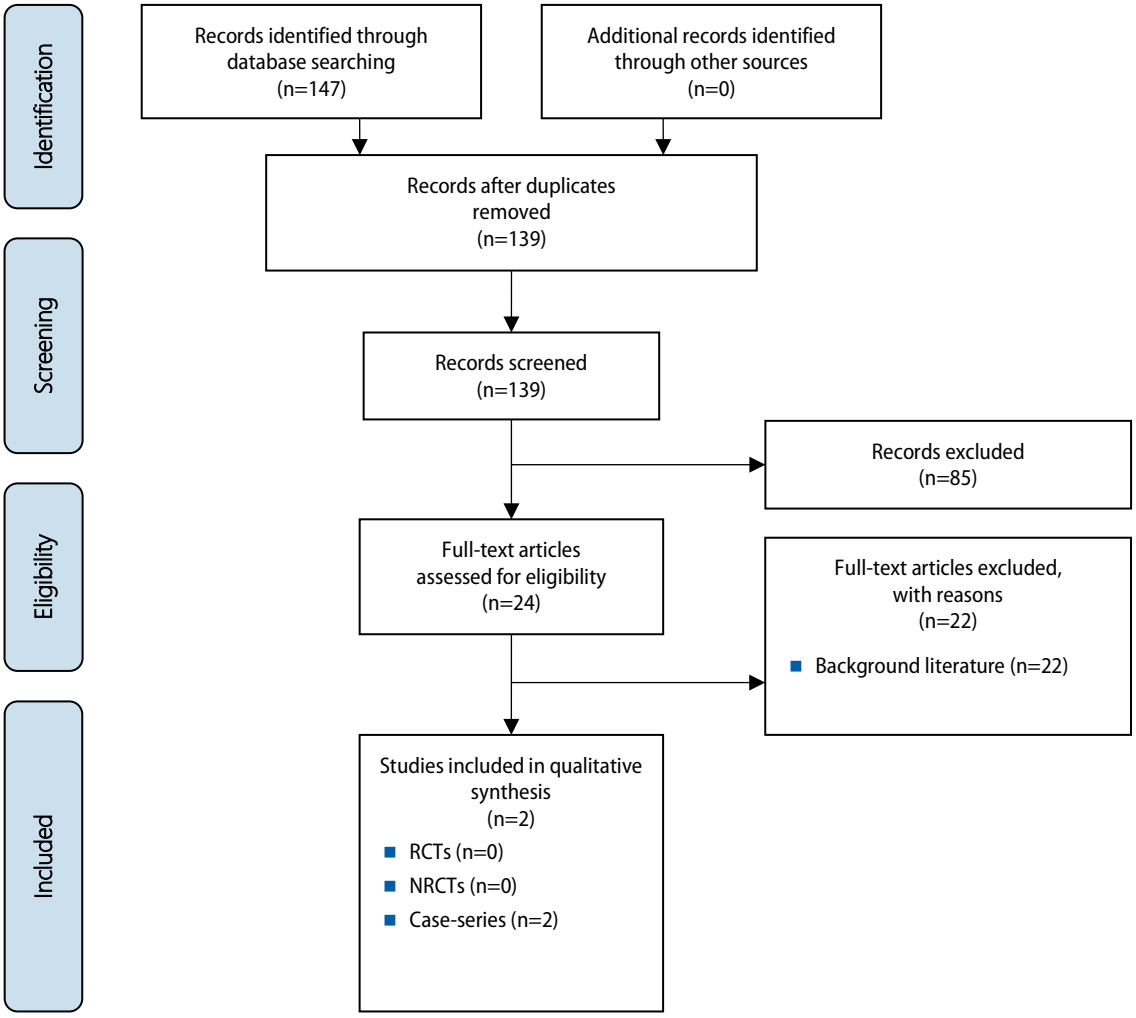


Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

Abbreviations: NRCT: nonrandomised studies of interventions, RCT: randomised controlled trial.

3.2.4 Data analysis and synthesis

RoB und Datenextraktion und -kontrolle nach dem 4-Augen Prinzip

Certainty was assessed using the Risk of Bias tool IHE checklist for single-arm case-series (see Table A - 2 and Table A - 3) [30]. Risk of bias (RoB) appraisal was conducted in duplicate by two reviewers (EM and ER); differences were settled via consensus.

One reviewer (EM) systematically extracted relevant data from the included studies into data extraction tables. A second reviewer (ER) cross-checked the data extraction tables for accuracy.

Due to the quality of the data (single-arm studies), data is synthesized qualitatively only. No further analysis on direct or indirect comparisons were conducted.

3.3 Results

3.3.1 Resulting list of included studies: overall and by PICO question

2 ein-armige Studien

Two clinical Phase 2/3 single-arm studies, published by Frangoul et al [31] and Locatelli et al [31] were identified. The following Table 3-2 lists the studies used for the assessment including the available documentation and identifies which studies are relevant for the PICO questions of the assessment, respectively.

Table 3-2: Included studies – list of relevant studies used for the assessment

Study reference/ID Study type Study interventions	Sponsored or third-party study of the technology under assessment	Available documentation
PICO		
CTX001-111 [a,b] (**CLIMB THAL-111**) *Single-arm study with study intervention*	Sponsored	■ CSR: not provided ■ Registry entry [c]: NCT03655678 ■ Publication or other reference: [31]
CTX001-121 [a,b] (**CLIMB SCD-121**) *Single-arm study with study intervention*	Sponsored	■ CSR: not provided ■ Registry entry [c]: NCT03745287 ■ Publication or other reference: [32]
a: study sponsored by the HTD or in which the HTD participated financially in some other way b: in the following tables, the study is referred to with this abbreviated form c: study registry entry, number (NCT-Number, EudraCT-Number)		
CSR: clinical study report; HTD: health technology developer; RCT: randomised controlled trial		

3.3.2 Characteristics of included studies

3.4.2.1 Study design and study populations

Table 3-3 presents the intervention and co-medications, and Table 3-4 characterises the studies included in the assessment.

Study CTX001-111: The study was a phase 3, open-label, single-dose study of exa-cel conducted at 13 sites in Canada, Germany, Italy, the United Kingdom, and the United States. Patients twelve to 35 years of age were eligible if they had a confirmed diagnosis of transfusion-dependent β-thalassemia and a transfusion history of at least 100 ml of packed red cells per kilogram of body weight per year or ten units of packed red cells per year for two years before screening.

Study CTX001-111: TDT
Phase 3, unverblindet
Patient*innen 12-35 Jahre

transfusionsabhängig

After the 2-year study period was completed, patients were offered enrollment in a 13-year long-term follow-up study (CLIMB-131; ClinicalTrials.gov number, NCT04208529).

nach CTX001-111 13 Jahre FU in CLIMB-131

According to the protocol [31], the primary endpoint was the proportion of subjects achieving transfusion reduction for at least 6 months. The key secondary endpoints were the Proportion of subjects achieving transfusion reduction for at least twelve months and the Proportion of subjects achieving transfusion independence for at least twelve months. The endpoints were defined differently in the article by Locatelli et al. [31] compared to the endpoints defined in the study protocol (Table 3-8). The primary end point was transfusion independence, defined as a weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least twelve consecutive months. The key secondary end point was a weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least six months.

Endpunkte laut Protokoll:
Anteil der Patient*innen mit Reduktion an Transfusionen 6 Monate, 12 Monate, Transfusions-Unabhängigkeit 12 Monate

Endpunkte in Publikation:
Transfusions-Unabhängigkeit 6 und 12 Monate

Data included in this assessment are from the third prespecified interim analysis (data cutoff of January 16, 2023);

Study CTX001-121: The study was a phase 3, open-label, single-dose study of exa-cel conducted at 16 sites in Belgium, Canada, France, Germany, Italy, the United Kingdom, and the United States. Patients twelve to 35 years of age with a confirmed diagnosis of severe sickle cell disease and a history of at least two vaso-occlusive episodes per year during the two years before screening were eligible. Exa-cel was administered intravenously through a central venous catheter at least 48 hours but no more than seven days after completing the Busulfan infusion.

Study CTX001-121: SDC
Phase 3, unverblindet
Patient*innen 12-35 Jahre

zumindest 2 vasookklusive Krisen (VOC) p.a.

After completion of this study, patients were encouraged to enroll in the 13-year long-term follow-up study (CLIMB-131; ClinicalTrials.gov number, NCT04208529).

nach CTX001-121 13 Jahre FU in CLIMB-131

The primary end point, as defined in the study protocol [32], was the proportion of subjects with sustained HbF ≥20% for at least 3 months starting six months after CTX001 infusion in the absence of treatment with hydroxyurea. The secondary endpoints were a reduction in annualized rate of severe VOC from baseline by at least 50%, starting six months after CTX001 infusion and a reduction in annualized rate of severe VOC from baseline by at least 65%, starting six months after CTX001 infusion. The endpoints were defined differently in the article by Frangoul et al. [32] than those defined in the study protocol (Table 3-5). The primary endpoint was freedom from any severe

Endpunkte laut Protokoll:
Anteil der Patient*innen mit HbF ≥20% für 6 Monate,
12 Monate, Reduktion der VOC

Endpunkte in Publikation:
ohne VOC für 12 Monate

vaso-occlusive crises for at least twelve consecutive months. A severe vaso-occlusive crisis was defined as an event of acute pain that led to a visit to a medical facility and the administration of pain medications (opioids or intravenous nonsteroidal antiinflammatory drugs) or red-cell transfusion, acute chest syndrome, priapism that lasted for more than two hours and led to a visit to a medical facility, or splenic sequestration. The two key secondary efficacy end points were freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least twelve consecutive months and freedom from severe vaso-occlusive crises for at least nine consecutive months.

Data included in this assessment are from the third prespecified interim analysis (data cutoff of June 2023).

Table 3-3: Characterisation of the interventions and co-interventions of included studies

Study reference/ID	Study intervention
Study CTX001-111 [31]	*Intravenous single infusion**
	Exa-cel was administered intravenously through a central venous catheter at least 48 hours but no more than 7 days after completing the Busulfan infusion. Pre-treatment is not reported.
Study CTX001-121 [32]	*Intravenous single infusion**
	Exa-cel was administered intravenously through a central venous catheter at least 48 hours but no more than 7 days after completing the Busulfan infusion. Pre-treatment is not reported.
Pre-treatment	*Patients received a combination of G-CSF and plerixafor for HSPC mobilisation followed by apheresis for up to 3 consecutive days to collect CD34+ HSPCs. Exa-cel was manufactured from CD34+ cells using CRISPR-Cas9 and a single guide RNA molecule. Before the exa-cel infusion, patients received a myeloablative, pharmacokinetically adjusted Busulfan conditioning regimen for 4 days. Exa-cel was infused intravenously through a central venous catheter at least 48 hours but no more than 7 days after completion of the Busulfan infusion.*

Table 3-4: Characteristics of the included studies

Study reference/ID	Study type and design	Study population	Study arms (n of included patients)	Study duration, data cut-off (s) and locations	Study endpoints
CTX001-111 [31]	Single-arm, open-label	Patients 12 to 35 years of age with transfusion-dependent β-thalassemia and a β0/β0, β0/β0-like, or non–β0/β0-like genotype[c] and a transfusion history of at least 100 ml of packed red cells per kilogram of body weight per year or ten units of packed red cells per year for 2 years before the screening.	Group 1 (N = 52)	■ Study duration: 2 years ■ Completion date: 12/ 2025 ■ 1. Data cut-off: 16.01.2023(planned I ■ nterim analysis)d ■ 2. Data cut-off: 16.04.2023 (not pre-specified) ■ Number of centres by continent: 13 sites	*Primary*: Transfusion independence, *Key secondary*[a]: Weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 6 months *Other*[b]: Duration of transfusion independence, total and fetal haemoglobin concentrations, reduction in red-cell transfusions, percentage of alleles with intended genetic modification in peripheral blood and bone marrow cells, change in iron overload measures and measures of ineffective erythropoiesis, and change from baseline in patient-reported outcomes (EuroQol Visual Analogue Scale [EQ VAS], Functional Assessment of Cancer Therapy–General [FACT-G], and Bone Marrow Transplantation Subscale [BMTS]).
CTX001-121 [32]	Single-arm, open-label	Patients 12 to 35 years of age with sickle cell disease who had had at least two severe vasoocclusive crises in each of the 2 years before screening.	Group 1 (N = 44)	■ Study duration: 2 years ■ Completion date: 10/ 2024 ■ 1. Data cut-off: 02/2023 (planned interim analysis)d ■ 2. Data cut-off: 06/2023 ■ Number of centres by continent: 16 sites	*Primary*: Freedom from any severe vaso-occlusive crises for at least 12 consecutive months. *Key secondary*[a]: Freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months and freedom from severe vaso-occlusive crises for at least nine consecutive months. *Other*[b]: Duration of time free from severe vaso-occlusive crises, total and fetal haemoglobin concentrations, the percentage of red cells with fetal haemoglobin, the percentage of alleles with intended genetic modification in the nucleated peripheral blood cells and CD34+ cells of the bone marrow, the change in hemolysis markers and the change from baseline in patient-reported outcomes (the Adult Sickle Cell Quality of Life Measurement Information System [ASCQ-Me; a validated quality of life measure that is used specifically for patients with sickle cell disease], the EuroQol Visual Analogue Scale [EQ VAS], the Bone Marrow Transplantation Subscale, and the Pain Numeric Rating System).
a: only secondary endpoints controlled for multiplicity b: only if included in at least one PICO c: Documented homozygous β-thalassemia (with the exception of the β0/β0 genotype) or compound heterozygous β-thalassemia including β-thalassemia/haemoglobin E (HbE). Subjects can be enrolled based on historical data, but a confirmation of the genotype using the study central laboratory will be required before Busulfan conditioning. The β0/β0 genotypes are defined using the HbVar Database. A history of at least 100 ml/kg/year or 10 units/year of packed RBC transfusions in the prior 2 years. d: first and second interim analyses were not conducted					
N: number of included patients; RCT: randomised controlled trial;					

Table 3-5: Study endpoints as defined in the study Protocol version 1

Study reference / ID Outcome category	Endpoints as defined in the study Protocol version 1
Study CTX001-111 (TDT) [31]	
Primary endpoint	Proportion of subjects achieving transfusion reduction for at least 6 months.
Key Secondary Efficacy Endpoint	Proportion of subjects achieving transfusion independence for at least 6 months.
Secondary Endpoints	Proportion of subjects achieving transfusion reduction for at least 12 months. Proportion of subjects achieving transfusion independence for at least 12 months. Proportion of alleles with intended genetic modification present in peripheral blood leukocytes over time. Intended genetic modifications are indels that modify the sequence of the erythrocyte-specific enhancer in intron 2 of BCL11A. Proportion of alleles with intended genetic modification present in bone marrow cells over time. Change in fetal haemoglobin concentration (pre-transfusion) over time. Change in health-related quality of life (HRQoL) from baseline over time using EuroQol Questionnaire – 5 dimensions – 5 levels of severity (EQ-5D-5L). Change in HRQoL from baseline over time using the Functional assessment of cancer therapy-bone marrow transplant questionnaire (FACT-BMT). Change in parameters of iron overload, including: o Liver iron concentration (LIC) and cardiac iron content (CIC) from baseline as assessed by T2* magnetic resonance imaging (MRI) o Change in serum ferritin level from baseline over time Proportion of subjects receiving iron chelation therapy over time.
Study CTX001-121 (SCD) [32]	
Primary endpoint	Proportion of subjects with sustained HbF ≥20% for at least 3 months starting 6 months after CTX001 infusion, in the absence of treatment with HU.
Key Secondary Efficacy Endpoint	Relative change from baseline in annualized rate of severe VOC starting 6 months after CTX001 infusion.
Secondary Endpoints	Reduction in annualized rate of severe VOC from baseline by at least 50%, starting 6 months after CTX001 infusion. Reduction in annualized rate of severe VOC from baseline by at least 65%, starting 6 months after CTX001 infusion. Absence of severe VOC events for at least 12 months at the time of the analysis. Change from baseline in annualized duration of hospitalisation for severe VOC, starting 6 months after CTX001 infusion. Proportion of subjects with sustained HbF ≥20% for at least 3 months, starting 3 months after CTX001 infusion, in the absence of treatment with HU. Proportion of subjects with sustained HbF ≥20% for at least 3 months, starting at the time of CTX001 infusion, in the absence of treatment with HU. Change in number of units of RBC transfused for SCD-related indications over time. HbF concentrations over time. Hb concentrations over time. Proportion of alleles with intended genetic modification present in peripheral blood leukocytes over time. Proportion of alleles with intended genetic modification present in bone marrow cells over time. Change in patient reported outcomes (PROs) over time using weekly Pain-Scale (11 point numerical rating scale [NRS]), EuroQol Quality of Life Scale (EQ-5D-5L), functional assessment of cancer therapy-bone marrow transplant (FACT-BMT), Patient-reported Outcome Measurement Information System (PROMIS)-Fatigue, PROMIS-Cognitive function, and Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me).

Table 3-6 provides information on treatment duration and observations periods in the included studies.

in Publikationen berichtete Endpunkte und Nachbeobachtung

Study CTX001-111 (TDT): The primary efficacy outcome was transfusion independence, an objectively measured endpoint used in the studies with curative treatments [33]. This endpoint was measured either for at least twelve months (primary endpoint) or six months (secondary endpoint).

Study CTX001-121 (SCD): The primary endpoint was freedom from any severe vaso-occlusive crises for at least twelve consecutive months. The VOC is a subjective endpoint, and its definition can vary between the trials since there are different definitions of pain episodes [34].

Table 3-6: Information on the follow-up for respective endpoints

Study reference / ID Outcome category	Planned follow-up	Median duration of follow-up [Min; Max] at the time of data cut-off
Study CTX001-111 (TDT)		
Transfusion independence: Defined as a weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 12 consecutive months.	2 years (24 months) and then 13 years of follow-up	20.4 months (2.1-48.1) at the time of data cut-off
Transfusion independence: Weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 6 months.		
Study CTX001-121 (SCD)		
Freedom from any severe vaso-occlusive crises for at least 12 consecutive months	2 years (24 months) and then 13 years of follow-up	19.3 months (0.8-48.1)
Freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months		
Freedom from severe vaso-occlusive crises for at least nine consecutive months		

Study population

Study CTX001-111 (TDT): The first patient was enrolled on September 10, 2018, and enrollment has now been completed. As of January 16, 2023 (the date of the prespecified third interim analysis), 59 patients had started HSPC mobilisation, 53 of whom started myeloablative Busulfan conditioning and 52 of whom received exa-cel (full analysis population). At the time of the prespecified interim analysis, the median duration of follow-up after exa-cel infusion was 20.4 months (range, 2.1 to 48.1). Additionally, 14 patients completed the 2-year study period and are enrolled in the long-term followup study, CLIMB-131. A total of 35 patients had at least 16 months of follow-up and were eligible for analysis of the primary and key secondary end points. For details on the patient's characteristics, see Table 3-13; for details on in- and exclusion criteria, see Table 3-7.

Study CTX001-111 (TDT):
59 Patient*innen begannen Mobilisierung,
53 erhielten Busulfan,
52 erhielten Exa-cel

35 hatten für Auswertung ausreichend Nachbeobachtung

Table 3-7: In- and exclusion criteria in Study CTX001-111 (TDT)

Inclusion criteria	Exclusion criteria
1. Age ≥18 and ≤35 years of age. 2. Able to provide written informed consent. 3. Diagnosis of transfusion-dependent β-thalassemia (TDT) as defined by: a. Documented homozygous β-thalassemia (with the exception of the β0/β0 genotype) or compound heterozygous β-thalassemia including β-thalassemia/ haemoglobin E (HbE). Subjects can be enrolled based on historical data, but a confirmation of the genotype using the study central laboratory will be required before Busulfan conditioning. The β0/β0 genotypes are defined using the HbVar Database. b. A history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the prior 2 years before signing the consent. 4. Karnofsky performance status of ≥80%. 5. Eligible for autologous stem cell transplant as per investigator's judgment. 6. Access to detailed medical records on packed RBC transfusions, including volume or units of packed RBCs and associated pre-transfusion Hb values, and in-patient hospitalisations, for at least the 2 years prior to consent. 7. Female subjects of childbearing potential (postmenarcheal, has an intact uterus and at least 1 ovary, and is less than 1 year postmenopausal) must agree to use acceptable method(s) of contraception from consent through at least 6 months after CTX001 infusion. 8. Male subjects must agree to use effective contraception (including condoms) from start of Busulfan conditioning through at least 6 months after CTX001 infusion. 9. Willing to participate in an additional long-term follow-up study or registry after completion of this study.	1. An available 10/10 human leukocyte antigen (HLA)-matched related donor. 2. Prior allogeneic HSCT. 3. Subjects with associated α-thalassemia and >1 alpha chain deletion. 4. Subjects with a β0/β0 thalassemia genotype or sickle cell beta thalassemia variant. 5. Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator. 6. White blood cell count <3 × 109/L or platelet count <50 × 109/L not related to hypersplenism. 7. History of a significant bleeding disorder. 8. History of any illness or any clinical condition that, in the investigator's opinion, might confound the study results or pose an additional risk in administering the study drug to the subject. This may include, but is not limited to, a history of relevant drug allergies, a history of cardiovascular or central nervous system disease, a history or presence of clinically significant pathology, or a history of mental disease. 9. Any prior or current malignancy, myeloproliferative disorder, or a significant immunodeficiency disorder. 10. Advanced liver disease, defined as: a. Aspartate transaminase (AST), alanine transaminase (ALT) >3 x the upper limit of normal (ULN), or direct bilirubin value >2 x the ULN, or: b. Baseline prothrombin time (International Normalized Ratio; INR) >1.5 x ULN, or c. History of cirrhosis or any evidence of bridging fibrosis or active hepatitis on liver biopsy. A liver biopsy is required when LIC is ≥15 mg/g on T2* MRI of the liver. If a liver biopsy has been performed less than 6 months prior to consent, it does not need to be repeated. 11. A cardiac T2* <10 ms by MRI or left ventricular ejection fraction (LVEF) <45% by echocardiogram. 12. Baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2. 13. Diffusing capacity of the lungs for carbon monoxide (DLco) <50% of predicted (corrected for haemoglobin and/or alveolar volume). 14. Prior treatment with gene therapy. 15. Intolerance or known sensitivity to plerixafor, granulocyte colony stimulating factor (G-CSF) products (e.g., filgrastim), or Busulfan. Prior anaphylaxis with excipients of CTX001 product (Dimethyl sulfoxide [DMSO], Dextran). 16. Positive serology for human immunodeficiency virus-1 (HIV-1) or human immunodeficiency virus-2 (HIV-2), hepatitis B virus (HBV; hepatitis B core antibody [HBcAb] and positive HBV polymerase chain reaction [PCR]), or hepatitis C virus (HCV) (positive HCV PCR). Positive serology for syphilis, toxoplasmosis or any other infectious disease marker as required by local testing for cellular processing. 17. Participation in another clinical study with an investigational drug within 30 days of screening or fewer than 5 half-lives of the investigational agent, whichever is longer from screening. 18. An assessment by the investigator that the subject would not comply with the study procedures outlined in the protocol. 19. Pregnant or breastfeeding females.

With regard to the CTX001-111 (TDT) trial, no patients discontinued the study before mobilisation, but 3 patients discontinued after the start of mobilisation (see Figure 3-2).

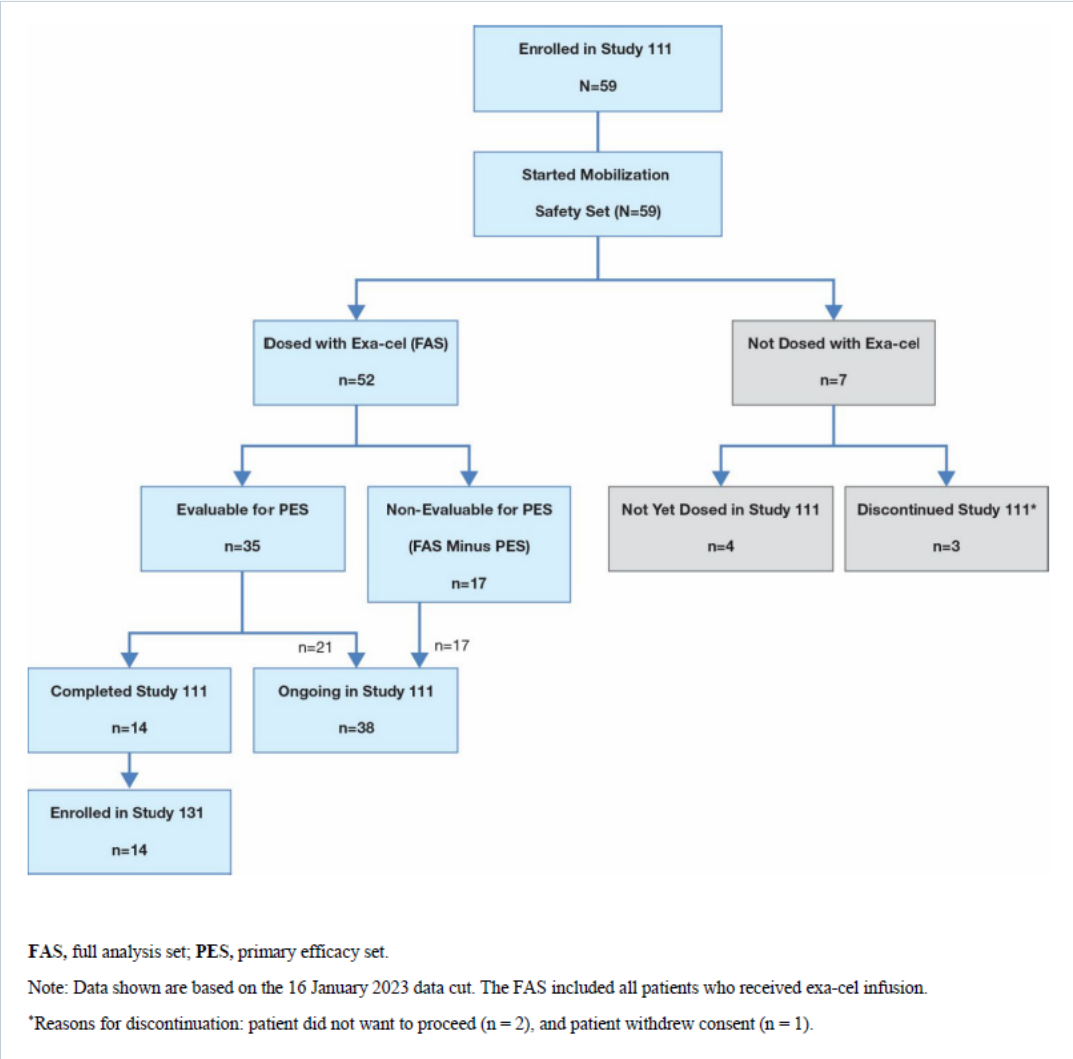


Figure 3-2: Diagram of patients in the study (extracted from [31])

Study CTX001-121 (SCD):

Enrollment has now been completed, with 63 patients enrolled. The first patient was enrolled on November 27, 2018. As of June 14, 2023, a total of 58 patients had started mobilisation, 44 of whom had completed myeloablative Busulfan conditioning and received exa-cel (full analysis population). At the time of the interim analysis, the median follow-up after the exa-cel infusion was 19.3 months (range, 0.8 to 48.1). A total of 17 patients (39%) completed the 2-year study and enrolled in the long-term follow-up study, CLIMB-131. Details on the patients characteristics see Table 3-9 and details on in- and exclusion criteria see Table 3-8.

Study CTX001-121 (SCD): 58 Patient*innen begannen Mobilisierung, 44 erhielten Exa-cel

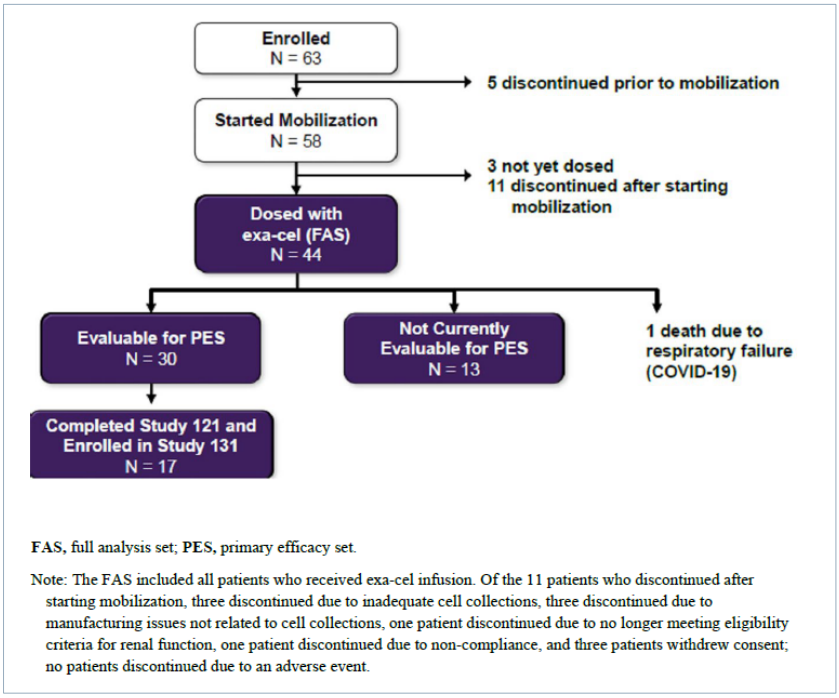
30 hatten für Auswertung ausreichend Nachbeobachtung

Table 3-8: In- and exclusion criteria in Study CTX001-121 (SCD)

Inclusion criteria	Exclusion criteria
1. Subject will sign and date an informed consent form (ICF). 2. Subjects 18 to 35 years of age, inclusive on the date of informed consent. 3. Documented βS/βS, βS/β0, βS/β+ genotype. Subjects can be enrolled based on historical βS/βS genotype result, but confirmation of genotype is required before Busulfan conditioning. 4. Subjects with severe SCD. Severe SCD is defined by the occurrence of at least 2 of the following events per year during the 2-year period before screening, while receiving appropriate supportive care (e.g. pain management plan, HU) as judged by the investigator: ■ Acute pain events that requires a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions ■ Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate associated with by pneumonia-like symptoms, pain, or fever ■ Priapism lasting >2 hours ■ Splenic sequestration 5. Karnofsky performance status of ≥80%. 6. Eligible for autologous stem cell transplant as per investigator's judgment. 7. Female subjects of childbearing potential (postmenarcheal, has an intact uterus and at least 1 ovary, and is less than 1 year postmenopausal) must agree to use acceptable method(s) of contraception from consent through at least 6 months after CTX001 infusion. 8. Male subjects must agree to use effective contraception from start of mobilisation through at least 6 months after CTX001 infusion 9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, contraceptive guidelines, and other study procedures. 10. Willing to participate in an additional long-term follow-up study after completion of this study.	1. An available 10/10 human leukocyte antigen (HLA)-matched related donor. 2. Prior HSCT. 3. Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator. 4. White blood cell (WBC) count <3 × 109/L or platelet count <50 × 109/L, not related to hypersplenism per investigator judgment. 5. Treatment with regular RBC transfusions that, in the opinion of the investigator, cannot be interrupted after engraftment. 6. Subjects with history of alloimmunization to RBC antigens and for whom the investigator anticipates that there will be insufficient RBC units available for the duration of the study. 7. More than 10 unplanned hospitalisations or emergency department visits related to SCD in the 1 year before screening. 8. HbF level >15.0%, irrespective of concomitant treatment with HbF inducing treatments such as HU. 9. History of untreated Moyamoya disease or presence of Moyamoya disease at Screening that in the opinion of the investigator puts the subjects at the risk of bleeding. 10. History of a significant bleeding disorder. 11. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the subject. This may include, but is not limited to: history of relevant drug allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; history of mental disease, or history of familial cancer syndrome. 12. Any prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder. 13. Advanced liver disease, defined as a. Alanine transaminase (ALT) >3 × the upper limit of normal (ULN) or direct bilirubin value >2 × ULN, or b. Baseline prothrombin time (PT) (international normalized ratio [INR]) >1.5 × ULN, or c. History of cirrhosis or any evidence of bridging fibrosis, or active hepatitis on liver biopsy 14. Baseline estimated glomerular filtration rate <60 mL/min/1.73 m2. 15. Lung diffusing capacity for carbon monoxide (DLco) <50% of predicted value (corrected for haemoglobin and/or alveolar volume). 16. Left ventricular ejection fraction (LVEF) <45% by echocardiogram. 17. Prior treatment with gene therapy/editing product. 18. Intolerance, contraindication, or known sensitivity to plerixafor or Busulfan. Prior anaphylactic reaction with excipients of CTX001 product (dimethylsulfoxide [DMSO], dextran). 19. Positive serology for human immunodeficiency virus-1 (HIV-1) or human immunodeficiency virus-2 (HIV-2), hepatitis B virus (HBV) (Hepatitis B core antibody [HBcAb] or nuclei acid testing [NAT]), or hepatitis C virus (HCV) (NAT). Positive serology for syphilis or any other infectious disease marker as required by local testing for cellular processing. 20. Participation in another clinical study with an investigational drug/product within 30 days of screening or fewer than 5 half-lives of the investigational agent, whichever is longer from screening. 21. Subjects who are not able to comply with the study procedures outlined in the protocol as judged by the investigator. 22. Pregnant or breastfeeding females.

With regard to the CTX001-121 (SCD) trial, five patients discontinued the study prior to mobilisation. 11 patients discontinued the study after starting mobilisation (see Figure 3-3).

SCD: 5 Patient*innen brachen vor der Mobilisierung und weitere 11 danach ab



FAS, full analysis set; **PES,** primary efficacy set.

Note: The FAS included all patients who received exa-cel infusion. Of the 11 patients who discontinued after starting mobilization, three discontinued due to inadequate cell collections, three discontinued due to manufacturing issues not related to cell collections, one patient discontinued due to no longer meeting eligibility criteria for renal function, one patient discontinued due to non-compliance, and three patients withdrew consent; no patients discontinued due to an adverse event.

Figure 3-3: Diagram of patients in the study (extracted from [32])

Table 3-9: Patient baseline characteristics including treatment/study discontinuations for population with transfusion-dependent β-thalassemia

Study reference / ID Characteristics Category	Study intervention	Study intervention
CTX001-111 **(TDT)**	Full Analysis Population Exa-cel N = 52	Primary Efficacy Population Exa-cel N = 35
Sex [f / m], (%)	25 (48%) / 27 (52%)	17 (49%) / 18 (51%)
Age [years], mean (SD)	21.5±6.7	21.1±6.1
12 to <18 yr	18 (35)	11 (31)
≥18 to 35 yr	34 (65)	24 (69)
Genotype, n (%)		
β0/β0-like	31 (60)	20 (57)
β0/β0	19 (37)	10 (29)
β0/IVS-I-110	9 (17)	7 (20)
IVS-I-110/IVS-I-110	3 (6)	3 (9)
Non–β0/β0-like	21 (40)	15 (43)
β+/β+ 4	4 (8)	3 (9)
β+/β0	12 (23)	8 (23)
βE/β0	5 (10)	4 (11)
Race or ethnic group — no. (%)		
White	18 (35)	15 (43)
Asian	22 (42)	13 (37)
Data not collected per local regulations	7 (13)	4 (11)
Other	2 (4)	0
Multiracial	3 (6)	3 (9)
Annualised volume of red-cell transfusions — ml/kg		
Mean	196.8±63.0	202.0±57.1
Median (range)	Median (range) 201.0 (48.3–330.9) 205.2 (115.2–330.9)	Median (range) 201.0 (48.3–330.9) 205.2 (115.2–330.9)
Median annualised red-cell transfusions (range) — units	35.0 (11.0–71.0)	35.0 (20.5–71.0)
Total haemoglobin concentration — g/dl	10.4±2.0	10.4±1.9
Total fetal haemoglobin concentration — g/dl	0.6±1.0	0.5±0.6
Spleen intactn — no. (%)	36 (69)	26 (74)
Iron status		
Median liver iron concentration (range) — mg/g	3.5 (1.2–14.0)	4.0 (1.4–14.0)
Median cardiac iron content by T2-weighted MRI (range) — msec	34.0 (12.4–61.1)	34.8 (19.6–61.1)
Median serum ferritin concentration (range) —pmol/liter	2891.9 (584.2–10,837.3)	2653.7 (674.1–10,740.7)
Median no. of mobilisation cycles (range)	1 (1–4)	1 (1–2)
Median Exa-cel dose (range) — CD34+ cells/kg	7.5×10^6 (3.0×10^6–19.7×10^6)	6.4×10^6 (3.0×10^6–19.7×10^6)
f: female; m: male; n: number of patients in the category, N: number of randomised patients		

Table 3-10: Patient baseline characteristics including treatment/study discontinuations for population with sickle cell disease

Study reference / ID Characteristics Category	Study intervention	Study intervention
CTX001-121 **(SCD)**	Full Analysis Population Exa-cel N = 44	Primary Efficacy Population Exa-cel N = 30
Age [years], mean (SD)	21.2±6.1	22.1±6.0
Sex [f / m], (%)	20 (45) / 24 (55)	14 (47) / 16 (53)
12 to <18 yr	12 (27)	6 (20)
≥18 to 35 yr	32 (73)	24 (80)
Genotype — no. (%)		
βS/βS	40 (91)	29 (97)
Non-βS/βS		
βS/β0	3 (7)	1 (3)
βS/β+	1 (2)	0
Race — no. (%)		
White	3 (7)	1 (3)
Black	38 (86)	26 (87)
Other	3 (7)	3 (10)
Annualised rate of severe vaso-occlusive crises		
No. of severe vaso-occlusive crises/yr	4.1±3.0	3.9±2.1
Distribution — no. (%)		
≥3 vaso-occlusive crises/yr	26 (59)	17 (57)
<3 vaso-occlusive crises/yr	18 (41)	13 (43)
Total haemoglobin — g/dl	9.1±1.6	9.0±1.6
Total fetal haemoglobin — %	5.4±3.9	5.2±3.8
Median no. of mobilisation cycles (range)	2 (1–6)	2 (1–5)
Median Exa-cel dose (range) — CD34+ cells/kg	4.0×10^6 (2.9×10^6–14.4×10^6)	4.0×10^6 (2.9×10^6–14.4×10^6)
f: female; m: male; n: number of patients in the category, N: number of randomised patients		

3.3.3 Study results on relative effectiveness and relative safety

keine vergleichende Evidenz verfügbar

There is no direct evidence for relative effectiveness and relative safety for exa-cel

- for the treatment of transfusion-dependent β-thalassemia (TDT) 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 and
- for the treatment of severe sickle cell disease (SCD) 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.

3.3.4 Study results of non-comparative evidence for patient population with TDT and SCD

2 ein-armige Studien mit 52 (TDT) und 44 (SCD) Patient*innen 35 (TDT) resp. 30 (SCD) auswertbar

Only two single-arm studies were identified, one for TDT and one for SCD patients. The study on TDT enrolled 52 subjects, of which 35 reached the primary endpoint at the time of analysis. The study on SCD enrolled 44 subjects, of which 30 reached the primary endpoint at the time of analysis (see Table 3-11).

Table 3-11: Studies included patient populations with transfusion-dependent β-thalassemia and sickle cell disease; analysed populations

Study reference/ID Relevant study arms (number of randomised/included patients)	Analysed population (number of randomised/included patients)
TDT	
Single-arm trial with exa-cel	
Study CTX001-111 *Group 1 (n = 52)*	*n=35*[a] *Primary efficacy population: Proportion of population that achieved the timepoint for primary efficacy endpoint analysis (12 months) at the time of interim analysis.*
SCD	
Single-arm trial with exa-cel	
Study CTX001-121 *Group 1 (n = 44)*	*n=30*[a] *Primary efficacy population: Proportion of population that achieved the timepoint for primary efficacy endpoint analysis (12 months) at the time of interim analysis.*
n: number of patients	

Critical Efficacy outcomes for TDT

wichtige Endpunkte zur Beurteilung der Wirksamkeit

Unabhängigkeit von Transfusionen
Dauer der Unabhängigkeit
HrQoL
PRO

Proportion of subjects achieving transfusion independence for at least twelve consecutive months: This outcome was defined as transfusion independence, defined as a weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 12 consecutive months.

Duration of transfusion independence: Similarly, this outcome measured the total time for which the patient did not require transfusion.

Change from baseline in PROs (EQ VAS, FACT-G, BMTS): The FACT-G is the generic CORE of the Functional Assessment of Chronic Illness Therapy Measurement System. The EQ-VAS score measures scores between 0 and 100, which an individual records for their current overall health-related quality of life using the EQ VAS [35]. Bone Marrow Transplantation Subscale (BMTS) measures the quality of life in bone marrow transplant patients [36].

Patient-reported Outcomes (PRO) from patient questionnaires: The AIHTA has received written input via questionnaires from several TDT and SCD patients. For specific questions asked, see Appendix (Table A - 4).

Critical Efficacy outcomes for SCD

wichtige Endpunkte zur Beurteilung der Sicherheit

keine VOC für mindestens 12 Monate
keine Hospitalisierungen für mindestens 12 Monate
Dauer ohne VOC
Schmerz, QoL
PRO

Freedom from severe vaso-occlusive crises for at least twelve consecutive months: A severe vaso-occlusive crisis was defined as an event of acute pain that led to a visit to a medical facility and the administration of pain medications (opioids or intravenous nonsteroidal antiinflammatory drugs) or red-cell transfusion, acute chest syndrome, priapism that lasted for more than 2 hours and led to a visit to a medical facility, or splenic sequestration [32].

Freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least twelve consecutive months: This secondary efficacy endpoint tracked freedom from hospitalisations for severe vaso-occlusive crises for at least 12 consecutive months.

Duration of time free from severe vaso-occlusive crises: This outcome measured the total time the patient did not require transfusion.

Change from baseline in PROs (ASCQ-Me, EQ-VAS, BMTS, Pain Numeric Rating System): ASCQ-Me is a patient-reported outcome measurement system that assesses the physical, social, and emotional impact of SCD [37]. The EQ-VAS score measures scores between 0 and 100, which an individual records for their current overall health-related quality of life using the EQ VAS [35]. BMTS measures the quality of life in bone marrow transplant patients [36]. The Pain Numeric Rating System is a segmented numeric version of the visual analogue scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of his/her pain [38].

PROs from patient questionnaires: The AIHTA has received written input via questionnaires from several TDT and SCD patients. For specific questions asked, see Appendix (Table A - 4).

Critical Safety outcomes for TDT and SCD

wichtige Endpunkte zur Beurteilung der Sicherheit

Mortalität

Mortality: Transplant-related mortality (TRM) within 100 days after CTX001 infusion was recorded, as well as all-cause mortality.

Nebenwirkungen

Adverse Events (AE) and serious adverse events (SAE): AE summaries are presented by MedDRA System Organ Class and Preferred Term using frequency counts and percentages (i.e., number and percentage of subjects with an event).

Assessment of neutrophil and platelet engraftment: Successful neutrophil engraftment within 42 days after CTX001 infusion was observed, as well as Time to neutrophil engraftment and Time to platelet engraftment.

Available outcomes for TDT and SCD

erhobene vs. berichtete Endpunkte

The following Table 3-12 provides an overview of all outcomes available in the studies included in the assessment of PICO.

Table 3-12: Matrix of outcomes in the studies on TDT and SCD

Study reference/ID Study CTX001-111 (TDT)		Study reference/ID Study CTX001-121 (SCD)	
Outcomes			
Efficacy			
Proportion of subjects achieving transfusion independence for at least 12 consecutive months	*yes*	Freedom from any severe vaso-occlusive crises for at least 12 consecutive months	*yes*
Average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 6 months	*yes*	Freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months	*yes*
Duration of transfusion independence	*yes*	Freedom from severe vaso-occlusive crises for at least 9 consecutive months	*yes*
Total and fetal haemoglobin concentrations	*yes*	Duration of time free from severe vaso-occlusive crises	*yes*
Reduction in red-cell transfusions	*yes*	Total and fetal haemoglobin concentrations	*yes*
Percentage of alleles with intended genetic modification in peripheral blood and bone marrow cells	*yes*	Percentage of red cells with fetal haemoglobin	*yes*
Change in iron-overload measures	*yes*	Percentage of alleles with intended genetic modification in the nucleated peripheral blood cells and CD34+ cells of the bone marrow	*yes*
Measures of ineffective erythropoiesis	*yes*	Change in hemolysis markers (absolute reticulocyte count and indirect bilirubin, lactate dehydrogenase, and haptoglobin levels	*yes*
Change from baseline in PROs (EQ VAS, FACT-G, BMTS)	*yes*	Change from baseline in PROs (ASCQ-Me, EQ-VAS, Bone Marrow Transplantation Subscale, Pain Numeric Rating System)	*yes*
PROs from patient questionnaire/interview (AIHTA)	*no*	PROs from patient questionnaire/interview (AIHTA)	*no*
Safety			
Assessments of neutrophil and platelet engraftment	*yes*	Assessment of neutrophil and platelet engraftment	*yes*
AEs	*yes*	AEs	*yes*
Mortality	*yes*	Mortality	*yes*
Clinical laboratory assessments: CBC with differential, serum chemistry, urinalysis, infectious pathogens testing, immunological testing, hemolysis testing, iron studies, coagulation, dyserythropoiesis testing, other blood tests (% edited cells, CD34+ cell count, globin assessment, genotyping of HBB and alpha loci, serum pregnancy test if applicable).	*yes*	Clinical laboratory assessments: CBC with differential, serum chemistry, urinalysis, infectious disease marker testing, immunological testing, hemolysis testing, coagulation, other tests (at screening only: genotyping of HBB and alpha loci, haemoglobin fractionation, allelic editing blood, allelic editing bone marrow aspirate, HbF distribution, F-cells, CD34+ cell count, inflammatory and endothelial activation markers, pregnancy test if applicable).	*yes*
Clinical evaluation of vital signs: blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry; subject weight (kg) and height (cm).	*yes*	Physical examination and vital signs: blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry; subject weight (kg) and height (cm).	*yes*
Electrocardiograms	*yes*	Electrocardiograms	*yes*
Physical examinations: examination of general appearance, head, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen (including spleen size), lymph nodes, extremities, vascular and neurological systems and Karnofsky performance status.	*yes*	Physical examinations includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat; respiratory; cardiovascular; lymph nodes; abdomen (including spleen); skin; musculoskeletal; neurological systems, and Karnofsky performance status.	*yes*

The outcomes listed in the PICO are all included in the Study CTX001-111 (TDT) and CTX001-121 (SCD) except for PROs from the patient questionnaires collected at the AIHTA.

Results of Efficacy outcomes for TDT

Proportion of subjects achieving transfusion independence for at least 12 consecutive months; Duration of transfusion independence

35 auswertbare Patient*innen mit FU 16M: 91% Transfusionsunabhängig

A total of 35 patients had at least 16 months of follow-up and were eligible for analysis of the primary and key secondary end points. Transfusion independence occurred in 32 (91%; 95% confidence interval [CI], 77 to 98; P<0.001 against the null hypothesis of a 50% response); the results were the same for the key secondary end point (weighted average haemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 6 months) (91%; 95% CI, 77 to 98; P<0.001) (Table 3-13).

Table 3-13: Efficacy results – primary efficacy and key secondary efficacy endpoints in TDT

Time point Outcome Study reference/ID	Exa-cel Proportion of patients, n (%)
CTX001-111	
Transfusion independence at 12 months[a]	n=32/35 (91%, CI, 77 to 98), p<0.001*
Transfusion independence at 6 month[a]	n=32/35 (91%, CI, 77 to 98), p<0.001*
	Mean duration
Transfusion independence	22.5 months (range, 13.3 to 45.1)
a: transfusion independence, defined as a weighted average haemoglobin level of at least 9 g per dec litre without red-cell transfusion for at least 6/12 consecutive months.	
CI: confidence interval, n: number of patients, * Confidence interval widths were not adjusted for multiplicity and may not be used in place of hypothesis testing. Both P values are two-sided against a null hypothesis of a 50% response.	

alle (erwachsenen) Patient*innen haben wesentliche Verbesserungen in PRO

Change from baseline in PROs (EQ VAS, FACT-G, BMTS)

All EQ VAS, FACT-G and BMT patient-reported outcomes have shown that all patients eligible for analysis have reached minimally clinically important differences from month twelve to month 24 (see Table 3-14).

Table 3-14: Efficacy results – Patient-Reported Outcome Measures Following Exa-cel Infusion for TDT Adults (n=24)

Study	CTX001-111 (TDT)		
Visit	EQ VAS Score (Range: 0 to 100)	FACT-G Score (Range: 0 to 108)	BMT Score (Range: 0 to 40)
Baseline — mean (SD)	80.8 (18.0) n=24	82.4 (15.8) n=24	27.3 (4.8) n=24
Change at Month 6 — mean (SD)	+5.3 (17.4) n=24	+4.1 (16.6) n=24	+1.8 (6.2) n=24
Change at Month 12 — mean (SD)	+8.6 (17.8) n=24	+5.4 (19.6) n=24	+3.8 (6.3) n=24
Change at Month 18 — mean (SD)	+6.8 (21.2) n=23	+9.1 (15.6) n=21	+4.3 (5.7) n=21
Change at Month 24 — mean (SD)	+10.2 (20.9) n=15	+10.3 (17.0) n=15	+6.8 (4.7) n=15
MCID	7 to 10	3 to 7	2 to 3
BMT Score: bone marrow transplant subscale; FACT-G: Functional Assessment of Cancer Therapy-General; MCID, minimal clinically important differences; SD, standard deviation. Notes: A positive change in score indicates improvement. The data shown are from the Primary Efficacy Set and are based on the 16 January 2023 data cut.			

Results on EQ VAS, FACT-G, BMTS were not reported for adolescents.

Results of Safety outcomes for TDT

Mortality

No patient has died during the study from any cause.

Adverse Events (AE) and serious adverse events (SAE)

All the patients had at least one adverse event (AE) after the exa-cel infusion, most of which were of grade 1 or 2 in severity. A total of 46 patients (88%) also had adverse events of grade 3 or 4 in severity. Most adverse events occurred within the first six months after the exa-cel infusion, and the frequency decreased thereafter. Serious adverse events occurred in 17 patients (33%). The most common serious adverse event was veno-occlusive liver disease (in five patients), which was attributed to the Busulfan conditioning regimen [31] (Table 3-15 and Table 3-16).

100% der Patient*innen haben AE
88% Grad 3und 4
17% SAE

Assessment of neutrophil and platelet engraftment

Only one patient had neutrophil engraftment that occurred later than day 42; this patient had neutrophil engraftment on day 56 without the use of backup cells. Patients with a history of splenectomy had faster neutrophil and platelet recovery than patients with an intact spleen.

Table 3-15: Safety outcomes for TDT

Study CTX001-111		Exa-cel				
		time point				
Outcome		**Exa-cel Infusion to <6 months**	**6 Months to <12 Months**		**12 Months to <18 Months**	**≥18 Months**
		Patients with event n (%)				
Adverse events	**Evaluable patients N**	52	45		43	32
At least one adverse event		52 (100)	29 (64.4)	21 (48.8)	11 (34.4)	
Serious adverse events		17 (33)	N/A	N/A	N/A	
Grade 3 or 4		46 (88.5)	N/A	N/A	N/A	
Treatment discontinuation due to adverse events		N/A	N/A	N/A	N/A	
Treatment interruption due to adverse events		N/A	N/A	N/A	N/A	
Assessments of neutrophil and platelet engraftment	29 days (range, 12 to 56) and 44 days (range, 20 to 200), respectively					
Mortality	0					

Table 3-16: Detailed adverse events of Grade 3 and 4 for TDT

Study CTX001-111	
Grade 3 or 4 events occurring in ≥5% of patients	Full Analysis Population (N = 52), no. of patients (%)
Febrile neutropenia	28 (54)
Stomatitis	21 (40)
Anaemia	20 (38)
Platelet count decrease	18 (35)
Thrombocytopenia	18 (35)
Mucosal inflammation	17 (33)
Neutrophil count decrease	14 (27)
Decrease in appetite	12 (23)
Epistaxis	7 (13)
Neutropenia	7 (13)
White-cell count decrease	7 (13)
Veno-occlusive liver disease	5 (10)
Blood bilirubin increase	4 (8)
Hypokalemia	4 (8)
Hypophosphatemia	4 (8)
Iron overload	4 (8)
Nausea	4 (8)
Vomiting	4 (8)
CD4 lymphocyte count decrease	3 (6)
Hematuria	3 (6)
Headache	3 (6)
Hypoxia	3 (6)

Results of Efficacy outcomes for SCD

Freedom from severe vaso-occlusive crises for at least twelve consecutive months; Freedom from inpatient hospitalisation for severe vaso-occlusive crises for at least twelve consecutive months; Duration of time free from severe vaso-occlusive crises

30 auswertbare Patient*innen mit FU 16 Monate: 97% ohne VOC und 100% ohne Hspitalisierung

A total of 44 patients received exa-cel, and the median follow-up was 19.3 months (range, 0.8 to 48.1). Of the 30 patients who had sufficient follow-up of 16 months to be evaluated, 29 (97%; 95% confidence interval [CI], 83 to 100) were free from vaso-occlusive crises (VOC) for at least twelve consecutive months, and all 30 (100%; 95% CI, 88 to 100) were free from hospitalisations for vaso-occlusive crises for at least 12 consecutive months (P<0.001 for both comparisons) (Table 3-17).

Table 3-17: Efficacy results – primary efficacy and key secondary endpoints in SCD

Time point Outcome Study reference/ID	Exa-cel Proportion of patients, n (%)
CTX001-121	
Freedom from severe vaso-occlusive crises for ≥12 mo [a]	n=29/30 (97%, CI, 83 to 100), p<0.001*
Freedom from inpatient hospitalisation for severe vasoocclusive crises for ≥12 mo	n=30/30 (100%, CI, 88 to 100), p<0.001*
	Mean duration
Freedom from vaso-occlusive crises	22.4 months (range, 14.8 to 45.5)
a: transfusion independence, defined as a weighted average haemoglobin level of at least 9 g per dec litre without red-cell transfusion for at least 6/12 consecutive months.	
CI: confidence interval, n: number of patients, * Confidence interval widths were not adjusted for multiplicity and may not be used in place of hypothesis testing. Both P values are two-sided against a null hypothesis of a 50% response.	

Change from baseline in PROs (ASCQ-Me, EQ VAS, BMTS, Pain Numeric Rating System)

All EQ VAS, FACT-BMT and BMT patient-reported outcomes have shown that all patients eligible for analysis have reached minimally clinically important differences from month six to month 24. The PRO, Pain NRS has reached a minimally clinically important difference from month twelve to month 24 (Table 3-18).

alle (erwachsenen) Patient*innen haben wesentliche Verbesserungen in PRO

Table 3-18: Patient-Reported Outcome Measures Following Exa-cel Infusion in Adult Patients for SCD

Study	CTX001-121 (SCD)			
Visit	EQ VAS Score (Range: 0 to 100)	FACT-BMT Total Score (Range: 0 to 148)	BMT Score (Range: 0 to 40)	Pain NRS (Range: 0 to 10)
Baseline — mean (SD)	68.8 (22.7) n=24	102.2 (23.3) n=24	28.0 (4.4) n=24	2.6 (2.5) n=24
Change at Month 6 — mean (SD)	+23.1 (25.2) n=21	+18.0 (22.3) n=21	+2.9 (6.2) n=21	-0.9 (3.6) n=21
Change at Month 12 — mean (SD)	+20.6 (21.4) n=24	+22.4 (20.0) n=24	+4.8 (4.4) n=24	-1.3 (2.2) n=24
Change at Month 18 — mean (SD)	+25.3 (24.9) n=20	+23.2 (24.9) n=20	+5.1 (5.0) n=20	-2.0 (2.5) n=21
Change at Month 24 — mean (SD)	+26.9 (22.6) n=17	+24.9 (19.4) n=17	+3.9 (5.3) n=17	-1.7 (2.5) N=17
MCID	7 to 10	N/A	2 to 3	30% or 1-point reduction
BMT, Bone Marrow Transplant; Exa-cel: exagamglogene autotemcel; EQ VAS, EuroQol Visual Analog Scale; MCID, minimal clinically important difference; NRS: numeric rating system; SD, standard deviation. Notes: The data shown are from the Primary Efficacy Set. The baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.				

Results on EQ VAS, FACT-G, BMTS were not reported for adolescents.

Concerning the ASCQ-Me score, the following aspects changed with a minimally clinically important difference at months 6, 12, 18 and 24: Emotional Impact, Pain Impact, Social Functioning Impact, Pain Episode Frequency. On the other hand, the impact of stiffness, sleep impact, and pain episode severity did not change, with a minimal clinically important difference in any month (Table 3-19).

aber: in einigen Bereichen keine klinisch relevanten Unterschiede

Table 3-19: Patient-Reported Outcome Measures (ASCQ-Me Scores) Following Exa-cel Infusion in Adult Patients Age in SCD

Visit	Statistics	Emotional Impact Standardized Score (Range: 0-100)	Pain Impact Standardized Score (Range: 0-100)	Social Functioning Impact Standardized Score (Range: 0-100)	Stiffness Impact Standardized Score (Range: 0-100)	Sleep Impact Standardized Score (Range: 0-100)	Pain Episode Frequency Standardized Score (Range: 0-100)	Pain Episode Severity Standardized Score (Range: 0-100)
Baseline — mean (SD)	n Mean (SD)	23 51.9 (7.5)	23 53.7 (8.8)	23 50.2 (11.1)	23 53.3 (8.4)	23 47.6 (8.3)	24 53.0 (6.2)	24 52.6 (9.0)
Change at Month 6 — mean (SD)	n Mean (SD)	20 +8.6 (9.7)	20 +5.5 (8.8)	20 +11.2 (12.4)	20 0.0 (11.5)	20 +4.2 (12.2)	21 -16.1 (9.1)	21 -0.6 (12.2)
Change at Month 12 — mean (SD)	n Mean (SD)	23 +9.4 (8.9)	23 +5.2 (8.6)	23 +13.7 (11.7)	23 +3.6 (10.5)	23 +4.4 (7.0)	24 -19.3 (8.1)	24 -3.6 (12.2)
Change at Month 18 — mean (SD)	n Mean (SD)	19 +9.7 (9.3)	19 +9.0 (9.2)	19 +14.0 (12.7)	19 +4.8 (8.3)	19 +2.9 (8.9)	20 -20.6 (8.8)	20 -1.9 (11.1)
Change at Month 24 — mean (SD)	n Mean (SD)	16 +10.3 (10.9)	16 +9.1 (10.5)	16 +16.4 (11.0)	16 +6.6 (10.5)	16 +4.7 (8.0)	17 -21.0 (7.7)	17 -3.3 (13.3)
MCID		5	5	5	5	5	-5	-5

ASCQ-Me: Adult Sickle Cell Quality of Life Measurement System; MCID: minimal clinically important difference; n: the size of the subsample.
Note: Data shown are from the Primary Efficacy Set. The baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.

Results of safety outcomes for SCD

Mortality

One death from respiratory failure due to SARS-CoV-2 infection occurred in an adult patient (who also had Busulfan-associated lung injury and preexisting lung disease) 268 days after the exa-cel infusion. After the exa-cel infusion, this patient had an uneventful course, with neutrophil and platelet engraftment observed at times consistent with other patients in the study.

1 Todesfall (Covid-19)

Adverse Events (AE) and serious adverse events (SAE)

All 44 (100%) patients had at least one adverse event after the exa-cel infusion, most of which were of grade 1 or grade 2 in severity. A total of 42 patients (95%) also had adverse events of grade 3 or 4, the most common of which were stomatitis (in 55% of the patients), febrile neutropenia (in 48%), a decreased platelet count (in 48%), and decreased appetite (in 41%). Most adverse events occurred within six months after the infusion. Graft failure or cancer did not develop in any patient (see Table 3-20 and Table 3-21).

100% der Patient*innen haben AE
95.5% Grad 3 und 4
45% SAE

Assessment of neutrophil and platelet engraftment

Neutrophils and platelets are engrafted in each patient; however, the timing of these engraftments is not reported.

Table 3-20: Safety outcomes for SCD

Study CTX001-121		Exa-cel			
		time point			
Outcome		**Exa-cel Infusion to <6 months**	**6 Months to <12 Months**	**12 Months to <18 Months**	**≥18 Months**
		Patients with event n (%)			
Adverse events	**Evaluable patients N**	44	41	33	29
At least one adverse event		44 (100.0)	29 (70.7)	22 (66.7)	16 (55.2)
Serious adverse events		20 (45.5)	N/A	N/A	N/A
Grade 3 or 4		42 (95.5)	N/A	N/A	N/A
Treatment discontinuation due to adverse events		N/A	N/A	N/A	N/A
Treatment interruption due to adverse events		N/A	N/A	N/A	N/A
Assessments of neutrophil and platelet engraftment	Median 27 days (range, 15 to 40) and 35 days (range, 23 to 126), respectively.				
Mortality	1				

Table 3-21: Detailed adverse events of Grade 3 and 4 for SCD

Study CTX001-121	
Grade 3 or 4 events occurring in ≥5% of patients	Full Analysis Population, (N = 44), no. of patients (%)
Febrile neutropenia	21 (48)
Stomatitis	24 (55)
Platelet count decrease	21 (48)
Appetite decrease	18 (41)
Neutrophil count decrease	17 (39)
Mucosal inflammation	14 (32)
Anaemia	11 (25)
Thrombocytopenia	11 (25)
Neutropenia	10 (23)
White-cell count decrease	6 (14)
Abdominal pain	5 (11)
CD4 lymphocyte count decrease	5 (11)
Cholelithiasis	5 (11)
Pruritus	5 (11)
Constipation	4 (9)
Headache	4 (9)
Nausea	4 (9)
Noncardiac chest pain	4 (9)
Pneumonia	4 (9)
Upper abdominal pain	3 (7)
Arthralgia	3 (7)
Back pain	3 (7)

3.3.5 Quality of the evidence

Risk of Bias

moderates Verzerrungsrisiko

Both single-arm studies were judged to have a moderate risk of bias for the following reasons (see Table A - 2 and Table A - 3 in Appendix): Both studies did not report whether the participants entered the study at a similar point of the disease and both studies were unblinded. While all outcomes were measured before and after the intervention in the TDT-study, the outcomes were only partially reported in the SCD study. Hence, the internal validity and the confidence that the causal relationship is not influenced by other factors or variables is moderate.

Inconsistencies in statistical analysis of Study CTX001-111 (TDT)

3 Interimanalysen geplant, nur 1 durchgeführt

einseitige p-Wertanalyse geplant zweiseitige durchgeführt

The study protocol [31] included three prespecified interim analyses. The first and second interim analyses were not conducted. The data shown are from the third interim analysis. The primary and key secondary endpoints were considered to be significant if the corresponding one-sided P value was less than 0.01692 against a response of 50% in the primary efficacy population. Although the statistical analysis plan specified that a one-sided P value would be used for hypothesis testing, test results are reported here with two-sided P values.

Inconsistencies in statistical analysis of Study CTX001-121 (SCD)

3 Interimanalysen geplant, nur 2 durchgeführt

einseitige p-Wertanalyse geplant
zweiseitige durchgeführt

The study protocol [32] included three prespecified interim analyses. The protocol-specified second interim analysis (which included 20 patients) was the first of the interim analyses to be performed (data-cutoff date in February 2023); the first interim analysis was not performed. Another data cutoff was conducted in June 2023, when the sample included 30 patients; the sample size at this data cutoff was similar to that of the prespecified third interim analysis. Because the first interim analysis was not conducted and the statistical boundary was crossed at the second interim analysis, the alpha from the first and second interim analyses was recovered. The alpha for the June data cutoff was 0.0198 (i.e., 0.01074 + 0.00366 + 0.00540), and so the results for the primary endpoint and the first key secondary endpoint would be considered to be significant if the corresponding one-sided P values were less than 0.0198 for the comparison with a response in 50% of the patients for the primary efficacy population. Although the statistical analysis plan specified that a one-sided P value would be used for hypothesis testing, test results are reported here with two-sided p values.

External validity and applicability

Übertragbarkeit der Ergebnisse fraglich

The extent to which the results can be generalized to other contexts depends on the selection of the patients and whether they are compliant with the comedications. No information is available on the TDT and SCD patient characteristics in Austria. The TDT and SCD patients interviewed for this assessment are described in Table 3-22.

Table 3-22: Characteristics of patients included in the PRO conducted by AIHTA

N=9			
Sex	Female	Male	Unknown
	6	3	0
Indication	SCD	TDT	Unknown
	4	5	0
Role	Patient	Carer	Unknown
	7	2	0
Member of patient organisation	Yes	No	Unknown
	6	0	3

Heterogeneity and inconsistency across studies

nur 1 Studie je Indikation: keine Aussage zu Heterogeneität möglich

Since only a few data (only 1 study per indication) and short follow-ups are available, no statement on heterogeneity or inconsistency can be made. On quality of evidence see Table 3-23).

Table 3-23: Quality of the evidence

Outcome	Design	Factors that may affect the certainty of evidence	Detail
All outcomes	Single-arm open-label	Internal validity	The study did not contain a placebo nor an active control group and was thus not randomised and double-blinded. It is not clear at what stage of the disease the participants started the treatment.
		Applicability	The population, intervention, and outcomes are in line with PICO except for the QoL measured by the AIHTA. However, the study does not contain any comparators.
		Heterogeneity and Inconsistency	N/A (only 1 study per indication)
		Other	

3.3.6 Ongoing Studies

10 laufende Studien
Long-term monitoring in CLIMB-131

Studien mit Kindern

A total of 10 clinical trials with exa-cel treatment were identified, all sponsored by the marketing authorization holder. Among these are the two studies included in this assessment, which are highlighted in grey in Table 3-24. After completion of the 2-year study period, patients from both CTX001-111 (TDT) and CTX001-121 (SCD) study were offered enrollment in a 13-year long-term follow-up study (CLIMB-131; NCT04208529) that is currently enrolling patients. Two clinical studies of Phase 3 are investigating efficacy and safety in paediatric patients with either TDT or SCD (NCT05356195, NCT05329649). Another clinical trial investigates the efficacy and safety of SCD patients with βS/βC genotype (NCT05951205). Other clinical trials are further assessing the efficacy and safety of exa-cel in TDT and SCD patients. For details, see Table 3-24.

Table 3-24: List of ongoing studies with exa-cel

Title	Trial ID	Other IDs	Phase	Status
A Long-term Follow-up Study in Participants Who Received CTX001	NCT04208529	CTX001-131|2024-512654-19-00	Phase 3	Enrolling by invitation
Evaluation of Safety and Efficacy of CTX001 in Paediatric Participants With Transfusion-Dependent β-Thalassemia (TDT)	NCT05356195	VX21-CTX001-141|2021-002172-39	Phase 3	Recruiting
Evaluation of Safety and Efficacy of CTX001 in Paediatric Participants With Severe Sickle Cell Disease (SCD)	NCT05329649	VX21-CTX001-151|2021-002173-26	Phase 3	Recruiting
Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease	NCT05477563	VX21-CTX001-161|2021-006390-37	Phase 3	Recruiting
A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia	NCT03655678	CTX001-111	Phase 2/3	Active, not recruiting
A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease	NCT03745287	CTX001-121	Phase 2/3	Active, not recruiting
Evaluation of Efficacy and Safety of a Single Dose of Exa-cel in Participants With Severe Sickle Cell Disease, βS/βC Genotype	NCT05951205	VX21-CTX001-171|2023-503247-34-00|2021-006375-41	Phase 3	Not yet recruiting
A Phase 1/2/3 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in subjects with Transfusion-Dependent ß-Thalassemia	CTIS2024-516894-57-00	2017-003351-38	Phase 3	Not Recruiting
A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease	CTIS2024-516067-83-00	2018-001320-19	Phase 1/2	Not Recruiting
A Long-term Follow-up Study of Subjects with ß-Thalassemia or Sickle Cell Disease Treated with Autologous CRISPR-Cas9 Modified Hematopoietic Stem Cells (CTX001)	CTIS2024-512654-19-00	2018-002935-88	Phase 3	Recruiting
Highlighted in grey are the studies included in this assessment.				

3.4 Discussion and conclusion on clinical data and alternatives

umfassende (in Österreich verfügbare) Behandlungen haben SCD und TDT zu chronischen Erkrankungen gemacht SCD zuweilen auch fatal

In Western countries, the prognosis for patients with TDT and SCD has improved enormously in recent decades due to comprehensive treatment. The disease has developed from a fatal disease to a chronic disease, provided that treatment is continuous with the current treatment alternatives (transfusion therapy combined with daily tablets of iron chelate for TDT and daily tablets of hydroxycarbamide for SCD). This treatment is available to all affected persons in Austria. In contrast to TDT, however, life-threatening, potentially fatal complications can occur at any time with SCD.

als kurativ vermarket

Bezeichnung zu früh verwendet, da die Dauer der Therapieantwort noch ungewiss ist

Exa-cel (Exagamglogene autotemcel) is marketed as a “curative” treatment. However, only short follow-up data is available, and the label “curative” is premature due to the lack of knowledge on the duration of the response to the treatment. Currently, data from only two small case series with 77 patients (35 TDT, 44 SCD) addressing the efficacy and safety of exa-cel are available for each indication. No comparative effectiveness data is available.

aufgrund des Studiendesigns ist keine Aussage zu vergleichenden Wirksamkeit möglich

The small recruitment number and the lack of a placebo group due to ethical concerns are understandable when considering the rare nature of the diseases. However, assessing the value of the provided evidence based on a small open-label study is challenging. Since no comparator or real-world evidence exists, no relative effectiveness can be assessed. The **absence of blinding** and the consequential knowledge of the patients and physicians regarding the treatments administered might have altered the results of the studies.

kurz-zeitige Ergebnisse sind bemerkenswert, aber: 88% und 95% der Patient*innen haben Grad 3+4 Nebenwirkungen

The **short-term treatment response** is remarkable, indeed: in TDT patients, 32 of 35/ 91% achieved transfusion independence; in SCD patients, 29 of 30/ 97% achieved freedom from any severe vaso-occlusive crises. However, adverse events occurred in all patients, mostly grade 1 or 2 in severity. 88% of patients (TDT) and 95% (SCD) also had adverse events of grade 3 or 4.

Limitationen der Studie: Patient*innen mit sehr unterschiedlicher Schwere der Erkrankung

The studies' limitations are numerous: besides the **uncontrolled study design**, the TDT and SCD **populations** seemed to be **heterogeneous**:

- While only transfusion-dependent TDT patients with severe diseases were enrolled, it is unclear whether their transfusion needs were comparable. The median annualised volume of red-cell transfusions varied among the patients (196.8±63.0 ml/kg), suggesting a different need for transfusions and, thus, heterogeneous severity of the disease.
- The same applies to SCD patients: the number of severe vaso-occlusive crises per year varied among the patients (4.1±3.0). The VOC is a subjective endpoint, and its identification can vary between trials since pain episodes have different definitions [34]. It is not clear if the previous VOC events calculated at the baseline for each patient were determined consistently among the patients.

Protokollverletzungen: 3 Interimauswertungen geplant, nur 1 durchgeführt

Three **interim analyses** were **pre-specified** in the study protocols [31, 32]. The results from the third interim analysis are presented in this report (the first and second interim analyses were not conducted). With regard to the TDT study, the investigator mentions an additional data cut-off, which was not prespecified and is a part of the supplementary data [31]. In addition, the abstract submitted by the applicant contains a further data cut-off. Thus, It is unclear how many interim analyses were pre-specified, which might cause multiplicity issues.

Also, there is no information on the **previous or concomitant treatments** of the patients, which might have impacted the results. Additionally, the primary and secondary endpoints defined in the publications by Locatelli et al. [31] and Frangoul et al. [32] do not match the endpoints described in the study protocols attached to these publications.

keine Information zu vorherigen und begleitenden Therapien

Overall, the **risk of bias** for both studies was calculated to be moderate based on the above-mentioned methodological limitations. In addition to that, the studies were sponsored by the marketing authorisation holder (Vertex), which adds to the possible bias.

moderates Verzerrungsrisiko

Another issue is that patients need to undergo Busulfan conditioning, which is connected to various AEs [54] and need to be hospitalised for a long time (5-6 weeks). Additionally, the administration must take place in a transplantation centre with a skilled medical team. Indeed, some patients included in these studies have discontinued the treatment after starting the mobilisation. It is thus unknown how many patients will be compliant with the whole process of exa-cel treatment in the real-world setting under these circumstances.

Verabreichung nur nach belastender und langer Vorbehandlung in hoch-spezialisierten Kliniken

3.5 International HTA Reports

Three HTA-reports were identified:

Institute for Clinical and Economic Review (ICER) 2023 [39]

ICER/ USA 2023

ICER rated exa-cel (or lovo-cel) for treatment of severe SCD, exa-cel compared with standard of care as “comparable or better”.

insuffiziente Evidenz, um zwischen Exa-cel und lovo-cel zu unterscheiden

ICER provides the following four recommendations to payers based on efficacy and safety data from September 2022:

1. Given that there is insufficient evidence at present to distinguish between the safety or effectiveness of lovo-cel and exa-cel and that clinical experts see no clinical reasons to favour one of the therapies for certain patient subgroups, payers may consider negotiating a lower price by covering only one of the two therapies. However, payers considering this coverage approach should be aware of important access and patient preference issues that may outweigh the benefit of achieving a lower price.

Maßnahmenpaket abseits von Gentherapie: Maßnahmen für Fertilitätserhalt

2. If the announced prices for lovo-cel and exa-cel align with expected patient benefits and are set toward the lower edge of their estimated cost-effectiveness ranges. In that case, payers should use the FDA label as the guide to coverage policy without narrowing coverage by including specific clinical trial restrictions unrelated to the likelihood of benefit from treatment.
3. Since patients will need coverage for therapies that will only be accessible in specific medical centres, payers should design coverage policies to support travel for patients and their families to receive therapy. Geographical and income constraints should not undermine the tenets of fair access to which all patients have a fundamental right.

fairen Zugang gewährleisten

4. Payers should cover fertility preservation in concert with coverage of gene therapies. Both patient stakeholders and clinical experts noted that future fertility is a key consideration in management. There are many complex issues regarding fertility (e.g., prepubescent patients, ongoing storage). Payers must be pro-active and transparent about what will be covered.

National Institute for Health and Care Excellence (NICE) [40]

NICE/ UK 2024

NICE recommends exa-cel with managed access to treat transfusion-dependent beta-thalassaemia in people twelve years and over.

kurze Nachbeobachtungszeit

Unsicherheit über Langzeiteffekte
Therapieabbrüche
Häufigkeit von Komplikationen
Überleben und QoL

1. Clinical trial evidence shows that exa-cel removes the need for blood transfusions in most people. But, in the trial, people were only followed up for a relatively short time, and exa-cel was not compared with any other treatment. Evidence from an indirect comparison shows that exa-cel reduces the need for transfusions compared with standard care. However, the number of transfusions that most people have as part of standard care needs confirmation.

As well as the uncertainties in the clinical evidence, there are several issues with the economic modelling, including:

- how long the treatment effect with exa-cel lasts
- how often people withdraw from exa-cel treatment before the infusion takes place
- the survival and quality-of-life outcomes used for people having exa-cel and standard care
- the frequency of complications.

IQWiG/ DE 2023

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) [41]

IQWiG has not conducted a full assessment but an evaluation of a number of patients and potential registries for data collection for quality assurance.

Canada´s Drug Agency (CDA-AMC, former CADTH)

CDA/ CA 2024
empfiehlt Refundierung unter Konditionen

als Zweit- oder Drittlinientherapie

CDA-AMC recommends reimbursement with conditions: exa-cel should be reimbursed for patients 12 years of age and older with transfusion-dependent β-thalassemia (TDT) and for the treatment of patients 12 years of age and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises only if certain conditions are met [42, 43]. The short follow-up in the trials is highlighted as a significant evidence gap as it does not inform on whether there could be a waning of efficacy leading to a loss of response over time. Limitations to generalizability include the fact that available evidence was insufficient to assess with certainty whether patients in the study had an adequate trial of first-line treatments, though exa-cel would be positioned as second- or later-line therapy in clinical practice. In addition, SCD patients who had important healthcare utilisation that was consistent with chronic pain were excluded from the study. However, they may also benefit from treatment in order to prevent further deterioration in their condition. However, the magnitude of the response to exa-cel in these patients is unknown.

unter Preisreduktion

The ICER for exa-cel is $194,807 per QALY gained when compared with the the standard of care. A price reduction of 55% (SCD) would be required for exa-cel to achieve an ICER of $50,000 per QALY gained compared to SoC.

The estimated price reduction is associated with high uncertainty because of limitations in the economic model that could not be addressed. Additional price reduction may be necessary to achieve cost-effectiveness if the effects are not sustained indefinitely and due to infrastructure costs associated with establishing specialised treatment centres.

Unsicherheit über Langzeiteffekte

unterversorgte Population, aber Engpässe in der Versorgung

großer Infrastruktur-Bedarf

Uncertainty regarding exa-cel's clinical effectiveness and safety and, in turn, cost-effectiveness limits assessing its value as a one-time therapy. Exa-cel has the potential to meet unmet needs for people with SCD and TDT, historically under-funded and under-researched conditions, which disproportionately impacts groups experiencing health inequities. Treatment with exa-cel is resource-intensive, requiring pre-treatment, month-long hospitalisation, and follow-up and administration by experienced personnel in authorised transplant and cell therapy centres. These factors, alongside current health systems capacity constraints, will severely limit the number of eligible patients that can be treated each year and necessitate prioritising patients for access. Clinical experts reported that, among people with SCD and TDT who are ineligible for allo-HSCT, they would prioritise those experiencing the most severe disease but who were still fit and eligible for treatment with exa-cel.

4 Experiences with application and administration of the medicinal product

4.1 Experiences with administration

To date, no data on the administration of exa-cel outside of clinical trials is available. Additionally, no information is available regarding the different dosage forms or strengths of exa-cel.

keine Daten außerhalb von klinischen Studien

4.2 Applicability of results

According to the manufacturer, no information is available on the applicability of the trial results [22]. Additionally, experts have indicated that the applicability of these results is limited, as the patient population in Austria tends to be older and has a higher prevalence of comorbidities [6].

eingeschränkte Anwendbarkeit der Studienergebnisse

4.3 HTAs and status of reimbursement in Europe

In general, once the EMA grants marketing authorisation, decisions regarding pricing and reimbursement are made at the level of each Member State, considering the potential role or use of the medicine within the context of the national health system of that country [44].

über Kosten und Erstattung wird auf nationaler Ebene entschieden

According to the manufacturer, exa-cel is reimbursed in Luxembourg [22].

Luxenburg: Exa-cel wird erstattet

On 7th August 2024, the manufacturer announced a reimbursement agreement with the National Health Service (NHS) England for eligible TDT patients to access exa-cel, following the issuance of positive guidance by the National Institute for Health and Care Excellence (NICE) recommending the use of exa-cel within the NHS [45].

England: Erstattungsvereinbarung mit NHS

5 Treatment costs, budget impact and price comparison

5.1 Methods

For this chapter about the treatment costs, budget impact analysis and price comparison, we used different data sources:

- For the summary of the existing budget impact analyses, we used the literature identified through the systematic search (see chapter 03) and additional manual searches via Google. US dollars (2023) were converted into euros (2024) via an online tool using the International Monetary Fund data for purchasing power parities (PPP) [46].
- Information on international prices on exa-cel was retrieved by the Gesundheit Österreich GmbH (GÖG).
- Since the manufacturer did not submit a budget impact analysis for Austria, we calculated the BIA using the following method:
  - We identified information on the type and volume of medical services connected with exa-cel and the standard of care (SoC) via the European public assessment report of exa-cel, guidelines (AWMF, Onkopedia) and clinical experts.
  - Unit costs on each cost item were retrieved from hospital providers. Seven providers (organisations) provided unit cost data. We used average values in case more than one unit cost information was available for a single cost item. The unit costs used for the analysis are presented in the appendix (Table A - 6).
  - Cost categories with a very minor contribution to the overall costs were excluded (e.g., Paracetamol).
  - We calculated the **gross drug budget impact** (drug acquisition costs based on the eligible population and predicted market share), **the net drug budget impact** (drug acquisition costs and cost-offsets anticipated from the increased utilisation and/or displacement of other drugs) **and additional costs**, such as costs of preparing for the intervention or concomitant medication.
  - Clinical experts provided information on the number of patients with the diseases in Austria. Information on the number of eligible patients for exa-cel came from the manufacturer and was validated by clinical experts. The number of patients experiencing serious adverse events was taken from the clinical studies.

Literaturübersicht: systematische Suche & Handsuchen; Preise konvertiert in € 2024 mit Online-Tool

Preis-Infos Exa-cel internat.: GÖG

keine Hersteller-Info zu Budget Imact

eigene Analyse: Kostenkategorien aus Leitlinien u. Befragung klinischer Expert*innen

unit costs: Krankenhausverbünde

Brutto-, Netto-Budgetfolgen und zusätzliche Kosten im Rahmen der Verabreichung berechnet

Info zu Patient*innenzahlen von Expert*innen, Hersteller und klinischen Studien

5.2 Summary of existing budget impact analyses

2 publizierte Bugetfolgenanalysen zu Exa-cel identifiziert

We identified two budget impact analyses, one from a Belgian healthcare perspective and one from a US perspective, about exa-cel of patients with SCD. We identified no budget impact analysis of exa-cel for patients with severe TDT.

1 belgische Analyse (2024) verglich die Kosten des Szenarios „30,5% Crizanlizumab, 10% Voxelotor, 41,8% Exa-cel" mit dem Szenario OHNE diese Behandlungen für Pat. Sichelzellenanämie

direkte medizinische Kosten wurden berücksichtigt

The hypothetical budget impact analysis for Belgium published in 2024 compared the costs between a scenario *with* the introduction of crizanlizumab[7], voxelotor[8], and exa-cel and one *without* these treatments [47]. The analysis used a five-year time horizon, focusing on chronic management, acute VOC, and curative hematopoietic HSCT. The estimated number of SCD patients in Belgium was 1,029, with 18 new patients added annually. The assumed mortality rate was 0.24%. Patient eligibility for each intervention was estimated as follows: 30.5% for crizanlizumab (patients aged ≥16 years with at least one crisis per year), 10% for voxelotor (patients aged ≥12 years with haemoglobin levels between 5.5 and 10.5 g/dl), and 41.8% for exa-cel (approximately eight patients aged 12–35 years with two or more crises annually). The proportion of treated patients was assumed to remain stable over the five years. Patients treated with exa-cel or HSCT were considered cured and thus removed from the patient pool in subsequent years. From the third year onward, exa-cel was assumed to replace HSCT for 2% of eligible patients each year, with no discontinuation rate due to its one-time administration. The analysis included direct medical costs, covering drug acquisition and related healthcare expenses such as examinations, vaccinations, medical visits, and administrative costs. In addition, it also considered costs associated with hospitalisation, pre- and post-procedure care, and managing common drug-related adverse events or the potential lack of efficacy [47].

Szenario MIT Interventionen: 5-Jahres kumulative Kosten €81 Mio vs. Szenario OHNE Interventionen: rund €51 Mio.

In the scenario "world with interventions," the five-year cumulative costs for comprehensive SCD care were estimated at €80.8 million, with costs increasing about twofold from the first to the fifth year. In the scenario "world without interventions," the five-year cumulative cost was estimated at €50.8 million, with costs increasing by roughly half a million euros from the first to the fifth year. Many expenses were designated to acute management, specifically for overnight hospitalisations and medical examinations. Closely following were expenses for chronic management, with most of the costs for medical examinations and blood transfusions, followed by expenditures related to curative HSCT.

[7] The marketing authorisation for crizanlizumab (Adakveo) for SCD has been revoked by the European Commission.

[8] Oxbryta (voxelotor) is currently suspended from use in the European Union.

The five-year net budget impact amounted to €30.0 million, with most of the impact attributed to exa-cel, with a five-year budget impact of €25.6 million (85% of total budget impact) after adoption in year three. In contrast, the five-year budget impact of crizanlizumab and voxelotor was estimated at €2.3 million and €2.1 million or 8% and 7% of the total cumulative five-year budget impact, respectively. At 91%, drug acquisition costs comprised a significant proportion of the five-year budget impact. For each intervention, drug acquisition costs consisted of 97.24% for crizanlizumab (€51,801 per patient per year), 99.93% for voxelotor (€106,099 per patient per year), and 90.20% for exa-cel (€ 1.4 million per patient) from the individual cumulative budget impacts. About 5.83% of crizanlizumab and 22.45% of exa-cel's five-year budget impact was attributed to hospitalisation costs. Managing adverse events or lack of efficacy incurred negligible costs of €14,387 or 0.05% of the five-year total budget impact, with 65% of costs attributed to treatment failure with exa-cel. Besides, patient population size and the proportion of treated patients had a similar strong influence on the budget impact outcome. Conversely, in descending order, discontinuation rate, acute vaso-occlusive crisis (VOC) rate, and adverse event rate showed little to no impact on the budget impact [47].

5-Jahres Netto-Budgetfolgen: €30 Mio., 85% davon Exa-cel

22% der 5-Jahres Budgetfolgen von Exa-cel waren Krankenhauskosten

Einflussfaktoren: Anzahl der Patient*innen gesamt und Exa-cel Behandlungen

Diskontierungsrate, VOD-Rate, Nebenwirkungen hatten geringen Einfluss

Considering annual budget impact thresholds for orphan drugs in France (€30 million) and Germany (€50 million), above which specific assessment of orphan drugs takes place, the three different uptake scenarios indicated budget impacts for crizanlizumab and voxelotor (ranging from €100,000 to €1.5 million) considerably below these thresholds. Contrarily, the annual budget impact of exa-cel takes on several million, ranging from € 8 to 18 million at 2% and 4% respective uptakes from all potentially eligible patients and exceeding France's annual €30 million threshold at an 8% uptake, which would equal 66 treated patients in total [47].

Budgetfolgen von Exa-cel übersteigt Grenzwert von €30 Mio. bei einem Uptake von 8% (n=66) der möglichen Pat.

The Final Evidence Report about gene therapies for SCD of the Institute of Clinical and Economic Review (ICER) conducted a budget impact analysis next to their health economic evaluation, presented in chapter 6.2. The analysis showed that at the placeholder price of $2 million per treatment course for exa-cel (to be paid upfront), 15.5% of people (n=388 people per year) could be treated over five years without crossing the ICER budget impact threshold of $777 million (€663 million) per year. Similarly, 31.1%, 23.0%, and 18.3% could be treated with exa-cel without reaching the potential budget impact threshold at three threshold prices (approximately $1 million/ €852,893; $1.35/ €1.15 million; and $1.7/ €1.4 million per treatment). The total economic costs of SCD were estimated at $2.98/€2.54 billion per year in the USA. However, the US patient population is not comparable to the Austrian patient population (a higher proportion of African Americans, with a higher prevalence of SCD and TDT), so the results cannot be transferred to the Austrian context [48].

1 US-amerikanische Analyse (ICER 2023) für Sichelzellenanämie:
bei Exa-cel Preis von $2 Mio. können nur 16% der Patient*innen innerhalb eines Limits von $777 Mio. behandelt werden;
halber Preis-> doppelte Anzahl an Patient*innen

US-Population nicht mit Ö vergleichbar

5.3 Price comparison and managed entry agreements

Preisvergleich Exa-cel (3 Länder): Preise rund um € 1,9 Mio.

12 EU-Länder keine Preisinformationen

Out of 15 EU countries and the UK, the GÖG identified exa-cel prices for three countries, ranging from €1,900,000 (FR and LU) to €1,969,341 (UK) without confidential discounts. These prices align with the pricing information presented by the manufacturer for Austria. Overall, pricing information is difficult to retrieve since exa-cel is only applied in the hospital. Table 5-1 presents an overview of the price comparison.

Table 5-1: Price comparison exa-cel

Country	Indication	Setting	Exa-cel price	Managed entry agreements	Reference
AT	TDT /SCD	Hospital	One-time payment: €1,900,000 without confidential discounts	NI	Information from manufacturer
UK	TDT	Hospital	List price: GBP1,651,000 (€1,969,341)* without confidential discounts	Available	[49]
FR	TDT (n~200) SCD (n~1,000-1,700)	Hospital	Ex-factory price: €1,900,000 without confidential discounts	Early access programmes for reimbursement by health insurance. The manufacturer sets a maximum price. Products in the early access programme are subject to discounts of 10%-80% based on total sales.	[50]
LUX	NI	Hospital	Ex-factory price: €1,900,000 without confidential discounts	NI	Information from GÖG
IT	NI	Hospital	NI	Early access programmes for single patients	Information from GÖG
BE, DE, DK, EL, ES, FI, IE, NL, NO, PT, SE	NI	NI	NI	NI	NI

*Abbreviations: AT – Austria, BE - Belgium, DK – Denmark, EL – Greece, ES Espagnole, FI – Finland, FR – France, GER – Germany, IE – Ireland, IT – Italy, LU – Luxemburg, NI – No information available, NL – Netherlands, NO – Norway, PT – Portugal, SE – Sweden, UK – United Kingdom; *Cost converter: [46]*

5.4 Budget impact analysis for the Austrian context before negotiation

5.4.1 TDT

Eligible population and market share in years 1-3

ca. 70-84 Pat./Jahr in den kommenden 3 Jahren mit TDT, davon 12 mit Exa-cel behandelt

According to information from clinical experts, there are currently around 70 persons living with TDT in Austria. We assumed a slight increase in patients yearly, resulting in 84 patients in year three. Based on information on patients eligible for exa-cel and the percentage for who a donor is available in those

eligible for HSCT, three would receive HSCT, and 15 would finally be eligible for treatment with exa-cel in the forthcoming three years. From those, we assumed that one per year would withdraw during the preparatory phase, resulting in twelve TDT patients receiving exa-cel over the 3-year period (Table 5-2).

Table 5-2: population TDT

Population	Year 1 (n)	Year 2 (n)	Year 3 (n)	Total (n)
Estimated patient population with TDT in Austria, n	70	77	84	**231***
Patients eligible for HSCT, n	6	6	6	**18**
Number of HSCT eligible patients for who a donor is available (10-15 %), n	1	1	1	**3**
Potential number of eligible patients for Exa-cel, n	5	5	5	**15**
Withdrawals before exa-cel administration, n	1	1	1	**3**
Patients receiving exa-cel, n	4	4	4	**12**

*Source: estimations based on the input of clinical experts and clinical studies [15, 31, 32]; * Cumulative patient number.*

Treatment costs of therapy under evaluation and alternative therapies/standard of care per patient

Treatment costs with exa-cel in patients with TDT equal those in patients with SCD (€ 1.9 million per patient).

selber Preis/Pat.: € 1,9 Mio.

The costs for the SoC per patient per year are roughly € 35,000 (treatment with blood transfusion incl. hospital admissions, and iron chelation). A small proportion would be eligible for HSCT and have a donor, which would cost € 184,000 per patient. For the estimated patient population in Table 5-2, the total direct health care cost of illness with the current SoC would be around € 2 to 3 million per year and € 8.5 million over the next three years, respectively (Table 5-3).

derzeitige Behandlung € 35.000/ Pat. + vereinzelt HSCT

€ 4-5 Mio/Jahr für alle Pat.

Table 5-3: Cost of illness TDT

	Cost/patient/year (€)	Year (€)	Year 2 (€)	Year 3 (€)	Total (€)	%
SoC						
A: regular treatment	35,235	2,290,278	2,536,924	2,783,569	**7,610,771**	94
B: HSCT	184,038	184,038	184,038	184,038	**552,114**	6
Total A+B SoC		***2,615,256***	***2,861,902***	***3,108,547***	***8,585,705***	*100*

HSCT: haematopoietic stem cell transplantation; SoC: standard of care

Gross drug budget impact in years 1-3

Equal to SCD, the gross drug budget impact (drug acquisition costs based on four patients treated) per year is € 7.6 million, equalling € 22.8 million over three years.

Budget Impact Exa-cel: € 7,6 Mio./Jahr

Net drug-budget impact in years 1-3

ca. € 141.000 Einsparungen bei SoC/Jahr

The net budget impact (drug acquisition costs and cost offsets anticipated from the displacement of SoC drugs and treatments) would be € 7.5 million per year and € 22.3 million over three years. This results in savings with SoC of € 141,000 per year and € 423,000 over three years.

Additional costs

zusätzliche Kosten für alle Behandelten: ca. € 165,000/Jahr + € 68.000 für schwere Nebenwirkungen

direkte Kosten gesamt: € 7.8 Mio/Jahr

The additional costs per TDT patient treated with exa-cel are roughly the same as in SCD patients (€ 33,000), resulting in a budget impact of around € € 509,000 over three years. In addition, as in patients with SCD, costs arise due to adverse events, costing € 68,000 per patient. This results in an overall budget impact of roughly € 205,000 over three years, assuming that one exa-cel patient experiences a yearly VOD adverse event. The overall 3-year budget impact of additional costs is around € 714,000. Equal to SCD patients, total direct costs are roughly € 7.8 million annually and € 23.5 million over three years (Table 5-4).

Table 5-4: Budget impact exa-cel for TDT

	Cost/patient (€)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Total (€)	%
A: drug acquisition costs	1,900,000	7,600,000	7,600,000	7,600,000	**22,800,000**	97
B: additional costs	33,292	164,816	169,868	174,920	**509,604**	2
C: adverse events	68,160	68,160	68,160	68,160	**204,480**	1
A-C: Total direct costs		***7,832,976***	***7,838,028***	***7,843,080***	***23,514,084***	*100*

Comparison of exa-cel scenario with current SoC in full TDT population

Exa-cel Szenario Gesamtkosten über 3 Jahre: € 31,7 Mio.

fast 4x so hoch wie derzeit

Based on the total number of patients with severe TDT in Austria and the eligibility for HSCT and exa-cel, total costs for all patients would be € 31.7 million for three years if exa-cel is introduced and received by four patients per year, while the remaining patients would be treated as usual (including HSCT for a tiny proportion). Costs for acquiring exa-cel and the additional costs associated with its administration account for roughly 74% of the costs, while the treatment for the remaining patients with the current SoC sums up to almost one-third. In contrast, if exa-cel is not introduced, and patients continue receiving SoC as usual, less than half of the budget (€ 8.6 million) would be needed (Figure 5-1).

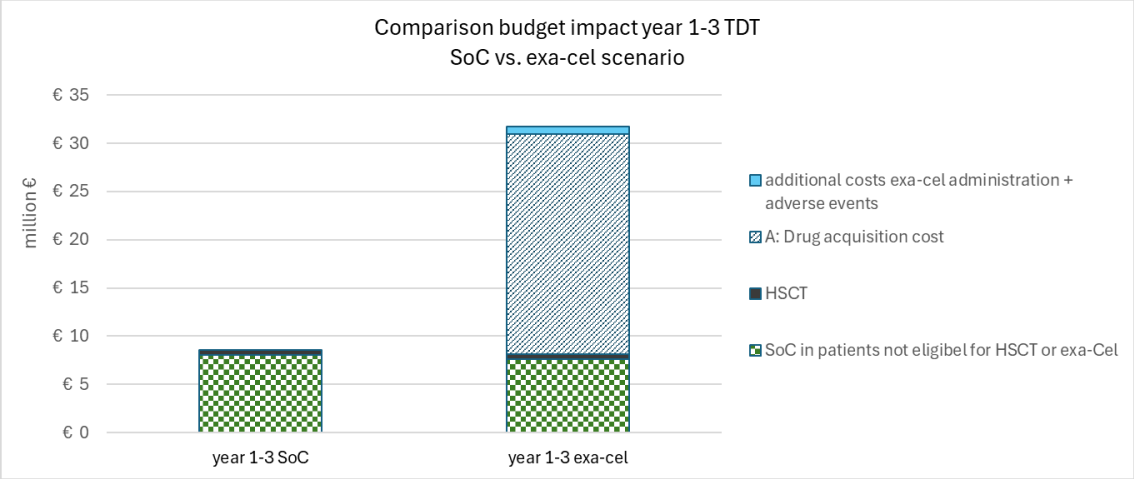


Figure 5-1: Comparison SoC vs. Exa-cel scenario TDT; HSCT: haematopoetic stem cell transplantation; SoC: standard of care; TDT: transfusion-dependent β-thalassemia

5.4.2 SCD

Eligible population and market share in years 1-3

Annahme: ca. 132-160 Pat./Jahr mit schwerer SCD, davon 12 mit Exa-cel behandelt

According to information from clinical experts, there are currently around 132 persons living with severe SCD in Austria. We assumed a slight increase in patients yearly, resulting in 160 patients in year three. Based on information on patients eligible for exa-cel and the percentage for who a donor is available in those eligible for HSCT, five would receive HSCT, and 15 would finally be eligible for treatment with exa-cel in the forthcoming three years. From those, one per year would withdraw during the preparatory phase, resulting in twelve SCD patients receiving exa-cel over the three years (Table 5-5).

Table 5-5: Population SCD

Population	Year 1 (n)	Year 2 (n)	Year 3 (n)	Total (n)
Estimated patient population with SCD in Austria, n	132	145	160	**437***
Patients eligible for HSCT, n	6	7	7	**20**
Number of HSCT eligible patients for who a donor is available (10-15 %), n	1	2	2	**5**
Potential number of eligible patients for exa-cel, n	5	5	5	**15**
Withdrawals before exa-cel administration, n	1	1	1	**3**
Patients receiving exa-cel, n	4	4	4	**12**

*Source: estimations based on the input of clinical experts and clinical studies [6, 15, 31, 32]; * Cumulative patient number.*

Treatment costs of therapy under evaluation and alternative therapies/standard of care per patient

Exa-cel Preis laut Unternehmen: € 1,9 Mio/Pat.

Exa-cel treatment is administered as a single dose. Based on the price for exa-cel provided by the manufacturer (without confidential discounts), treatment per patient (without costs for additional treatment required prior, during, and after exa-cel application) is €1,900,000.

derzeitige Behandlung € 10.600/Pat. + vereinzelt HSCT

€ 1.8 Mio/Jahr für alle Pat.

The costs for the SoC per patient per year are € 10,642 (treatment with Hydroxycarbamid and hospital stays). A small proportion would be eligible for HSCT and have a donor, which would cost € 184,000 per patient. For the estimated patient population in Table 5-5, the total direct healthcare cost of illness with the current SoC would be around € 1.8 million per year and € 5.4 million over the next 3 three years, respectively (Table 5-6).

Table 5-6: Cost of illness SoC

	Cost/patient/year (€)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Total (€)	%
SoC						
A: regular treatment	10,624	1,351,471	1,479,169	1,638,791	4,469,430	83
B: HSCT	184,038	184,038	368,076	368,076	920,190	17
Total A+B: SoC		***1,535,508***	***1,847,244***	***2,006,867***	***5,389,620***	***100***

HSCT: haematopoietic stem cell transplantation; SoC: standard of care

Gross drug budget impact in years 1-3

Budget Impact Exa-cel: € 7,6 Mio./Jahr

The gross drug budget impact (drug acquisition costs based on four patients treated) per year is € 7.6 million, equalling € 22.8 million over three years.

Net drug-budget impact in years 1-3

geringfügige Einsparung bei SoC

Patients in the clinical studies (see 3.3) treated with exa-cel did not need SoC treatment. If this holds true in real-world practice, the net budget impact (drug acquisition costs and cost offsets anticipated from the displacement of SoC drugs and treatments) would be € 7,557,434 per year and € 22.6 million over three years. This results in savings with SoC of € 43,000 per year and € 128,000 over three years.

Additional costs

Treatment with exa-cel requires several interventions before, during and after the treatment. The additional costs per patient treated with exa-cel amount to € 32,294, resulting in a budget impact of around € 159,452 per year and € 493,511 over three years. In addition, costs arise due to adverse events. The adverse event with the highest cost impact is VOD, costing € 68,000 per patient, resulting in an overall budget impact of roughly € 205,000 over three years, assuming that one exa-cel patient each year experiences a VOD adverse event. The overall 3-year budget impact of additional costs is around € 697,991.

zusätzliche Kosten vor, während, nach Behandlung: € 159.000 für alle Pat.

+ € 205.000 für Behandlung schwerer Nebenwirkungen

Total direct costs for the treatment with exa-cel plus the additional interventions and the management of adverse events are around € 7.8 million annually, resulting in a 3-year budget impact of € 23.5 million (see Table 5-7).

direkte Kosten gesamt: € 7.8 Mio/Jahr

Table 5-7: Budget impact exa-cel for SCD

	Cost/patient/year €)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Total (€)	%
A: drug acquisition costs	1,900,000	7,600,000	7,600,000	7,600,000	**22,800,000**	97
B: additional costs	32,294	159,452	164,504	169,556	**493,511**	2
C: adverse events	68,160	68,160	68,160	68,160	**204,480**	1
A-C: Total direct costs		**7,827,612**	**7,832,664**	**7,837,716**	**23,97,991**	100

Comparison of exa-cel scenario with current SoC in the full SCD population

Based on the total number of patients with severe SCD in Austria and the eligibilities for HSCT and exa-cel, total costs over the next three years would be € 28.9 million if exa-cel is introduced and received by four patients per year, and the remaining patients would be treated as usual (including a low proportion undergoing HSCT). The costs for exa-cel drug acquisition and additional costs account for almost 82%, while only 18% are incurred by treating the remaining patients with the current SoC. Costs in the exa-cel scenario would be five times higher than the € 5.4 million required if exa-cel were not introduced, and the current SoC would continue (Figure 5-2).

Exa-cel Szenario Gesamtkosten für alle Pat. über 3 Jahre: € 28.9 Mio.

5x höher als derzeitige Kosten

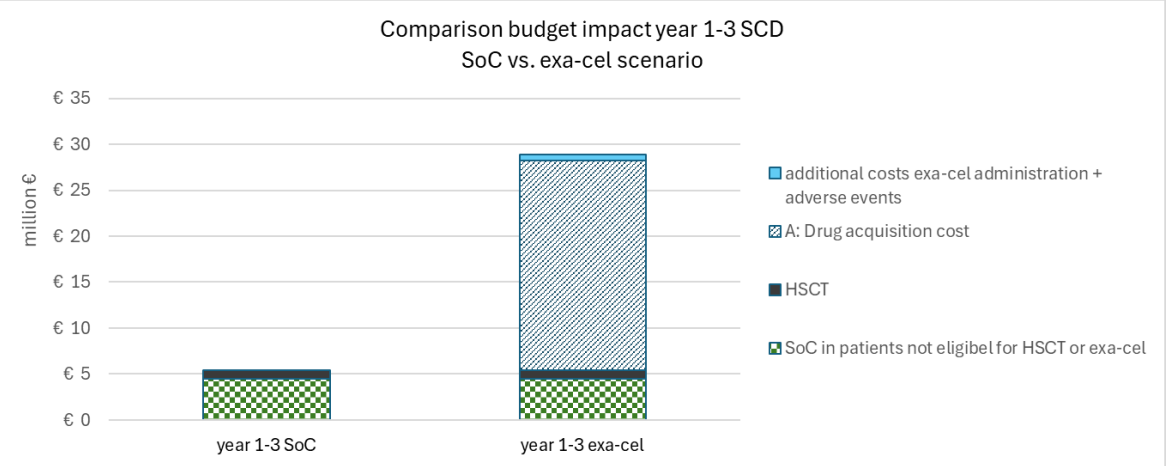


Figure 5-2: Comparison SoC vs. exa-cel scenario SCD; HSCT: haematopoetic stem cell transplantation; SCD: sickle cell disease; SoC: standard of care;

5.4.3 Summary budget impact SCD + TDT

Budget Impact Exa-cel beide Indikationen: € 15.6 Mio pro Jahr, 45.6 Mio in 3 Jahren

Drug acquisition costs for treating both indications result in an annual and 3-year budget impact of € 15.2 million and € 45.6 million, respectively. Additional costs plus costs for adverse events will be € 1.4 million, resulting in an overall budget impact of € 47 million over three years. Drug acquisition costs account for by far the largest share of costs at 97% (Table 5-8).

Table 5-8: Budget impact SCD+TDT

	Year 1 (€)	Year 2 (€)	Year 3 (€)	Total (€)	%
A: drug acquisition costs	15,200,000	15,200,000	15,200,000	**45,600,000**	97
B: additional costs	324,267	334,372	344,476	**1,003,115**	2
C: adverse events	136,320	136,320	136,320	**408,960**	1
A-C: Total direct costs	***15,660,587***	***15,670,692***	***15,680,796***	***47,012,075***	*100*

gesamte Behandlungskosten für SCD und TDT in drei Jahren inkl. Exa-cel: € 60.6 Mio. Fortsetzung derzeitiger Behandlung: ein Viertel der Kosten

The total costs for the following three years for treating all SCD and TDT patients would be € 60.6 million if exa-cel is introduced and received by eight patients annually and the remaining patients are treated as usual. Three-quarters of the costs would be incurred for the exa-cel drug acquisition and the associated additional costs, while one-quarter would be incurred for treating all other patients with the current SoC. In contrast, total costs would be roughly a quarter of those in the exa-cel scenario (€ 14 million over three years) if the assumed patient population were treated as usual (see Figure 5-3).

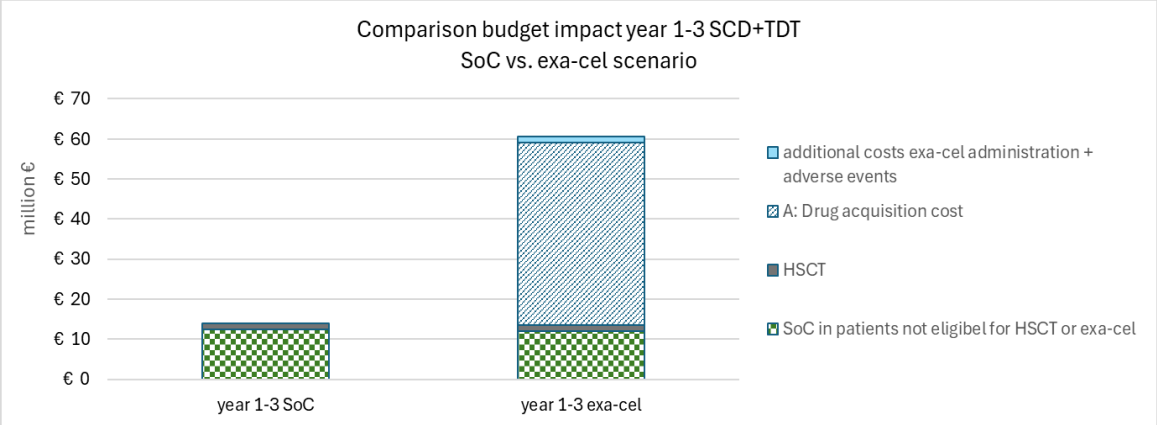


Figure 5-3: Comparison SoC vs. Exa-cel scenario SCD+TDT; HSCT: haematopoietic stem cell transplantation; SCD: sickle cell disease; SoC: standard of care; TDT: transfusion-dependent β-thalassemia

Table A - 6 in the Appendix presents the unit costs used for this budget impact analysis.

5.4.4 Limitations

Limiationen: tatsächliche Anzahl Pat. unbekannt, Bundesländer-Unterschiede bei Unit Costs->Durchschnitt limitiert Repräsentativität, fehlender Standard zur Berechnung von Unit Costs, Behandlungsunterschiede zwischen Klinikern

The limitations of the budget impact calculation are that due to the lack of an epidemiological study for Austria, we do not know the exact number of patients in each indication and how the population would change over the next three years. Secondly, the unit costs for some cost components differed considerably between the different regional hospital providers, and our average price may not reflect the costs for each provider. The basis for calculation was not always stated and might differ between the providers due to the lack of standards for unit cost calculations in Austria. The type of treatments, dosages and volumes for the additional treatments required when administering exa-cel and for the current SoC in Austria is primarily based on the opinions of three clinical experts. There might be variations across Austria. According to expert insights, exa-cel is expected to be primarily administered to adolescents in Austria, who may require slightly different additional therapies. Consequently, the actual costs for these therapies might be somewhat lower than initially presented.

nur, wenn Anzahl Exa-cel Behandlung abweicht, großer Einfluss auf Budget Impact

All of the limitations introduce uncertainty into the budget impact calculation. However, since the price for exa-cel largely drives the overall budget impact, only the population size and if more or fewer patients would, in reality, be eligible for the treatment of exa-cel would have a significant consequence on the overall budget impact.

6 Economic evaluation based on pharmaco-economic models

6.1 Methods

kein gesundheitsökonomisches Modell vom Hersteller

daher Übersicht publizierter Modelle

As the manufacturer did not submit a pharmaco-economic model, we can only summarise published models from other countries. We used the literature identified through the systematic search (see chapter 3.2.1) and additional manual searches via Google to summarise existing economic evaluations. US dollars (2023) were converted into euros (2024) via an online tool using the International Monetary Fund data for purchasing power parities (PPP) [46].

6.2 Summary of existing economic evaluations

6.2.1 Characteristics of the economic evaluations and applied models

2 gesundheitsökonomische Analysen identifiziert:

1 US-amerikanisches Markov Model (ICER Institut 2023) für schwere Sichelzellenanämie

We identified two health economic evaluations, both of which are based on decision-analytic models. Table A - 7 summarises their main characteristics.

One cost-utility analysis of the ICER Insitute in the USA evaluated the cost-effectiveness of exa-cel compared to SoC in adolescents and adults with **severe SCD** who do not have a matched sibling donor or haploidentical donor for haemopoietic stem cell transplant (HSCT) or are too old for safe HSCT. Therefore, a cohort-level Markov model with three health states (acute complications, chronic complications and death) and a one-year cycle length was applied for a lifetime horizon.

Base-Case: direkte medizinische Kosten
weitere Szenarien: z.B. Berücksichtigung von Produktivitätsversluste und Pflegekosten

Outcomes: gewonnene Lebensjahre, QALYs, evLY, VOCs

Exa-cel Preis: € 1,7 Mio.

The base-case scenario pictured the healthcare system perspective including only direct medical costs, while the societal perspective additionally captured indirect costs, such as productivity changes and caregiver costs. Outcomes were presented as life years gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLY) gained, and total VOCs avoided. Cost and outcomes were applied with an annual discount rate of 3%. For the base-case scenario, it was assumed that the patient characteristics were similar to those of patients with severe SCD enrolled in Medicaid, that 28% were adolescents, and that 72% were adults. A proportion of patients were assumed to die in the first model cycle due to the acute risk associated with transplant. In addition, the model included an evidence-based estimate of treatment failure in the first model cycle. Furthermore, a placeholder price of $2,000,000 (€1,705,786) was assumed, and costs for patients who started the process of pretransplant assessments and preparation but did not proceed with the actual treatment were also included in the model [48].

1 Markov Model von NICE (UK 2024) für schwere Beta-Thalassämie

zusätlich: distributional cost-effectiveness analaysis, um gesundheitliche Ungleichheien bei Beta-Thalassämie zu berücksichtigen

The second cost-utility analysis of the National Institute of Clinical Excellence (NICE) in the UK assessed the cost-effectiveness of exa-cel compared to SoC in patients 12 years or older who suffer from **severe transfusion-dependent beta-thalassemia (TDT)** when an HSCT was suitable, but a human donor was not available. Therefore, a Markov model with four mutually exclusive health states (transfusion dependent, transfusion reduction, transfusion independent and death) was applied. Each transfusion health state included four mutually exclusive iron-level health substates (high, medium, low and regular). In addition, a distributional cost-effectiveness analysis (DCEA) was applied to account for health inequalities because TDT mainly affects people from Mediterranean, South Asian, Southeast Asian and Middle Eastern ethnic groups. Information about the applied perspective and time horizon was not reported. Regarding utility, different values were used depending on the CLIMB-THAL-111 trial. Both cost and utility values were applied with an annual discount rate of 3.5%. The model assumed a 0% relapse rate for the exa-cel group. Like the first cost-utility analysis, withdrawals from exa-cel treatment before the first infusion were still included [49].

6.2.2 Results of the health economic evaluations

SCD

Sichelzellenanämie (USA): ICER Gesundheitssystem-Perspektive: €165.000/QALY ICER gesellschaftliche Perspektive: €138.000/QALY

Base-case results of the cost-utility analysis provide a mixed picture of the cost-effectiveness of exa-cell in patients with severe SCD (see Table A - 8). From a healthcare system perspective, the total direct medical costs in the exa-cel group were €2,411,128, compared to €1,270,810 in the SoC group. Given total QALYs of 16,38 in the exa-cel and 9,44 in the SoC group, respectively, this resulted in an incremental cost-effectiveness ratio (ICER) of €164,608 per QALY gained. Considering a societal perspective, with total direct and indirect costs of €2,419,657 for the exa-cel group and €1,461,858 for the SoC group, the ICER was slightly lower and thus more favourable with €138,169 per QALY gained [48].

bei Grenzwert von €170.000/QALY liegt Wahrscheinlichkeit für Kosten-Effektivität von Exa-cel zwischen 23% (Base-Case) und 75% (gesellschaftliche Perspektive)

A probabilistic sensitivity analysis showed that, from a healthcare perspective, exa-cel had a 0% probability of being cost-effective at a threshold of $150,000 (€127,934) per QALY gained (or below) while at a threshold of $200,000 (€170,579) per QALY gained, exa-cel had a 23% probability of being cost-effective. From a societal perspective, exa-cel had a 5% probability of being cost-effective at a threshold of $150,000 (€127,934) per QALY gained (or below), and a 75% probability at a threshold of $200,000 (€170,579) per QALY gained. Threshold analysis also showed that exa-cel would achieve ICERs between $100,000 (€85,289) and $200,000 (€170,579) per QALY gained with prices between €1,151,405 and €1,748,430, from a healthcare perspective, and €1,339,0412 and €1,927,538, from a societal perspective [48].

Anzahl & Kosten der VOC, sowie Nutzwerte & Exa-cel Erfolgsrate größte Einflussfaktoren auf Kosten/QALY

In general, the annual number of VOCs, the cost of the VOCs, and the utilities of patients successfully treated with exa-cel were the significant drivers of the cost per QALY. In addition, another major driver of the cost-effectiveness of exa-cel was the uncertainty around the treatment success rate due to the small sample size in the trial. Moreover, the population's age might impact the cost-effectiveness of gene therapies; namely, younger people are associated with a lower (more favourable) ICER (ceteris paribus) [48].

bevorzugte Population für Exa-cel: diejenigen, die für HSCT in Frage kommen, aber keinen Spender haben

Besides, the model assumes risk neutrality in estimating the expected lifetime health gains associated with exa-cel versus SoC. Therefore, the expected lifetime health gains summarised in the analysis may be best thought of as conditioned on the narrower subpopulation of those who would have considered allogenic HSCT but did not have a matched donor (i.e., those who would consider the net health benefit of opting for gene therapy to be positive) [48].

Exa-cel bei Preis von $ 2 Mio. gemäß üblichen Grenzwerte nicht kosten-effektiv

Overall, assuming a placeholder price of €1,705,786, exa-cel has an ICER above commonly cited cost-effectiveness thresholds from a healthcare and societal perspective. Further results of cost per life year gained, evLY gained, and VOC averted, as well as additional scenarios, are presented in Table A - 8 in more detail.

TDT

Beta-Thalassämie (UK): keine Angaben von Kosteneffektivitäts-verhältnissen aufgrund vertraulicher Preise

jedoch ICER in fast allen Szenarien über dem üblichen Grenzwert -> nicht kosten-effektiv

No incremental costs and incremental utilities were reported for the cost-utility analysis of exa-cel compared to SoC in patients with TDT. Furthermore, no ICER was presented due to the confidential price of the exa-cel. However, it was reported that the ICER was above the range considered cost-effective (even when health inequalities were considered and thus a higher ICER than usual, £20,000 (€24,034) per QALY gained, was accepted). An annual discount rate of 1.5% instead of 3.5% resulted in an ICER below the committee's preferred cost-effectiveness range (optimistic scenario). In contrast, when including the costs for patients who withdrew from exa-cel pre-infusion, a 10% relapse rate in the exa-cel group, and an assumption of 13.7 RBC transfusions per year for the SoC group, the ICER was above the committee's preferred cost-effectiveness range (pessimistic scenario) [49].

Unsicherheiten in der Kosteneffektivität aufgrund unklarer langfristiger Effekte von Exa-cel inkl. Lebensqualität

im NHS nicht für die routinemäßige Anwendung empfohlen

Overall, the cost-effectiveness estimates were highly uncertain due to the uncertainty in exa-cel`s long-term effects and impact on quality of life. Given the high base-case ICER exceeding acceptable cost-effectiveness ranges, exa-cel was not recommended for routine use in the National Health Service (NHS) but recommended for use with managed access. These managed access agreements include the collection of additional data for CLIMB-THAL-111 from the CLIMB-131 follow-up study, additional exa-cel safety and clinical-effectiveness data from the European Society for Blood and Marrow Transplantation Registry, additional rates of complications or adverse events for people having exa-cel and additional data about the number of people who withdraw pre-infusion [49]. All results are presented in Table A - 8.

Ongoing health economic evaluation on exa-cel

laufende gesundheitsöknomische Analysen zu Exa-cel bei Sichelzellenanämie (erwartet Dez. 2024) & 2 weitere vom Hersteller

A second health economic evaluation of the National Institute on Clinical Excellence (UK) on exa-cel for severe SCD is in progress. The website states that publication is expected by 18 December 2024 [51].

Besides, there are two economic evaluations on exa-cel from the manufacturer, one for patients with SCD and one with TDT. However, results are currently only available in abstracts and/or posters [52, 53].

6.3 Submitted pharmaco-economic model

Although a manufacturer model exists and has been presented as a poster at a conference, the manufacturer has not submitted a model as part of the dossier as requested.

6.3.1 Description of model structure

Not available. nicht verfügbar

6.3.2 Overview of input parameters in the model

Not available. nicht verfügbar

6.3.3 Results of economic evaluation (base-case)

Not available. nicht verfügbar

6.3.4 Results on alternative scenarios and sensitivity analyses

Not available. nicht verfügbar

6.4 Critical appraisal of submitted model

Not applicable, as no model has been submitted. Modell wurde nicht geliefert

7 Development costs and public contributions

7.1 Own development costs

The market authorization holder (Vertex) delivered no data on development costs.

keine Informationen zu Entwicklungskosten von Vertex

7.2 Public contributions to drug development, acqusition and licensing information

Table 7-1 provides an overview of the development history and ownership changes of CRISPR/Cas9 gene-edited therapy.

Entwicklungsgeschichte von Exa-cel

Table 7-1: Overview exa-cel deals

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
Casgevy® *Active substance:* Exagamglogene autotemcel (exa-cel) *Alternative names:* Autologous CRISPR-Cas9 modified CD34+ hHSPCs - CRISPR Therapeutics/Vertex Pharmaceuticals; Autologous CRISPR-Cas9 modified CD34+ human hematopoietic stem and progenitor cells - CRISPR Therapeutics/Vertex Pharmaceuticals; CRISPR/Cas9 gene-edited therapy - CRISPR Therapeutics/Vertex Pharmaceuticals; CTX-001; exa-cel *Medical specialty:* Haematology *Pharmacotherapeutic group:* Other haematological agents *Therapeutic area:* ß-Thalassemia AND Anaemia, Sickle Cell *Class:* Gene therapies; Haematopoietic stem cell therapies; Stem cell therapies *Orphan designation:* YES *Categorization:* ATMP *Additional monitoring:* YES *Conditional approval:* YES *Accelerated assessment:* NO *PRIME: priority medicines:* YES *Marketing authorisation issued:* 09.02.2024				
CRISPR Therapeutics	CRISPR Therapeutics; Vertex Pharmaceuticals	**Patent deal 2014, 2016:** The Broad Institute, Harvard, and Editas Medicine have signed a global license agreement granting Editas access to specific genome-editing IP for CRISPR/Cas9 (see Table A - 12) **Patent deal in 2023:** Nonexclsuive licensing deal for Editas Medicines' Cas9 gene editing technology for ex vivo gene editing (see Table A - 12) Editas will in turn pay the Broad Institute and Harvard a "mid-double digit of payments received from Vertex"	Basic research conducted in public research institutes None in late-stage development found	Basic and translational research funding

öffentliche Grundlagenforschung

1987: Indentifikation des CRISPR locus: Osaka University

1990er und 2000er: Universidad de Alicante, Utrecht University, weitere akademische Zentren

2012: CRISPR-Cas9 durch J. Doudna (University of California) und E. Charpentier (Umeå University)

Basic Research and Development of CRISPR Technology

The development of CRISPR technology emerged from mostly public but also private research institutions, as shown in Table A - 10. The initial identification of the CRISPR locus came from public research at Osaka University in 1987 (see Table A - 10).

Subsequent foundational discoveries were made primarily at public institutions, including Universidad de Alicante, Utrecht University, and other academic centres through the 1990s and early 2000s (see Table A - 10). A pivotal shift occurred in 2012 when Jennifer Doudna (University of California) and Emmanuelle Charpentier (then at Umeå University) demonstrated CRISPR-Cas9's potential for gene editing. Figure 7-1 shows the development milestones that ultimately led to the development of Casgevy based on the literature.

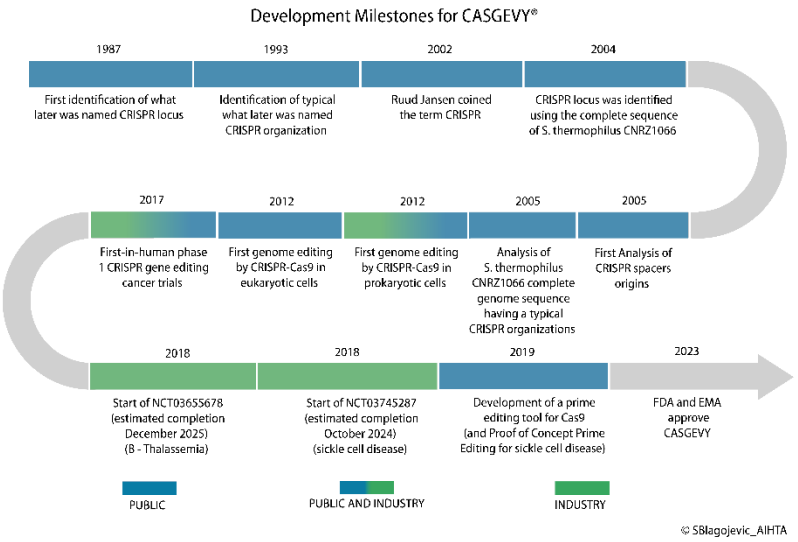


Figure 7-1: Timeline of the development of CRISPR/Cas9 that led to Casgevy

klinische Entwicklung durch Vertex und CRISPR Therapeutics

The discovery of Doudna and Charpentier bridged basic research and therapeutic applications, leading to increased industry interest and involvement. As detailed in Table A - 9, the clinical development of CRISPR-based therapies has been dominated by industry players, particularly Vertex Pharmaceuticals and CRISPR Therapeutics for sickle cell disease and ß-thalassemia. Vertex Pharmaceuticals has been particularly active in clinical trials, with several key studies: NCT03655678: Phase 1/2/3 study for β-Thalassemia; NCT03745287: Study evaluating CTX001 in severe Sickle Cell Disease; NCT04208529: Long-term follow-up study for participants who received CTX001. For none of the clinical trials, total clinical trial costs or per-patient costs were publicly disclosed.

Editas Medicine (founded by researchers from the Broad Institute, the University of California, Berkley and Harvard University) has also conducted trials. However, the firm's focus has been broader, as evidenced by its extensive patent portfolio showing a total of 97 granted patents related to CRISPR/Cas9 technology. This led to Vertex acquiring a nonexclusive patent 2023 from Editas Medicines for a 50 million USD upfront payment, up to an additional 50 million USD contingent payment. The annual license fee ranges from 10 million to 40 million USD, with sales-based increases continuing through 2034 (see Table A - 12).

Editas Medicine hält 97 Patente zur CRISPR/Cas9 technology

Vertex erwirbt nicht-exklusives Patent von Editas Medicines für 50 Millionen USD

Company Structure and Financials

Vertex Pharmaceuticals' financial information, as shown in Table A - 13, reveals that the company has demonstrated financial growth, with operating revenue increasing from $101,9 million in 2009 to $9,87 billion in 2023. The company has maintained consistent profitability since 2020, achieving a profit before tax of $4,38 billion in 2023. The company has shown significant growth in employee numbers, from 1.432 in 2009 to 5.400 in 2023, indicating substantial organizational expansion alongside its financial growth.

Vertex Pharmaceuticals:

Einnahmen stiegen von 2009 von $ 101,9 Mio auf $ 9,87 Milliarden in 2023

The ownership structure reveals that venture capital is the most important financier of Vertex Pharmaceuticals, as seen in Table A - 14. Capital World Investors holds the largest stake with 10,00% direct ownership, operating as an investment management organization. The Vanguard Group follows with 8,35%, State Street Corporation maintains 4,65% total ownership, and BlackRock Fund Advisors holds 3,36%. This means the "Big Three" index funds are with Capital World Investors, the most important shareholders.

Risikokapitalgesellschaften wie Capital World Investors, Vanguard Group, State Street Corporation, BlackRock besitzen große Anteile

Research Funding and Collaborations

Table A - 11 and Table A - 12 show significant public funding support for CRISPR/Cas9 research, particularly from the NIH. Key recipients include Stuart H. Orkin at Dana-Farber Cancer Institute Jennifer A. Doudna at the University of California Berkeley (who received, alongside Emmanuelle Charpentier, the Nobel Prize in Chemistry). Over the years, these researchers have received over 7,4 million USD from the NIH, and the Broad Institute has received over 73,3 million USD for their research on CRISPR/Cas9 or the application it from the NIH. Even though public funding has been essential for basic research in CRISPR technology development, the total amount of public funding for basic research is not available.

NIH (USA) war Hauptsponsor der Grundlagenforschung

The development of exa-cel represents a collaboration between industry (Vertex Pharmaceuticals, CRISPR Therapeutics, Editas Medicines) and academic institutions (especially the Broad Institute at Harvard but also the University of California, Harvard University and the Massachusetts Institue of Technology (MIT)), leveraging both public and private funding sources. The product received marketing authorization in February 2024, marking a significant milestone in commercialising CRISPR technology. This development pathway demonstrates the evolution from basic academic research to commercial therapeutic applications, with increasing industry involvement and investment as the technology matured. The successful development required substantial financial resources, which we only know partly from the public side. Vertex Therapeutics has not disclosed the total development costs for Casgevy.

Exa-cel ist das Ergebnis einer Zusammenarbeit zwischen Vertex Pharmaceuticals + CRISPR Therapeutics mit akademischen Institutionen

7.3 Landscape overview on further gene therapies (in development)

weitere Gentherapien bei Hämoglobinopathie

There are several further gene therapies in different stages of development (Table 7-2). Generally, four forms of genetic therapy can be distinguished [54],[55],[56]: gene addition, gene editing, gene silencing, and gene correction. All have the end goal of decreasing haemoglobin S (Hgb S) production with a concomitant increase in the production of non-sickling haemoglobin. Only two therapies (lovo-cel and exa-cel) are in clinical stages.

4 Techniken in Gentherapien werden erprobt

Gene Addition mittels viraler Vektoren werden modifizierte β-globin Sequenzen eingebracht

Gene addition techniques aim to introduce a non-sickling, modified β-globin sequence via a viral vector into the stem cells of affected individuals and reduce haemoglobin S polymerisation. Notably, gene addition therapy increases the expression of non-sickling haemoglobin but does not alter the expression of haemoglobin S.

Lovo-cel von Bluebird nur von FDA zugelassen $ 3.3 million

1. **Lovo-cel** (Lyfgenia) [57]: The HGB-206 study using BB111 – a lentiviral vector - (BB305, LentiGlobin, lovotibeglogene autotemcel, or lovo-cel, investigated in NCT02140554 (non-randomised, open-label, single-dose phase 1/2, 35 patients) and NCT04293185 (phase 3 non-randomised trial, eleven patients). So far, this is the only gene therapy-related clinical trial with patients (n=35 SCD patients) who are more than 24 months post-treatment and with published data regarding health-related quality of life. However, there are concerns regarding the development of myeloid dysplasia and subsequent acute myeloid leukaemia.

   Lovo-cel by Bluebird is not approved by EMA (only FDA) and sold for $ 3.3 million.

Beti-cel von Bluebird EMA zugelassen 2019, vom Markt genommen 2022, $ 2.8 million

2. **Beti-cel** (Zynteglo) by Bluebird was granted conditional approval by EMA 2019, but the market authorization was withdrawn in 2022.

   Zynteglo is still approved by the FDA and sold for $ 2.8 million.

Gene Editing: mittels CRISPR Cas9 wird ein Stück DNA herausgeschnitten

Gene editing techniques or CRISPR-Cas9 are cutting the DNA in the BCL11A gene, which usually suppresses the production of fetal haemoglobin, to turn off the suppression. The result is increased fetal haemoglobin expression with simultaneous decreased production of haemoglobin S.

$ 2.2 million

Exa-cel von Vertex von EMA 2024 und FDA 2023 zugelassen

3. **Exa-cel** (Casgevy®) [57, 58]: The CTX001 (exagamglogene autotemcel or exa-cel, investigated in NCT03745287 and NCT03655678) is the focus of this assessment (see chapter 3). Further, two trials sponsored by Vertex are ongoing: NCT05477563 (SCD, phase 3, twelve to 35 years, expected completion Feb 2025) and NCT05329649 (SCD, phase 3, children, expected completion May 2026).

   Exa-cel by Vertex is approved by EMA and the FDA and sold for $ 2.2 million.

weitere CRISPR/Cas9 Therapie in Entwicklung von Novartis in Zusammenarbeit mit Intellia Therapeutics

4. Further two trials are currently exploring a similar CRISPR/Cas9-mediated HbF reactivation approach, one by Bioverativ (NCT03653247, Precizn-1: phase 1/2, eight patients, 18 to 40 years) and the second one by Novartis Pharmaceuticals in collaboration with Intellia Therapeutics (NCT04443907) [59]. For this last trial

(phase 1/2, 20 patients, two to 17 years), promising data regarding sustained induction of fetal haemoglobin and clinical in three patients with SCD have been recently reported [60].

Gene silencing focuses on preventing the expression of fetal haemoglobin suppressors. Still, unlike a break in gene editing, gene silencing introduces an antisense oligonucleotide (ASO) to messenger RNA via a viral vector to turn off the production of the targeted gene.

Gene Silencing

5. The GRASP study (with lentiviral vector: BCH-BB694, NCT05353647, open-label, non-randomised, multi-centre, phase 2, 25 patients 13-40 years, expected completion in May 2025) sponsored by Boston Children's Hospital (David Williams) is based on early findings from phase 1 trial (BEACON, NCT03282656, in seven patients) that showed sizeable improvements in fetal haemoglobin.

in klinischer Entwicklung

Gene correction techniques, the newest gene therapy method, have focused on removing haemoglobin S production entirely while introducing non-sickling haemoglobin through DNA repair and correction.

Gene Correction

1. The CEDAR trial (NCT04819841, first-in-human, open-label, phase 1/2, 15 adults - 18 to 40 years—and adolescents -twelve to 17 years) by Graphite Biophase was halted due to severe pancytopenia after the treatment of the first patient with sickle cell disease was unsuccessful.

in präklinischer Entwicklung

2. Further gene therapies are in the experimental, preclinical or early clinical stage: EDIT-301 (RUBY, NCT04853576), BEAM-101 (BEACON, NCT05456880) by Beam Therapeutics [56],[55].

Table 7-2: SCD gene therapy clinical trials listed on ClinicalTrials.gov from [56]*, adapted*

Trial number	Status	Phases	Mechanism of action	Age (years)	Developer
NCT05456880 (BEACON)	Recruiting	1, 2	Gene editing on the γ-globin gene promoter to induce HbF, using a CRISPR-Cas9 protein coupled to a base-editing deaminase enzyme	18–35	Beam Therapeutics
NCT05353647 (GRASP)	Recruiting	2	Gene editing using a lentiviral vector with short hairpin RNA that suppresses BCL11A expression to induce fetal haemoglobin	13–40	David Williams, Boston Children's Hospital
NCT04853576 (RUBY)	Recruiting	1, 2	Gene editing on the γ-globin gene promoter to induce HbF, using a proprietary CRISPR-Cas system	18–50	Editas Medicine
NCT04293185 NCT02140554	Recruiting Active, not recruiting	3 1, 2	Gene addition using a lentiviral vector that expresses an anti- sickling β globin HbAT87Q [15]	2–50 12–50	Bluebird bio
NCT03964792(DREPAGLOBE)	Active, not recruiting	1, 2	Gene addition using a lentiviral vector that expresses an anti- sickling β globin AS3 [45]	12–20	Assistance Publique - Hôpitaux de Paris
NCT03745287 NCT05477563 NCT05329649	Active, not recruiting Recruiting Recruiting	2, 3 3 3	Gene editing to suppress BCL11A expression and induce HbF, using CRISPR-Cas9 [17, 18]	12–35 12–35 2–11	Vertex Pharmaceuticals
NCT03282656	Active, not recruiting	1	Gene editing using a lentiviral vector with short hairpin RNA that suppresses BCL11A expression to induce HbF [19]	3–40	David Williams, Boston Children's Hospital
NCT02247843	Active, not recruiting	1, 2	Gene addition using a lentiviral vector that expresses an anti- sickling β globin AS3	≥18	Donald B. Kohn, M.D., Univ.California
NCT02186418	Terminated due to funding	1, 2	Gene addition using a lentiviral vector that expresses a variant HbF	18–45	Children's Hospital Medical Center
NCT04443907	Active, not recruiting	1	Gene editing on the γ-globin gene promoters to disrupt repressor binding and induce HbF, using CRISPR-Cas9 [20]	2–40	Novartis Pharmaceuticals)

Note: The initial search criteria used were: condition = sickle cell disease; intervention = gene; study type = interventional; only trials investigating gene therapy with a status of 'Recruiting' or 'Active, not recruiting' are included. Abbreviations: HbF, haemoglobin F; SCD, sickle cell disease

8 Conclusion

1. Exa-cel received EMA approval in February 2024 under **conditional** marketing authorisation and is included in the EMA Priority Medicines (PRIME) scheme. Exa-cel is the 1st CRISPR/Cas9 gene therapy. Several others are in development, of which one (by Novartis in collaboration with Intellia Therapeutics) is currently exploring a similar CRISPR/Cas9 gene editing technique. The approval is based on two case series (without comparator and unblinded). A long-term observation is ongoing (13-year long-term follow-up study, CLIMB-131; ClinicalTrials.gov number, NCT04208529).

   Exa-cel erhielt bedingte Zulassung auf Basis von 2 Fallserien (ohne Vergleich zu SoC)

2. The approved indications are inherited haemoglobinopathies. Patients must be ≥12 years of age for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell transplant (HSC) donor is not available:

   - transfusion-dependent β-thalassaemia (TDT) **intermedia and major**
   - severe sickle cell disease (SCD) with **recurrent** vaso-occlusive crises (VOCs)

   zugelassene Indikationen:
   TDT intermedia und major sowie
   SCD mit wiederkehrenden VOC

   The estimated total number of TDT patients is 60 to 79 in Austria of which around 15 TDT patients could be eligible for treatment with exa-cel in the next three years, including three to four patients aged between 12 and 17 years. The estimated total number of SCD patients (including natives and people with a migration background) is around 132, of which around 15 SCD patients could be eligible for exa-cel in the next three years, nine to twelve of whom are aged between 12 and 17 years.

   geschätzte 30 Patient*innen über 3 Jahre,
   SCD: mehrheitlich Kinder

3. In Western countries, the prognosis for patients with TDT and SCD has enormously improved over the past decades due to comprehensive care. The diseases shifted from being a fatal illness to a **chronic disease** that is associated with progressive deterioration in the quality of life (QoL) and organ function. The therapeutic alternatives are **erythrocyte concentrates and iron chelation in TDT** and **hydroxycarbamide in SCD** and eventually, stem cell transplantation as a curative intervention.

   in westlichen Ländern chronische Erkrankungen, anderswo tödlich

4. The efficacy and safety of exa-cel in treating TDT and SCD have been investigated in **two prospective open-label non-comparative observational clinical studies** and on a limited number of patients for a maximum follow-up of one year. These studies have shown that exa-cel can **eliminate the need for transfusion** in 91% of TDT patients and **vaso-occlusive crises (VOC)** in 97% of SCD patients. Around 90% of patients had adverse events of grade 3 or 4.

   in Studien bis max. 1 Jahr nach Behandlung: keine Transfusion nötig und keine VOCs

einzeitige Verabreichung von Exa-cel, aber sehr belastende Vorbehandlung (Grund für Therapieabrüche)

5. The treatment with exa-cel consists of a single-dose infusion. Before exa-cel can be manufactured, patients must undergo myoablative mobilisation with Busulfan, followed by ev. several cycles of apheresis. **Pre-treatment conditioning** is very stressful for the patient and is a reason for discontinuation. The hospital stay for the entire procedure is estimated to be five to six weeks. Post-treatment, patients need to be monitored closely for an extended period.

Informationen zu Unsicherheiten der Therapie, zu den belastenden Vorbehandlungen unabdingbar

6. Informed consent, **management of expectations with information on uncertainties**, and compliance with stressful pre-treatment are prerequisites. It is estimated that 30 patients (out of 60-79 for TDT and 132 with SCD) could potentially be eligible for exa-cel. Language support might be needed.

Transplantationszentren haben limitierte Kapazitäten: sorgfältige Auswahl

7. Exa-cel requires several highly specialised pre-treatments, close monitoring after the treatment and less frequent but regular long-term monitoring. These experienced centres in HSC transplantation currently already have **limited capacities**. Careful selection of patients is of utmost importance.

Hochpreistherapie mit € 47 Mio Budgetbedarf in 3 Jahren

für alle Pat. 4,3x höherer Gesamtbudgetbedarf (€ 60.6 Mio.) als bisher

in anderen Ländern als nicht kosten-effektiv eingestuft

ergebnisabhägnige Bezahlmodelle zu erwägen

8. Exa-cel is a **high-price therapy** with drug acquisition costs of € 45.6 million over the next three years based on the estimated number of 30 eligible patients and the current manufacturer price. Furthermore, it comes with many **additional costs**, resulting in another € 1.4 million budget requirement. A reimbursement mechanism must be in place to cover the costs of the gene therapy itself and beyond. Exa-cel costs under the current price conditions are manifold higher than current treatment costs, estimated at €14 million (TDT: €8.6 million; SCD: €5.4 million) over the forthcoming three years. Since only a negligible proportion of the current costs will be replaced, adding exa-cel will lead to a **4.3-fold increase in total direct costs** for treating all patients, resulting in €60.6 million (TDT: €31.7 million; SCD: €28.9 million). International cost-effectiveness analyses have concluded that, at the current price, exa-cel therapy is **not cost-effective**. Decision-makers may consider outcome-based risk-sharing agreements to ensure sustainable coverage of these treatments.

CRISPR/ Cas9 Forschung in öffentliche Institutionen

Weiterentwicklung durch Firmen

9. Basic research and development (R&D) of CRISPR technology emerged from mostly public but also private research institutions in the USA, supported by the National Institute of Health (NIH) with around 7 million USD to individual research institutions/ researchers and further 73 million USD to the Broad Institute/ Havard, which granted Editas a license agreement for CRISPR/ Cas9 genome-editing IP. Editas made a **non-exclusive licensing deal with Vertex** in 2023 (for 50 million USD upfront and a further 50 million under conditions).

10. Exa-cel is a **potentially** curative treatment. However, there are **many uncertainties**:

    - How long the treatment effect with exa-cel lasts: only data from a median follow-up time of 20.4 months (TDT) and 19.3 months (SCD) is available, while a far longer FU is needed to validate whether exac-cel shows persistent effect and is truly curative.
    - The data for actual comparative survival and quality-of-life outcomes in patients treated by exa-cel vs. standard-of-care treatment are not available.
    - The frequency of complications and long-term adverse events. Data documentation in registries is needed to monitor the effects and potential long-term adverse events, such as blood cancer risks, due to the possibility of off-target editing of the genome.
    - The transferability of results from the highly selected patients in the pivotal studies is questionable due to older and more diseased patients in the real-world population.
    - Withdrawal from exa-cel treatment before the infusion occurs: 5-10% drop-outs were found in the highly selected groups of patients in the pivotal trials.

zahlreiche Unsicherheiten:

Dauer des Effektes
Vergleich mit Standardtherapie bezgl. Mortalität und Lebensqualität
Häufigkeit von Komplikationen
Langzeit Nebenwirkunge
Übertragbarkeit der Studienergebnisse auf reale Situation
Therapieabbrüche

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9.2 Further Sources

Interviews with three clinical experts (interview guidance see (Table A - 5)

Questionnaires from nine patients (questionnaire see Table A - 4)

10 Appendix

Table A - 1: Search strategies

Cochrane

ID	Search
#1	(Casgevy) (Word variations have been searched)
#2	("exagamglogene autotemcel") (Word variations have been searched)
#3	("ctx 001") (Word variations have been searched)
#4	(ctx001) (Word variations have been searched)
#5	(Exa-cel) (Word variations have been searched)
#6	(exacel) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6

Embase

No.	Query
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7.	'ctx 001'
#6.	ctx001
#5.	exacel
#4.	'Exa-cel'
#3.	casgevy*
#2.	'exagamglogene autotemcel*'
#1.	'exagamglogene autotemcel'/exp

Medline

1	Casgevy.mp.
2	exagamglogene autotemcel.mp.
3	"ctx 001".mp.
4	ctx001.mp.
5	Exa-cel.mp.
6	exacel.mp.
9	1 or 2 or 3 or 4 or 5 or 6

Search strategies to identify trials on **Casgevy** in Clinical Trials Registers, date of search: 17.09.2024

ClinicalTrials.gov
Search string: Casgevy OR Exagamglogene OR CTX001 OR "ctx 001" OR Exa-cel OR exacel in Intervention/treatment
7 studies identified

WHO ICTRP (Advanced search mode)
Search string: Casgevy OR Exagamglogene OR CTX001 OR "ctx 001" OR Exa-cel OR exacel in Intervention
16 (8 further) studies identified

EU Clinical Trials (EUdraCT)
Search string: Casgevy OR Exagamglogene OR CTX001 OR "ctx 001" OR Exa-cel OR exacel
6 (0 further) studies identified

Table A - 2: Risk of bias (non-randomised studies other than uncontrolled trials, cross-sectional studies and case series) report at study level (IHE checklist) - TDT

Risk of bias - study level (case series) [30]								
1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	no[5]	yes	yes	yes	no[6]
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	yes	yes	yes	yes	yes
Overall risk of bias: moderate								

5 disease stage was not defined and population was heterogeneous (age, number of prior medications, volume of transfusion), 6 open-label study design,

Table A - 3: Risk of bias (non-randomised studies other than uncontrolled trials, cross-sectional studies and case series) report at study level (IHE checklist) SCD

Risk of bias - study level (case series) [30]								
1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	no[1]	yes	yes	yes	no[2]
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	partial[3]	yes	yes	yes	yes	yes	yes	yes
Overall risk of bias: moderate								

1disease stage was not defined and population was heterogeneous (age, rate of VOC), 2 open-label study design, 3 unclear if the rate of VOC was measured objectively prior to study enrollment

Table A - 4: Questions asked to the TDT and SCD patients

Question 1	Rolle des Ausfüllenden (einzelne/ Patient/Angehörige/Andere)
Question 2	Hauptwohnsitz
Question 3	Mitglied einer Patient:innenorganisation a. Wenn ja, bitte nennen Sie die Patient:innenorganisation b. Wenn ja, welche Rolle haben Sie in der Patient:innenorganisation? c. Wenn ja, welche Erkrankung(en) wird/werden von der Organisation vertreten?
Question 4/1	Krankheitsstadium/ Schweregrad
Question 4/2	Krankheitsgeschichte a. Wie lange leben Sie schon mit der Krankheit/dem Leiden? b. Bitte beschreiben Sie Ihre Behandlungsgeschichte
Question 4/3	Zusätzliche Informationen, die Ihrer Meinung nach für die Ersteller des HTA-Berichtshilfreich wären
Question 5	Falls zutreffend, wo haben Sie Informationen über die Erfahrungen der Patient:innen eingeholt? Falls zutreffend, wie haben Sie Informationen über die Erfahrungen der Patient:innen gesammelt?
Question 6	Wie wirkt sich die transfusionsabhängige Beta-Thalassämie auf Ihr tägliches Leben (eines Patienten/einer Patientin) aus?
Question 7	Wie wirkt sich die transfusionsabhängige Beta-Thalassämie auf Angehörige aus?
Question 8	Wie gut bewältigen Patient:innen mit transfusionsabhängiger Beta-Thalassämie ihre Erkrankung mit den derzeit verfügbaren Therapien?
Question 9	Was erwarten diejenigen Patient:innen, die keine Erfahrung mit exa-cel haben, von neuen Therapien im Allgemeinen?
Question 10	Für diejenigen, die Erfahrung mit exa-cel haben: Welche Auswirkungen hatte/hat es auf Ihr Leben?
Question 11	Bitte geben Sie alles an, was Ihrer Meinung nach für das für die gemeinsame Bewertung zuständige HTA-Team wissenswert sein könnte
Question 12	Bitte fassen Sie Ihren Beitrag in maximal zehn Kernaussagen zusammen und listen Sie die wichtigsten Punkte auf

Table A - 5: Fragen an klinische Experten

*Patient*innen und Patient*innenpopulation Österreich*

1. Sind die Patient*innen (Einschluss in Studien) repräsentativ für reale die Patient*innen-Population in Ö? Wenn nicht: ist Übertagbarkeit der Ergebnisse gegeben?
2. Welches sind definitive Ausschlusskriterien?
3. Wie viele potenziell geeignete Patient*innen gibt es in Österreich für die Behandlung mit Casgevy, und welche spezifischen Kriterien müssen sie erfüllen (z. B. Alter, Schwere der Erkrankung, vorherige Therapien)?
4. Gibt es spezifische genetische Varianten in Österreich, die den Erfolg der Therapie beeinflussen könnten?
5. Welche medizinischen, psychologischen und entwicklungsbedingten Faktoren müssen bei der Behandlung von Jugendlichen (12- bis 18-Jährigen) mit Casgevy beachtet werden, insbesondere hinsichtlich Sicherheit, Wirksamkeit und Langzeitfolgen?

Intervention: klinische und ökonomische Bewertung

- Wo im Behandlungspfad ist exa-cel einzusetzen ?
- Welche begleitenden Therapien sind zu Casgevy notwendig?
- Nach welcher Leitlinie wird in Österreich behandelt?
- Vor der Gabe von Casgevy:
  - Welche Medikamente in welcher Dosierung werden verabreicht, um Infusionsreaktionen vorzubeugen (Paracetamol? Diphenhydramin?)
  - Welches Medikament in welcher Dosierung wird zur Prophylaxe von Krampfanfällen verabreicht?
  - Erfolgt die myeloablative Konditionierung mit Busulfan? In welcher Dosierung?
  - VOD-Prophylaxe bei SCD: welches Medikament in welcher Dosierung?
  - Laut EMA Produktinformation wurde vor der Behandlung der Studienpatienten mit Casgevy Plerixafor zur Freisetzung von Stammzellen in die Blutbahn (+G-CSF bei TDT, als single-agent bei SCD) eingesetzt. Entspricht das dem Vorgehen in Österreich?

Komparator

- Was ist der derzeitige SoC (Standard of Care)?
- Welche begleitenden Therapien sind zum aktuellen SoC notwendig?

Outcomes

- Welches sind kurzfristige, welches langfristige wichtige klinische Endpunkte?

Organisatorische Voraussetzungen

- Gibt es besondere organisatorische Strukturen, die für die Verschreibung und Verabreichung von Casgevy notwendig sind (z. B. spezielle Zentren, Schulungen für medizinisches Personal)?
  - Welche Anforderungen an spezialisierten Zentren bestehen für die Durchführung dieser Gentherapie in Österreich?
  - Welche Anpassungen an die Infrastruktur (z. B. Gentherapielabore) sind notwendig?
- Werden österr. Patient*innen in einem Register (Register für seltene Anämien; RADeep/ Rare Anaemia Disorders European Epidemiological Platform; EHR/ European Haemoglobinopathy Registry; TIF/ Thalassaemia International Federation) dokumentiert oder ist das geplant?

Langzeitüberwachung und Patientenmanagement

- Welche Anforderungen bestehen für die Langzeitüberwachung von Patient*innen, die Casgevy erhalten?
- Wie sollte die Nachsorge in Bezug auf mögliche Langzeit-Nebenwirkungen organisiert werden?
- Welche Monitoring-Strategien müssen während der Therapie mit Casgevy implementiert werden (z. B. Bluttests, regelmäßige Untersuchungen)?

Table A - 6: Unit cost data

	Average unit costs	Range	Reference
A: Exa-cel			
A1: Drug acquisition (exa-cel) AT	€ 1 900 000,00	-	Manufacturer
A2: Additonal treatments			
Hospital inpatient treatments			
Assessment der eligibility for haematopoet. stem cell transplantation	€ 3 981,92	-	Payer
CD34+ HSPC mobilisation (prior to exa-cel, inpatient):	€ 7,39	-	
-Plerixafor (prior to apheresis, inpatient) 20mg/ml, 1,2 ml	€ 1 977,80	€ 551,00-5 640,00	Payer
-only for TDT: G-CSF (prior to apheresis) Filgrastim (Nivestim FSPR, 48 Mio IE)	€ 332,60	-	EKO
RBC exchange or simple transfusion(s) (prior to apheresis, inpatient)	€ 126,43	€ 34,50-218,35	Payer
Myeloablative conditioning (Busulfan, prior to exa-cel, inpatient)	€ 1 548,93	€ 670,80-2 800,00	Payer
Central venous catheter (prior to exa-cel, inpatient)	€ 193,27	-	Payer
Iron chelation (Deferasirox, prior to exa-cel), EXJADE TBL 500 mg 28 Stk	€ 713,44	-	Payer
Anti-seizure prophylaxis (prior to exa-cel, inpatient) according to the SPC for the myeloablative conditioning medicinal product	Excluded due to low costs and low impact on overall costs	-	Clinical information
Pre-medication: paracetamol/ diphenhydramine, or equivalent products	Excluded due to low costs and low impact on overall costs	-	Clinical information
Irradiation of blood products required within first 3 months (after exa-cel, inpatient)	€ 125,07	€ 77,04-168,00	Payer
Hospital outpatient treatment			
HLA typing	€ 5,05	-	Payer
Apheresis (prior to exa-cel, outpatient hospital clinic)	€ 2 064,38	€ 1 341,75-2 697,00	Payer
Diagnostic imaging (head MRT, thorax CT, prior to exa-cel)			
- MRT (head)	€ 253,48	€ 106,26-414,20	Payer
- CT (Thorax)	€ 142,37	€ 61,41-238,00	Payer
Long-term follow-up			
Monitoring (including complete blood counts) (after Exa-cel, outpatient)	€ 20,70	-	Payer
Monitoring for gene-editing related oncogenesis (including complete blood count) (after Exa-cel, outpatient)	€ 1 242,36	-	Payer
Management of adverse events [very common (>1/10)]			
CD4 lymphocytes decreased	Excluded due to low costs and low impact on overall costs		Clinical information
Lymphopenia	Excluded due to low costs and low impact on overall costs		Clinical information
Treatment of hepatic VOD if indicated Defibrotide (Defitelio®)	€ 4 260,00	€4 260,00-4 260,00	Payer

	Average unit costs	Range	Reference
B: Standard of care for SCD in Austria			
SCD: Hydroxycarbamid (Hydroxyurea, Litarlir®, 90%)	€ 54,25	-	EKO
SCD: XROMI (10%: very small children)	€ 899,49	-	Payer
SCD: Hospital admission	€ 3 402,50	€ 3052,00-3753,00	Payer
C: Standard of care for TDT in Austria			
TDT: Hospital admission	€ 2 757,00	-	Payer
TDT: RBC transufsion(s)	€ 126,43	€ 34,50-218,35	Payer
TDT: Iron chelation (Deferasirox (Accord), 360 mg, 90 stk;	€ 304,80	€ 273,30-337,45	EKO
TDT: Iron chelation (Deferasirox (G.L.), 360 mg, 90 stk;			
TDT: Iron chelation (Deferasirox (ratiopharm), 360 mg, 90 stk;			
Management of adverse events [very common (>1/10)]			
Bone marrow depression including neutropenia (< 1.5 x 109/L), reticulocytopenia (< 80 x 109 /L), macrocytosis	Excluded due to low costs and low impact on overall costs		Clinical information
D: SCT with HLA-donor			
SCT with HLA-donor	€ 180 056,00	-	Payer
eligibility assessment before transplantation	€ 3 981,92	-	Payer

Table A - 7: Characteristics of the included economic evaluations

Author,year [Reference]	*Country*	*Intervention anc comparator*	*Target population (base case)*	*Economic evaluation*	*Model*	*Perspective and time horizon*	*Utility values*	*Severity modifier*	*Discount rate*	*Model assumption(s)*
Beaudoin et al. (ICER), 2023 [48]	*USA*	*Exagamglogene autotemcel (Exa-cel) vs standard care (SoC)*	*Adolescents (28%) and adults (72%) with* ***severe***[9] ***sickle cell disease (SCD)*** *who do not have a matched sibling donor or haploidentical donor for haematopoetic stem cell transplant (HSCT) or are too old for safe HSCT* *Mean age adolescents: 15 years* *Mean age adults: 24 years*	*Cost-utility analysis*	*De novo Markov model with one year cycle lenth.* *The model focused on key acute and chronic complications as well as risk of death.*	*Health care sector perspective (base-case)* *Modified societal perspective that also includes productivity changes and caregiver costs (scenario) 10* *Lifetime horizon*	*Life years gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLY) gained, total vaso-occlusive crisis (VOCs) avoided*	*NR*	*3% per year*	*A cohort-level de novo Markov model rather than a patient level simulation.* *Base-case: patient characteristics similar to patients with severe SCD enrolled in Medicaid, and categorised into adolescents and adults.* *Identical efficacy for the two therapies given the small number of people studied.* *Number of VOCs per year in the model were changed to 5.1 per year for patients on SoC (rather than the four VOCs per year used in the draft report).* *A proportion of patients were assumed to die in the first model cycle due to the acute risk associated with transplant and the model included an evidence-based estimate of treatment failure in the first model cycle.* *Costs for patients who start the process of pretransplant assessments and preparation but do not proceed with treatment are included in the model.*

[9] Severe SDC defined as having ≥4 severe VOCs in each of the two prior years.

[10] For patient productivity estimates, the proportional decrease in annual median income of 34.1% was used. This resulted in annual lost patient productivity of $19,250 (*€16,418*), which was applied to all adults in the SoC arm, and these costs were assumed to be eliminated after successful treatment with gene therapy. For caregiver estimates, the annual losses in unpaid work estimated as $19,662 (*€16,769*) per caregiver were used. Caregiver costs were applied for all adolescents in the standard of care arm, and as above, these costs were assumed to be eliminated after successful treatment with gene therapy.

Author,year [Reference]	*Country*	*Intervention anc comparator*	*Target population (base case)*	*Economic evaluation*	*Model*	*Perspective and time horizon*	*Utility values*	*Severity modifier*	*Discount rate*	*Model assumption(s)*
NICE, *2024* [49]	*UK*	Exa-cel vs SoC	*Transfusion-**dependent beta-thalassaemia** in people ≥12 years:* ■ *When a HSCT is suitable, but a human donor is not availabe.* *Only if the condition in the managed access agreement are followed.*	*Cost-utility analysis* *Distributional cost-effectiveness analysis (DCEA) to account for health inequalities 11*	*Markov model with four mutually exclusive health states (transfusion dependent, transfusion reduction, transfusion independent and death); each of the three transfusion health states included four mutually exclusive iron-level health substates (high, medium, low and normal); people started in the transfusion-dependent health state with abnormal iron levels (high, medium or low);* *Chronic complications were modelled based on iron levels: cardiac or liver complications, hypogonadism, diabetes and osteoporosis;* *DCEA: The company weighted the benefits and costs in each index of multiple deprivation group using a health inequality aversion parameter to create an equity-weighted incremental cost-effectiveness ratio (ICER). This needs information on how much the UK population prefers extending quality-adjusted life expectancy for a person from a deprived population compared with someone with less deprivation.*	NR	*CLIMB-THAL-111 trial (EQ-5D data): baseline utility values were 0.89 and the following health-state utility values:* ■ *0.73 for transfusion dependence* ■ *0.75 for transfusion reduction* *0.93 for transfusion independence*	*The committee did not think that the threshold for a severity modifier was met.*	*3.5% per year*	*All people treated with Exa-cel had permanent transfusion independence (0% relapse rate).* *People on SoC cannot become transfusion independent: being transfusion free starting 60 days after the last blood transfusion.* *Different outcome definition for transfusion independence than CLIMB-THAL-111.* *Including withdrawals from Exa-cel treatment before the infusion takes place.* *The number of transfusions for people having SoC (16.4 RBC transfusions per year)*

Abbreviations: ICER – Institute for Clinical and Economic Review, NICE – National Institute for Clinical Excellence,
**Parameters for extraction chosen from the CHEES and Drummond checklists.*
*** Reported cost data were converted to € (2024) based on the dataset for purchasing power parity (PPP) of the International Monetary Fund (IMF) [46]*

11 Thalassemia mainly affects people from Mediterranean, South Asian, Southeast Asian and Middle Eastern ethnic groups. In the UK, it is most prevalent in people in Pakistani, Indian and Bangladeshi ethnic groups.

Table A - 8: Main results of the included economic evaluations

Author, year [Reference]	*Country*	*Incremental costs (base-case)*	*Incremental effects (base-case)*	*ICER (base-case)*	*CE-threshold applied*	*Sensitivity and scenario analyses*	*Reflection*
Beaudoin et al. (ICER), 2023 [48]	*USA*	***Base-case 12: Healthcare*** *perspective (Exa-cel vs SoC): $2,827,000 (€2,411,128) vs $1,490,000 (€1,270,810)* ***Societal perspective*** *(Exa-cel vs SoC): $2,837,000 (€2,419,657) vs $1,714,000 (€1,461,858)*	***Base-case****:* *QALYs (Exa-cel vs SoC): 16.38 vs 9.44* *Life years (Exa-cel vs SoC): 21.87 vs 15.80* *evLYs (Exa-cel vs SoC): 17.31 vs 9.44* *VOCs (Exa-cel vs SoC): 4.18 vs 119.26*	***Base-case*** *(Exa-cel vs SoC)* ***Fehler! Textmarke nicht definiert.****:* ***Healthcare perspective****:* *$193,000 (€164,608) per QALY gained* *$220,000 (€187,636) per life year gained* *$170,000 (€144,991) per evLY gained* *$11,600 (€9,895) per VOC averted* ***Societal perspective****:* *$162,000 (€138,169) per QALY gained* *$185,000 (€157,785) per life year gained* *$143,000 (€121,964) per evLY gained* *$9,800 (€8,358) per VOC averted*	*Health Benefit Price Benchmarks (HBPBs) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 (€85,289) and $200,000 (€170,579) per QALY or per evLY gained:* *Healthcare perspective: the HBPB Exa-cel ranges from $1,350,000 (€1,151,405) to $2,050,000 (€1,748,430)*	***One-way sensitivity analysis:*** *The cost of the VOCs, the utility of patients successfully treated with gene therapy, and the annual number of VOCs are the major drivers of cost per QALY. Given the greater uncertainty around the treatment success rate of Exa-cel due to the small sample size in the Exa-cel trial, this was also a major driver of cost per QALY.* ***Probabilitic sensitivity analysis:*** *Healthcare perspective: Exa-cel had 0% probability of being cost-effective at a threshold of ≤$150,000 (€127,934) per QALY gained, while at a threshold of $200,000 (€170,579) per QALY gained, Exa-cel had a 23% probability of being cost effective. Societal perspective: 5% probability for Exa-cel of being cost-effective at a threshold of ≤$150,000 (€127,934) per QALY gained, and there is a substantial change at a threshold of $200,000 (€170,579) per QALY with a 75% probability of being cost-effective for Exa-cel.* ***Optimistic and conservative scenarios regarding the treatment benefits:*** *Optimistic: If the complication and mortality rates in the Exa-cel arm are closer to the US general population rates, then the gene therapies are likely to have an ICER <$150,000 (<€127,934) per QALY gained and $150,000 (€127,934) per evLY gained from the healthcare and societal perspective. Conservative: If the complication rates for patients in the Exa-cel arm are similar to patients with severe SCD who experience no VOCs, then the gene therapies are likely to have an ICER above $200,000 (€170,579) per QALY and >$150,000 (>€127,934) per evLY gained from the healthcare and societal perspective.*	*When assuming a placeholder price for Exa-cel of $2,000,000 (€1,705,786) and applying standard 3% per year discounting, these gene therapies have an ICER that is above commonly cited thresholds from the healthcare and societal perspective.* *If the number of VOCs or cost per VOC in real practice is lower than the values used in the model, this would result in an increase in the ICERs of gene therapies compared to SoC.* *The cost-effectiveness findings are sensitive to the assumptions around the impact of gene therapies in reducing the complications.* *The population's age will have impact on the cost-effectiveness of gene therapies (with all else equal, those of younger age are associated with a lower ICER).* *One major limitation in the model is that it assumes risk neutrality in estimating the expected lifetime health gains associated with gene therapies versus SoC. Therefore, the expected lifetime health gains summarised in this report may be best thought of conditioned on this narrower subpopulation of those who would have considered allogenic HSCT but did not have a matched donor (i.e., those that would consider the net health benefit of opting for gene therapy to be positive).*

12 Using placeholder price of $2million for Exa-cel.

Author, year [Reference]	*Country*	*Incremental costs (base-case)*	*Incremental effects (base-case)*	*ICER (base-case)*	*CE-threshold applied*	*Sensitivity and scenario analyses*	*Reflection*
						50/50 shared savings analyses*13:* *Healthcare perspective: $253,000 (€215,782) per QALY gained and $223,000 (€190,195) per evLY gained.* *Societal perspective: $243,000 (€207,253) per QALY gained and $214,000 (€182,519) per evLY gained.* ***Cost-offset cap****14: Cost offsets did not exceed $150,000 (€127,934) in any modeled year; therefore, results are aligned with the base-case findings.* ***Threshold analysis:*** *Unit price to achieve the threshold per QALY gained from healthcare perspective:* ***$50,000*** *(€42,644) à $1,000,000 (€852,893)* ***$100,000*** *(€85,289) à $1,350,000 (€1,151,405)* ***$150,000*** *(€127,934) à $1,700,000 (€1,449,918)* ***$200,000*** *(€170,579) à $2,050,000 (€1,748,430)* *Unit price to achieve the threshold per QALY gained from societal perspective:* ***$50,000*** *(€42,644) à $1,220,000 (€1,040,529)* ***$100,000*** *(€85,289) à $1,570,000 (€1,339,0412)* ***$150,000*** *(€127,934) à $1,910,000 (€1,629,025)* ***$200,000*** *(€170,579) à $2,260,000 (€1,927,538)* *Unit price to achieve the threshold per evLY gained from healthcare perspective:* ***$50,000*** *(€42,644) à $1,050,000 (€895,537)* ***$100,000*** *(€85,289) à $1,440,000 (€1,228,166)* ***$150,000*** *(€127,934) à $1,840,000 (€1,569,323)* ***$200,000*** *(€170,579) à $2,230,000 (€1,901,950)* *Unit price to achieve the threshold per QALY gained from societal perspective:* ***$50,000*** *(€42,644) à $1,270,000 (€1,083,174)* ***$100,000*** *(€85,289) à $1,660,000 (€1,415,802)* ***$150,000*** *(€127,934) à $2,050,000 (€1,748,430)* ***$200,000*** *(€170,579) à $2,440,000 (€2,081,058)*	

Author, year [Reference]	*Country*	*Incremental costs (base-case)*	*Incremental effects (base-case)*	*ICER (base-case)*	*CE-threshold applied*	*Sensitivity and scenario analyses*	*Reflection*
NICE, 2024 [49]	*UK*	*NR*	*NR*	*The exact ICER included a confidential price for Exa-cel and cannot be reported here.*	*In genereal, ICER of £20,000 (€24,034) per QALY gained. However, the committee was willing to take health inequality into account in its decision making by accepting a higher cost-effectiveness estimate than it otherwise would have done.*	***Optimistic scenario*** *with discount rate of 1.5%: the ICER was below the committee's preferred cost-effectiveness range.* ***Pessimistic scenario*** *including the costs for people who withdrew from Exa-cel pre infusion and the EAG's preferred utility values15, a 10% relapse rate in the Exa-cel group, and an assumption of 13.7 RBC transfusions per year for the SoC group à the ICER was above the committee's preferred cost-effectiveness range.*	*Cost-effectiveness estimates are highly uncertain, due to the uncertainty in Exa-cel`s long-term effects and impact on quality of life.* *ICER was above the range considered cost-effective, thus Exa-cel is NOT recommended for routine use in the National Health Service (NHS) but recommended for use with managed access.* *Intended data collection according to the current managed access proposal:* ■ *Additional data for CLIMB-THAL-111 from the CLIMB-131 follow-up study.* ■ *Additional Exa-cel safety and clinical-effectiveness data from the European Society for Blood and Marrow Transplantation Registry.* *Updated managed access proposal:* ■ *Rates of complications or adverse events for people having Exa-cel.* ■ *The number of people who withdraw pre-infusion.*

Abbreviations: ICER – Institute for Clinical and Economic Review, NICE – National Institute for Clinical Excellence,
**Parameters for extraction chosen from the CHEES and Drummond checklists.*
*** Reported cost data were converted to € (2024) based on the dataset for purchasing power parity (PPP) of the International Monetary Fund (IMF) [46]*

13 50% of lifetime healthcare cost offsets from a new treatment are assigned to the healthcare system instead of being assigned entirely to the new treatment.

14 Healthcare cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment.

15 General population utility value age and gender-matched to the trial population.

Table A - 9: Clinical Trials for sickle cell disease and ß-Thalassemia using CRISPR/Cas9 technology (as of 09/2024)

ClinicalTrials.gov ID	Primary investigator	Condition	Study Start (Actual)	Primary Completion (Estimated)	Collaborators	Type of sponsor	Source
Study of Safety and Efficacy of Genome-edited Hematopoietic Stem and Progenitor Cells in Sickle Cell Disease (SCD)							
NCT04443907	Novartis Pharmaceuticals	Sickle cell disease	25/08/2020	30/10/2024	n.a.	Industry	https://clinicaltrials.gov/study/NCT04443907?term=NCT04443907&rank=1
A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia							
NCT03655678 (EUCTR2017-003351-38-IT AND EUCTR2017-003351-38-DE)	**Vertex Pharmaceuticals Incorporated**	β-Thalassemia	14/09/2018	12/2025	CRISPR Therapeutics	Industry	https://clinicaltrials.gov/study/NCT03655678?term=NCT03655678&rank=1
A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease							
NCT03745287 (EUCTR2018-001320-19-BE)	**Vertex Pharmaceuticals Incorporated**	Sickle cell disease	27/11/2018	10/2024	CRISPR Therapeutics	Industry	https://clinicaltrials.gov/study/NCT03745287?term=NCT03745287&rank=1
PD-1 Knockout Engineered T Cells for Metastatic Non-small Cell Lung Cancer							
NCT02793856	Sichuan University	Metastatic Non-small Cell Lung Cancer	26/08/2016	17/03/2020	MedGencell	Public Industry	https://clinicaltrials.gov/study/NCT02793856?term=NCT02793856&rank=1
A Study to Assess the Safety, Tolerability, and Efficacy of BIVV003 for Autologous Hematopoietic Stem Cell Transplantation in Patients With Severe Sickle Cell Disease							
NCT03653247	Sangamo Therapeutics	Sickle cell disease	06/03/2019	14/07/2025	n.a.	Industry	https://clinicaltrials.gov/study/NCT03653247?term=NCT03653247&rank=1#collaborators-and-investigators
Evaluation of Safety and Efficacy of CTX001 in Paediatric Participants With Severe Sickle Cell Disease (SCD)							
NCT05329649	**Vertex Pharmaceuticals Incorporated**	Sickle Cell Disease	02/05/2022	05/2025	CRISPR Therapeutics	Industry	https://clinicaltrials.gov/study/NCT05329649?term=NCT05329649&rank=1#collaborators-and-investigators
Evaluation of Efficacy and Safety of a Single Dose of Exa-cel in Participants With Severe Sickle Cell Disease, βS/βC Genotype							
NCT05951205	**Vertex Pharmaceuticals Incorporated**	Sickle Cell Disease	04/2024	12/2029	n.a.	Industry	https://clinicaltrials.gov/study/NCT05951205?term=NCT05951205&rank=1#collaborators-and-investigators
BEACON: A Study Evaluating the Safety and Efficacy of BEAM-101 in Patients With Severe Sickle Cell Disease (BEACON)							
NCT05456880	Beam Therapeutics Inc.	Sickle Cell Disease	30/08/2022	01/02/2027	n.a.	Industry	https://clinicaltrials.gov/study/NCT05456880?term=NCT05456880&rank=1#collaborators-and-investigators
A Study Evaluating the Safety and Efficacy of EDIT-301 in Participants With Severe Sickle Cell Disease (RUBY)							
NCT04853576	**Editas Medicine, Inc.**	Sickle Cell Disease	04/05/2021	08/2025	n.a.	Industry	https://clinicaltrials.gov/study/NCT04853576?term=NCT04853576&rank=1#collaborators-and-investigators
Gene Correction in Autologous CD34+ Hematopoietic Stem Cells (HbS to HbA) to Treat Severe Sickle Cell Disease (Restore)							
NCT04819841	Kamau Therapeutics	Sickle Cell Disease	15/11/2021	31/07/2027	n.a.	Industry (spin-out)	https://clinicaltrials.gov/study/NCT04819841?term=NCT04819841&rank=1
Transplantation of Clustered Regularly Interspaced Short Palindromic Repeats Modified Hematopoietic Progenitor Stem Cells (CRISPR_SCD001) in Patients with Severe Sickle Cell Disease							
NCT04774536	Mark Walters, MD	Sickle Cell Disease	18/09/2024	01/03/2029	University of California, Los Angeles University of California, Berkeley	Public	https://clinicaltrials.gov/study/NCT04774536?term=NCT04774536&rank=1

ClinicalTrials.gov ID	Primary investigator	Condition	Study Start (Actual)	Primary Completion (Estimated)	Collaborators	Type of sponsor	Source
A Study to Assess the Safety, Tolerability, and Efficacy of ST-400 for Treatment of Transfusion-Dependent Beta-thalassemia (TDT)							
NCT03432364	Sangamo Therapeutics	ß-thalassemia	29/03/2018	17/11/2022	n.a.	Industry	https://clinicaltrials.gov/study/NCT03432364?term=NCT03432364&rank=1#collaborators-and-investigators
Evaluation of Safety and Efficacy of CTX001 in Paediatric Participants With Transfusion-Dependent β-Thalassemia (TDT)							
NCT05356195	**Vertex Pharmaceuticals Incorporated**	ß-thalassemia	03/05/2022	05/2026	CRISPR Therapeutics	Industry	https://clinicaltrials.gov/study/NCT05356195?term=NCT05356195&rank=1#collaborators-and-investigators
Safety and Efficacy Evaluation of γ-globin Reactivated Autologous Hematopoietic Stem Cells							
NCT04211480	Bioray Laboratories	ß-thalassemia	01/10/2020	27/11/2023	Xiangya Hospital of Central South University AND The 923rd Hospital of Joint Logistics Support Force of People's Liberation Army	Industry AND Public	https://clinicaltrials.gov/study/NCT04211480?term=NCT04211480&rank=1#collaborators-and-investigators
Safety and Efficacy Evaluation of BRL-101 in Subjects With Transfusion-Dependent β-Thalassemia							
NCT05577312	Bioray Laboratories	ß-thalassemia	01/11/2022	10/09/2026	First Affiliated Hospital of Guangxi Medical University AND Xiangya Hospital of Central South University AND Chinese Academy of Medical Sciences AND Nanfang Hospital, Southern Medical University	Industry AND Public	https://clinicaltrials.gov/study/NCT05577312?term=NCT05577312&rank=1
Safety and Efficacy Evaluation of ET-01 Transplantation in Subjects With Transfusion Dependent β-Thalassaemia							
NCT04390971	Institute of Hematology & Blood Diseases Hospital, China	ß-thalassemia	10/02/2023	15/08/2025	EdiGene Inc. AND The Affiliated Hospital Of Guizhou Medical University AND Zunyi Medical College	Public AND Industry (academic spin-out)	https://clinicaltrials.gov/study/NCT04390971?term=NCT04390971&rank=1#collaborators-and-investigators
A Study to Evaluate the Safety and Efficacy of ET-01 Transplantation in Subjects With Transfusion Dependent β-Thalassaemia.							
NCT05752123	EdiGene (Guangzhou) Inc.	ß-thalassemia	18/02/2023	15/08/2025	The 923rd Hospital of Joint Logistics Support Force of People's Liberation Army	Industry (academic spin-out) AND Public	https://clinicaltrials.gov/study/NCT05752123?term=NCT05752123&rank=1
A Safety and Efficacy Study Evaluating ET-01 in Subjects With Transfusion Dependent β-Thalassaemia (ET-01)							

ClinicalTrials.gov ID	Primary investigator	Condition	Study Start (Actual)	Primary Completion (Estimated)	Collaborators	Type of sponsor	Source
NCT04925206	EdiGene (Guang-Zhou) Inc.	ß-thalassemia	17/08/2021	30/06/2024	n.a.	Industry (academic spin-out)	https://clinicaltrials.gov/study/NCT04925206?term=NCT04925206&rank=1#collaborators-and-investigators
EDIT-301 for Autologous Hematopoietic Stem Cell Transplant (HSCT) in Participants With Transfusion-Dependent Beta Thalassemia (TDT)							
NCT05444894	**Editas Medicine, Inc.**	ß-thalassemia	29/04/2022	12/2025	n.a.	Industry	https://clinicaltrials.gov/study/NCT05444894?term=NCT05444894&rank=1
Safety and Efficacy Evaluation of Autologous CRISPR-Cas12b Edited Hematopoietic Stem Cells							
NCT06041620	Institute of Hematology & Blood Diseases Hospital, China	ß-thalassemia	31/08/2023	30/06/2026	Shanghai Vitalgen BioPharma Co., Ltd.	Public AND Industry	https://clinicaltrials.gov/study/NCT06041620?term=NCT06041620&rank=1#collaborators-and-investigators
Safety and Efficacy Evaluation of γ-globin Reactivated Autologous Hematopoietic Stem Cells							
NCT05442346	Bioray Laboratories	ß-thalassemia	25/12/2023	30/11/2024	First Affiliated Hospital of Guangxi Medical University	Industry AND Public	https://clinicaltrials.gov/study/NCT05442346?term=NCT05442346&rank=1#collaborators-and-investigators
β-globin Restored Autologous HSC in β-thalassemia Major Patients							
NCT04205435	Bioray Laboratories	ß-thalassemia	2021-11-01	2022-07-25	The 923rd Hospital of Joint Logistics Support Force of People's Liberation Army	Industry AND Public	https://clinicaltrials.gov/study/NCT04205435?term=NCT04205435&rank=1
iHSCs With the Gene Correction of HBB Intervent Subjests With β-thalassemia Mutations							
NCT03728322	Allife Medical Science and Technology Co., Ltd.	ß-thalassemia	2019-01	2021-01	n.a.	Industry	https://clinicaltrials.gov/study/NCT03728322?term=NCT03728322&rank=1#collaborators-and-investigators
A Long-term Follow-up Study in Participants Who Received CTX001							
NCT04208529 (EUCTR2018-002935-88-GB AND EUCTR2018-002935-88-DE)	**Vertex Pharmaceuticals Incorporated**	Sickle cell disease and ß-thalassemia	20/01/2021	09/2039	CRISPR Therapeutics	Industry	https://clinicaltrials.gov/study/NCT04208529?term=NCT04208529&rank=1#collaborators-and-investigators
Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease							
NCT05477563	**Vertex Pharmaceuticals Incorporated**	Sickle cell disease and ß-thalassemia	02/08/2022	02/2025	CRISPR Therapeutics	Industry	https://clinicaltrials.gov/study/NCT05477563?term=NCT05477563&rank=1#study-overview
A Phase 1/2/3 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in subjects with Transfusion-Dependent β-Thalassemia							
CTIS2024-516894-57-00	**Vertex Pharmaceuticals Inc.**	ß-thalassemia	10/09/2018	28/09/2021	n.a.	Industry	https://euclinicaltrials.eu/ctis-public/view/2024-516894-57-00?lang=en
A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease							
CTIS2024-516067-83-00	**Vertex Pharmaceuticals Inc.**	Sickle cell disease	02/05/2019	01/07/2025	n.a.	Industry	https://euclinicaltrials.eu/ctis-public/view/2024-516067-83-00?lang=en
A Long-term Follow-up Study of Subjects with β-Thalassemia or Sickle Cell Disease Treated with Autologous CRISPR-Cas9 Modified Hematopoietic Stem Cells (CTX001)							
CTIS2024-512654-19-00	**Vertex Pharmaceuticals Inc.**	Sickle cell disease and ß-thalassemia	06/03/2020	01/01/2040	n.a.	Industry	https://euclinicaltrials.eu/ctis-public/view/2024-512654-19-00?lang=en

Table A - 10: Studies that ultimately led to the development of CRISPR/Cas9 and CASGEVY®

Author(s)	Year	Advancement in CRISPR/Cas9	Research institute/ Affiliations	Type of sponsor	Source
Nucleotide sequence of the iap gene, responsible for alkaline phosphatase isozyme conversion in escherichia coli, and identification of the gene product. Published in *Journal of Bacteriology*					
Ishino, Y. Shinagawa, H. Makino, K. Amemura, M. Nakata, A.	1987	First identification of CRISPR locus	Osaka University	Public	https://doi.org/10.1128/jb.169.12.5429-5433.1987
Transcription at different salinities of haloferax mediterranei sequences adjacent to partially modified psti sites. Published in *Molecular Microbiology*					
Mojica, F.J. Juez, G. Rodriguez-Valera, F.	1993	Identification of typical CRISPR sequences	Universidad de Alicante	Public	https://doi.org/10.1111/j.1365-2958.1993.tb01721.x
Identification of genes that are associated with DNA repeats in prokaryotes. Published in *Molecular Microbiology*					
Jansen, R.	2002	Ruud Jansen coined the term CRISPR	Utrecht University	Public	https://doi.org/10.1046/j.1365-2958.2002.02839.x
Embden, JD.			National Insititute of Public Health and Environmental Protecion		
Gaastra, W.			Utrecht University		
Schouls, LM			National Insititute of Public Health and Environmental Protecion		
Complete sequence and comparative genome analysis of the dairy bacterium Streptococcus thermophilus. Published in *Nature Biotechnology*					
Bolotin, A. Quinquis, B. Renault, P. Sorokin, A. Ehrlich, S.D. Kulakauskas, S.	2004	CRISPR locus was identified using the complete sequence of S. thermophilus CNRZ1066	Institut National de la Recherche Agronomique	Public	https://doi.org/10.1038/nbt1034
Lapidus, A. Goltsman, E. Mazur, M. Pusch, G.D. Fonstein, M. Overbeek, R. Kyprides N.			Integrated Genomics		
Purnelle, B. Prozzi, D. Ngui, K. Masuy, D. Hancy, F. Burteau, S. Boutry, M. Delcour, J. Goffeau, A.			Université Catholique de Louvain		

Author(s)	Year	Advancement in CRISPR/Cas9	Research institute/ Affiliations	Type of sponsor	Source
Hols, P.					
Clustered regularly interspaced short palindrome repeats (CRISPRs) have spacers of extrachromosomal origin. Published in *Microbiology*					
Bolotin, A. Quinquis, B. Sorokin, A. Ehrlich, S.D.	2005	Analysis of S. thermophilus CNRZ1066 complete genome sequence having a typical CRISPR organizations	Institut National de la Recherche Agronomique	Public	https://doi.org/10.1099/mic.0.28048-0
Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements. Published in *Journal of molecular evolution*					
Mojica, F. J. Díez. Villaseñor, C. S., García-Martínez, J., Soria, E.	2005	First Analysis of CRISPR spacers origins	Universidad de Alicante	Public	https://doi.org/10.1007/s00239-004-0046-3
CRISPR Provides Acquired Resistance Against Viruses in Prokaryotes Published in *Science*					
Barrangou, R.,	2007	Demonstrated CRISPR-based immunity in bacteria	Danisco USA Inc.	Industry	https://doi.org/10.1126/science.1138140
Fremaux, C.,			Danisco France SAS	Industry	
Deveau, H.,			Université Laval	Public	
Richards, M.,			Danisco USA Inc.	Industry	
Boyaval, P.,			Danisco France SAS	Industry	
Moineau, S.,			Université Laval	Industry	
Romero, D.A.,			Danisco USA Inc.	Industry	
Horvath, P.			Danisco France SAS	Industry	
Human Fetal Haemoglobin Expression Is Regulated by the Developmental Stage-Specific Repressor *BCL11A* Published in *Science*					
Sankaran, V., G.	2008	Examination of BCL11A as a potential regulator of HbF expression	Children's Hospital Boston, Harvard Medical School AND Dana-Farber Cancer Institute Howard	Not-for-profit paediatric medical center AND Non-profit hospital	https://doi.org/10.1126/science.1165409
Menne, T. F.			Children's Hospital Boston, Harvard Stem Cell Institute, Harvard Medical School	Not-for-profit paediatric medical center	
Xu, J.			Children's Hospital Boston, Harvard Stem Cell Institute, Harvard Medical School	Not-for-profit paediatric medical center	
Akie, T. E.			Children's Hospital Boston, Harvard Stem Cell Institute, Harvard Medical School	Not-for-profit paediatric medical center	
Lettre, G.			Broad Institute AND Children's Hospital Boston	Nonprofit research organization AND Not-for-profit paediatric medical center	
Van Handel, B.			University of California	Public	
Mikkola, H. K. A.			University of California	Public	
Hirschhorn J. N.			Broad Institute AND Children's Hospital Boston	Nonprofit research organization AND Not-for-profit paediatric medical center	

Author(s)	Year	Advancement in CRISPR/Cas9	Research institute/ Affiliations	Type of sponsor	Source
Cantor, A. B.			Children's Hospital Boston, Harvard Stem Cell Institute, Harvard Medical School	Not-for-profit paediatric medical center	
Orkin, S. H.			Children's Hospital Boston, Harvard Stem Cell Institute, Harvard Medical School, AND Dana-Farber Cancer Institute AND Howard Hughes Medical Institute	Not-for-profit paediatric medical center AND Non-profit hospital AND Not for profit medical research organization	
CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III Published in *nature*					
Deltcheva, E.	2011	Novel pathway for CRISPR activation in the human pathogen Streptococcus pyogenes, in which a trans-encoded small RNA directs processing of precursor RNA into crRNAs through endogenous RNase III and the CRISPR-associated Csn1 protein.	Umeå University AND University of Vienna	Public	https://doi.org/10.1038/nature09886
Chylinski, K.					
Sharma, C. M.			University of Würzburg		
Gonzales, K.			University of Vienna		
Chao, Y.			University of Würzburg		
Pirzada, Z. A.			University of Vienna		
Eckert, M. R.			University of Vienna		
Vogel, J.			University of Vienna		
Charpentier, E.			Umeå Centre for Microbial Research AND University of Vienna		
Cas9–crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. Published in *Proceedings of the National Academy of Sciences*					
Gasiunas, G.	2012	First genome editing by CRISPR-Cas9 in prokaryotic cells	Vilnus University	Public	https://doi.org/10.1073/pnas.1208507109
Barrangou, R.			DuPont	Industry	
Horvath, P.			DuPont	Industry	
Siksnys, V			Vilnus University	Public	
A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity Published in *science*					
Jinek, M.	2012	First genome editing by CRISPR-Cas9 in eukaryotic cells	Howard Hughes Medical Institute AND University of California Lawrence Berkeley National Laboratory	Public	https://doi.org/10.1126/science.1225829
Chylinski, K.			University of Vienna AND Umeå University		
Fonfara, I.			Umeå University		
Hauer, M.			University of California		
Doudna, J. A.			Howard Hughes Medical Institute AND University of California AND Lawrence Berkeley National Laboratory		
Charpentier, E.			Umeå University		
Anerythroid enhancer of bcl11a subject to genetic variation determines fetal haemoglobin level Published in *science*					

Author(s)	Year	Advancement in CRISPR/Cas9	Research institute/ Affiliations	Type of sponsor	Source
Bauer, D.E.	2013	Enhancer was required for erythroid expression of *BCL11A* and thus for globin gene expression.	Boston Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School	Not-for-profit paediatric medical center AND Non-profit hospital AND Public	https://doi.org/10.1126/science.1242088
Kamran, S.C.			Montreal Heart Institute and Université Montréal	Public	
Lessard, S.			Harvard Medical School AND Howard Hughes Medical Institute	Public AND Not for profit medical research organization	
Xu, J.					
Fujiwara, Y.			Boston Children's Hospital	Not-for-profit paediatric medical center	
Lin, C.					
Shao, Z.					
Canver, M.C.			Harvard Medical School	Public	
Smith, E.C.			Boston Children's Hospital	Not-for-profit paediatric medical center	
Pinello, L.			Dana-Farber Cancer	Non-profit hospital	
Sabo, P.J.			University of Washington	Public	
Vierstra, J.					
Voit, R. A.			Stanford University	Public	
Yuan, G.			Dana-Farber Cancer Institute AND Harvard School of Public Health	Non-profit hospital AND Public	
Matthew, M. P.			Stanford University	Public	
Stamatoyannopoulos, J. A.			University of Washington		
Lettre, G.			Montreal Heart Institute and Université Montréal		
Orkin, S. H.			Boston Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School AND Howard Hughes Medical Institute	Not-for-profit paediatric medical center AND Non-profit hospital AND Public AND Not for profit medical research organization	
Multiplex Genome Engineering Using CRISPR/Cas Systems Published in *science*					
Cong, L.	2013	Engineering two different type II CRISPR/Cas systems and demonstrate that Cas9 nucleases can be directed by short RNAs to induce precise cleavage at endogenous genomic loci in human and mouse cells	Broad Institute AND Harvard Medical School	Not for profit AND Public	https://doi.org/10.1126/science.1231143
Ran, F. A.			Broad Institute AND Harvard University	Not for profit AND Public	
Cox, D.			Broad Institute AND Harvard Medical School	Not for profit AND Public	
Lin, S.			Broad Institute	Not for profit	

Author(s)	Year	Advancement in CRISPR/Cas9	Research institute/ Affiliations	Type of sponsor	Source
			AND Tsinghua University	AND Public	
Barretto, R.			Columbia University	Public	
Habib, N.			Broad Institute	Not for profit	
Hsu, P. D.			Broad Institute AND Harvard University	Not for profit AND Public	
Wu, X.			Massachusetts Institute of Technology	Public	
Jiang, W.			The Rockefeller University	Public	
Marraffini, L. A.			The Rockefeller University	Public	
Zhang, F.			Broad Institute	Not for profit	
BCL11A enhancer dissection by Cas9-mediated in situ saturating mutagenesis Published in *nature*					
Canver, M.C.	2015	BCL11A further understanding	Boston Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School	Not-for-profit paediatric medical center AND Non-profit hospital AND Public	https://doi.org/10.1038/nature15521
Smith, E.C.					
Sher, F.,					
Pinello, L.			Dana-Farber Cancer AND Institute and Harvard School of Public Health	Non-profit hospital AND Public	
Sanjana, N.E.			Broad Institute	Not for profit	
Shalem, O.			Broad Institute	Not for profit	
Chen, D.D.			Boston Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School	Not-for-profit paediatric medical center AND Non-profit hospital AND Public	
Schupp, P.G.					
Vinjamur, D.S.					
Garcia, S.P.			Dana-Farber Cancer Institute AND Harvard School of Public Health	Non-profit hospital AND Public	
Luc, S			Boston Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School	Not-for-profit paediatric medical center AND Non-profit hospital AND Public	
Kurita, R.			RIKEN BioResource Center	Publicly funded research institute	
Nakamura, Y.			RIKEN BioResource Center AND University of Tsukuba	Publicly funded research institute AND Public	
Fujiwar, Y.			Boston Children's Hospital AND Dana-Farber Cancer Institute AND	Not-for-profit paediatric medical center AND Non-profit hospital	

Author(s)	Year	Advancement in CRISPR/Cas9	Research institute/ Affiliations	Type of sponsor	Source
			Harvard Medical School AND Howard Hughes Medical Institute	AND Public AND Not for profit medical research organization	
Maeda, T.			Harvard Medical School	Public	
Yuan, G.			Dana-Farber Cancer	Non-profit hospital	
Fen, Z.			Broad institute	Not for profit	
Orkin, S.H			Boston Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School, Boston AND Howard Hughes Medical Institute	Not-for-profit paediatric medical center AND Non-profit hospital AND Public AND Not for profit medical research organization AND Not for profit medical research organization	
Bauer, D.E.			Children's Hospital AND Dana-Farber Cancer Institute AND Harvard Medical School	Not-for-profit paediatric medical center AND Non-profit hospital AND Public AND Not for profit medical research organization	
First-in-human phase 1 CRISPR gene editing cancer trials: are we ready? Published in *Current Gene Therapy*					
Baylis, F. McLeod, M.	2017	Critical examination of first-in-human phase 1 CRISPR gene editing cancer trials	Dalhousie University	Public	https://doi.org/10.2174/1566523217666171121165935
Search-and-replace genome editing without double-strand breaks or donor DNA. Published in *Nature*					
Anzalone, A.V., Randolph, P.B. Davis, J.R. Sousa, A.A., Koblan, L.W. Levy, J.M. Chen, P.J. Wilson, C. Newby, G.A. Raguram, A. Liu, David R.	2019	Development of a prime editing tool for Cas9 (and Proof of Concept Prime Editing for sickle cell disease)	The Broad Institute AND Harvard University AND Howard Hughes Medical Institute	Not for profit AND Public AND Not for profit medical research organization	https://doi.org/10.1038/s41586-019-1711-4

Table A - 11: Publicly funded research for CRISPR/Cas9 for sickle cell disease and ß-thalassemia (from NIHreporter)

Project leader	Awardee Organization	NIH Spending Category	Budget Start Date	Budget End Date	Funding organization	Funding amount (in USD)	Source
Structural Studies of Type III CRISPR-Cas Surveillance Complexes							
Doudna, Jennifer A.	University of California lawrenc berkeley lab	Genetics	01-June-2018	31-May-2021	National Institute of General Medical Sciences	210.288	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9535352
			01-June-2017	31-May-2018		125.000	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9280965
			01-June-2016	31-March-2017		210.100	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9074326
			01-June-2017	31-May-2018		210.213	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9280965
Expanding CRISPR-Cas editing technology through exploration of novel Cas proteins and DNA repair systems							
Doudna, Jennifer A.; Banfield, Jillian	University of California Berkeley	Biotechnology; Genetics; Human Genome	24-August-2018	31-July-2023	NIH Office of the Director	392.500	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9984951
			01-August-2019	31-July-2020		392.500	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9768324
			01-August-2022	31-July-2024		392.500	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/10459340
			24-August-2018	31-July-2019		392.500	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9677972
			01-August-2021	31-July-2022		392.500	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/10215491
Cas9 RNP delivery to immune cells in vivo via molecular targeting							
Wilson, Ross C.; Doudna, Jennifer A.	University of California Berkeley	Biotechnology; Genetics	01-August-2020	31-July-2021	NIH Office of the Director	781.190	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/10003948
			01-August-2021	31-August-2022		776.316	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/10214471
			28-August-2019	31-July-2020		800.300	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/9810686
			23-September-2022	31-August-2024		1.257.377	https://reporter.nih.gov/search/4tUMP8w8H0GvQRr9KV7_vQ/project-details/10664098
Extending GWAS at the BCL11A locus to novel therapeutics for HbF induction							
Orkin, Stuart H.	DANA-FARBER CANCER INST	Biotechnology; Cooley's Anaemia; Genetics; Hematology; Human Genome; Sickle Cell Disease	30-September-2009	31-August-2010	National Heart Lung and Blood Institute	1.094.197	https://reporter.nih.gov/search/mqp8AeL-WdEmD7Dp_L7rXHw/project-details/7853575
Identification of Novel Regulators of Fetal Haemoglobin Expression							
Canver, Matthew C.	HARVARD MEDICAL SCHOOL	Biotechnology; Cooley's Anaemia; Genetics; Hematology; Human Genome; Orphan Drug; Rare Diseases; Sickle Cell Disease	01-June-2015	31-May-2016	National Institute of Diabetes and Digestive and Kidney Diseases	33.646	https://reporter.nih.gov/search/fhLDmV2TQ0--DWNL4AOCNg/project-details/8908716

Table A - 12: Information on financing, public contributions and collaborations of all companies involved in the development of CRISPR/Cas9 technology leading to CASGEVY® (CRISPR/Cas9/Casgevy relevant in the corresponding colours)

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Vertex Pharmaceuticals *Founded:* 1989 *Company type*: Publicly traded *Headquarters:* Boston, Massachusetts, U.S. *Number of employees:* approximately 5,400 employees (as of December 2023) *Operating revenue:* 9.87 billion USD (as of 2023)					
Collaboration with Orum Therapeutics	pre-treatment for gene meds	n.a.	$15 million - up to $945 million	Vertex Pharmaceuticals	https://pharmaphorum.com/news/vertex-orum-partner-safer-pre-treatment-gene-meds
Acqusition	Acquisition of ViaCyte	2022	$320 million	Vertex Pharmaceuticals	https://www.fiercebiotech.com/biotech/vertex-absorbs-viacyte-320m-clearing-out-competition-stem-cell-based-diabetes-treatments
Collaboration that led to Casgevy	Collaboration with CRISPR Therapeutics	2021	$900 million	Vertex Pharmaceuticals	https://www.fiercebiotech.com/biotech/vertex-ups-arbor-ante-potential-1-2b-biobucks-for-crispr-cell-therapies
Collaboration	Collaboration with Arbor Biotechnologies	2021	$1.2 billion	Vertex Pharmaceuticals	https://pharmaphorum.com/news/vertex-builds-in-gene-editing-yet-again-with-1-2bn-arbor-deal https://news.vrtx.com/news-releases/news-release-details/vertex-and-arbor-biotechnologies-establish-collaboration
Collaboration	Collaboration with Obsidian Therapeutics	2021	$75 million	Vertex Pharmaceuticals	https://pharmaphorum.com/news/vertex-eyes-controllable-genetic-drugs-with-1-3bn-obsidian-alliance
Editas Medicines *Founded:* 2013 *Company type*: Publicly traded *Headquarters:* Cambridge, Massachusetts, U.S. *Number of employees:* 265 (as of February 1, 2024) *Operating revenue:* 78.1 million USD (as of 2023)					
Project specific funding	Vector-delivered CRISPR/Cas as a cure for HSV-1-induced keratitis	2015	225.000	National Institute of Allergy and Infectious Diseases	https://reporter.nih.gov/search/7fMvTHuUV06xW3G0sXghHg/project-details/8978393
Licensing	Licensing agreenement for Cas9 gene editing tool	2024	$57 million	DRI Healthcare	https://www.fiercebiotech.com/biotech/editas-cashes-portion-vertex-cas9-licensing-agreement-57m
Licensing	Non-exclusive licensing deal for Editas Medicines' Cas9 gene editing technology for ex vivo gene editing	2023	$100 million + annual payments between $10 million and $40 million until 2034	Vertex Pharmaceuticals	https://www.statnews.com/2023/12/13/editas-vertex-agreement-crispr-cas9/
Research agreement	Developing CRISPR/Cas9-based medicines for cystic fibrosis	2016	$5 million	Cystic Fibrosis Foundation	https://www.biopharmadive.com/news/editas-forges-5-million-crispr-research-deal-with-cystic-fibrosis-foundati/419322/
Research agreement	Research for the use of CRISPR/Cas9 for various types of cancer with guarantees of royalties if products are the result of the research	2015	$47 million	Corporate: Juno Therapeutics	https://www.biospace.com/editas-medicine-juno-therapeutics-hammer-out-727-million-car-t-r-and-d-deal
Financing round	Series B financing	2015	$120 million	Institutional: Casdin Capital, Deerfield, Google Ventures, Khosla Ventures, Viking Global Investors, Polaris Partners,	https://www.bioworld.com/articles/326878-editas-lands-120m-to-advance-crispr-cas9-platform-in-oversubscribed-series-b?v=preview

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
				Third Rock Ventures, Flagship Pioneering, Omega Funds Corporate: EcoR1, Fidelity Investments, Jennison Associates, T. Rowe Price, Partners Health Care Innovation Angel: Boris Nikoli	
Financing round	Series A financing	2013	$43 million	Institutional: Polaris Partners, Third Rock Ventures, Flagship Pioneering Corporate: Partners Health Care Innovation	https://www.bioworld.com/articles/437460
Broad Institute *Founded:* 2004 *Company type*: Nonprofit research organization *Headquarters:* Cambridge, Massachusetts, United States *Number of employees:* n.a. (The Broad Institute's faculty members are all faculty members of MIT, Harvard or one of the Harvard-affiliated hospitals.) *Operating revenue:* n.a.					
Research funding	Research funding with information and first refusal on the developed interventions	2018	up to $125 million	Editas Medicine	https://www.fiercebiotech.com/biotech/editas-commits-125m-to-broad-secure-source-genome-editing-inventions
Licensing	Licensing deal for CRISPR/Cas9	2016	$6.25 million (split between Broad, Harvard University, MIT, Wageningen University, the University of Iowa and the University of Tokyo)	Editas Medicine	https://www.biopharmadive.com/news/editas-locks-down-rights-to-add-on-crispr-tech/432662/
Project specific funding (all research projects that use CRISPR/Cas9 and that have received public contribution).*	Function of reactive astrocytes in aging and neurodegenerative disease	2024	93.197	NIA	https://reporter.nih.gov/project-details/11080548
	Identifying genetic vulnerabilities in KIAA1549-BRAF mutant paediatric low-grade gliomas	2024	78.892	NCI	https://reporter.nih.gov/project-details/10951512
	Development of platforms for sorting, production, editing of beta cells	2024	623.544	NIDDK	https://reporter.nih.gov/project-details/10920460
	Advanced development of the Cancer Dependency Map portal (DepMap.org)	2024	735.340	NCI	https://reporter.nih.gov/project-details/10904866
	Development of methods for highly multiplexed quantification of cancer proteomes using large-scale nanobody libraries	2024	210.516	NCI	https://reporter.nih.gov/project-details/10903802
	Development of p300/CBP histone acetyltransferase inhibitors for oncogene-driven cancers	2024	624.299	NCI	https://reporter.nih.gov/project-details/10843227
	Directed Clonal Evolution of Drug Resistant BRAF Mutant Melanoma for Cross-Sensitization to MAPK Hyperactivation	2024	74.284	NCI	https://reporter.nih.gov/project-details/10826684
	Mechanism of Action of Prion Protein-Lowering Small Molecules	2024	407.400	NINDS	https://reporter.nih.gov/project-details/10815872
	A visible machine learning system to discover targeted treatment solutions in cancer	2024	95.948	NCI	https://reporter.nih.gov/project-details/10806195
	A Chemoproteomic Approach to Identify Molecular Glues for Targeted Cancer Therapy	2024	171.180	NCI	https://reporter.nih.gov/project-details/10797075
	Stitch-seq for genome-wide pooled genomic screening with RNA-seq readout	2024	164.661	NCI	https://reporter.nih.gov/project-details/10792615

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
	A visible machine learning system to discover targeted treatment solutions in cancer	2023	92.988	NCI	https://reporter.nih.gov/project-details/10784808
	Chemical approaches for precision genome editing	2024	362.632	NIGMS	https://reporter.nih.gov/project-details/10783716
	Identifying genetic vulnerabilities in KIAA1549-BRAF mutant paediatric low-grade gliomas	2023	71.792	NCI	https://reporter.nih.gov/project-details/10752212
	Development of methods for highly multiplexed quantification of cancer proteomes using large-scale nanobody libraries	2023	221.595	NCI	https://reporter.nih.gov/project-details/10714023
	Establishing foundational tools and datasets for investigation of NSD1 gene function in neural development	2023	158.000	OD	https://reporter.nih.gov/project-details/10711291
	Development of platforms for sorting, production, editing of beta cells	2023	691.470	NIDDK	https://reporter.nih.gov/project-details/10682155
	Factors regulating strength and duration of STING signaling	2023	423.643	NIAID	https://reporter.nih.gov/project-details/10677771
	Advanced development of the Cancer Dependency Map portal (DepMap.org)	2023	731.592	NCI	https://reporter.nih.gov/project-details/10666538
	Expanding pharmacological modalities for targeted cancer therapy	2023	101.247	NCI	https://reporter.nih.gov/project-details/10656339
	Investigating epigenetic mechanisms in Down syndrome using human cellular models	2023	2.034.753	OD	https://reporter.nih.gov/project-details/10655152
	Mechanism of Action of Prion Protein-Lowering Small Molecules	2023	395.000	NINDS	https://reporter.nih.gov/project-details/10637745
	Development of p300/CBP histone acetyltransferase inhibitors for oncogene-driven cancers	2023	651.215	NCI	https://reporter.nih.gov/project-details/10627744
	Stitch-seq for genome-wide pooled genomic screening with RNA-seq readout	2023	167.252	NCI	https://reporter.nih.gov/project-details/10620301
	Characterization of structure-function relationships in distinct thalamic reticular nucleus networks	2023	390.000	NIMH	https://reporter.nih.gov/project-details/10615809
	Delineating a role for histone modifications in Down syndrome using human cellular models	2022	285.042	OD	https://reporter.nih.gov/project-details/10595812
	Chemical approaches for precision genome editing	2023	362.632	NIGMS	https://reporter.nih.gov/project-details/10557117
	Factors regulating strength and duration of STING signaling	2022	423.643	NIAID	https://reporter.nih.gov/project-details/10490901
	Advanced development of the Cancer Dependency Map portal (DepMap.org)	2022	774.119	NCI	https://reporter.nih.gov/project-details/10478033
	Advanced tools for HCMI model genetic perturbation and metastasis characterization	2022	787.646	NCI	https://reporter.nih.gov/project-details/10465033
	Expanding the Scope of Base Editing	2022	421.357	OD	https://reporter.nih.gov/project-details/10459380
	Characterization of structure-function relationships in distinct thalamic reticular nucleus networks	2022	390.000	NIMH	https://reporter.nih.gov/project-details/10455621
	Expanding pharmacological modalities for targeted cancer therapy	2022	96.632	NCI	https://reporter.nih.gov/project-details/10416087
	Stitch-seq for genome-wide pooled genomic screening with RNA-seq readout	2022	207.784	NCI	https://reporter.nih.gov/project-details/10413630
	Chemical approaches for precision genome editing	2021	74.047	NIGMS	https://reporter.nih.gov/project-details/10389932
	Chemical approaches for precision genome editing	2022	352.551	NIGMS	https://reporter.nih.gov/project-details/10378157
	Factors regulating strength and duration of STING signaling	2021	423.643	NIAID	https://reporter.nih.gov/project-details/10367563

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
	Development of p300/CBP histone acetyltransferase inhibitors for oncogene-driven cancers	2022	682.670	NCI	https://reporter.nih.gov/project-details/10344246
	Characterization of structure-function relationships in distinct thalamic reticular nucleus networks	2021	373.200	NIMH	https://reporter.nih.gov/project-details/10279075
	Advanced development of the Cancer Dependency Map portal (DepMap.org)	2021	791.314	NCI	https://reporter.nih.gov/project-details/10252924
	Characterizing TP53 and PPM1D mutations as resistance drivers to radiation therapy in Diffuse Intrinsic Pontine Gliomas	2021	523.271	NCI	https://reporter.nih.gov/project-details/10245071
	Comprehensive functional characterization and dissection of noncoding regulatory elements and human genetic variation	2021	1.496.338	NHGRI	https://reporter.nih.gov/project-details/10241056
	Advanced tools for HCMI model genetic perturbation and metastasis characterization	2021	789.862	NCI	https://reporter.nih.gov/project-details/10229465
	Expanding the Scope of Base Editing	2021	421.536	OD	https://reporter.nih.gov/project-details/10227955
	Chemical approaches for precision genome editing	2021	347.463	NIGMS	https://reporter.nih.gov/project-details/10211408
	High-content optical pooled genome-wide screens of SARS-CoV-2 infection	2020	357.840	NHGRI	https://reporter.nih.gov/project-details/10166221
	CRISPR screens for SARS-CoV-2 Host Factors	2020	440.000	NIAID	https://reporter.nih.gov/project-details/10163544
	Rapid ex vivo biosensor cultures to assess dependencies in gastroesophageal cancer	2021	566.213	NCI	https://reporter.nih.gov/project-details/10115675
	Advanced development of the Cancer Dependency Map portal (DepMap.org)	2020	791.050	NCI	https://reporter.nih.gov/project-details/10058960
	Advanced tools for HCMI model genetic perturbation and metastasis characterization	2020	789.862	NCI	https://reporter.nih.gov/project-details/10005595
	Comprehensive Characterization of Adaptive Regulatory Variation Linked to Human Disease	2020	125.378	NHGRI	https://reporter.nih.gov/project-details/10005404
	Characterizing TP53 and PPM1D mutations as resistance drivers to radiation therapy in Diffuse Intrinsic Pontine Gliomas	2020	517.874	NCI	https://reporter.nih.gov/project-details/9996517
	Expanding the Scope of Base Editing	2020	421.760	OD	https://reporter.nih.gov/project-details/9982216
	Integrating Chemistry and Evolution to Illuminate Biology and Enable Novel Therapeutics	2020	692.073	NIGMS	https://reporter.nih.gov/project-details/9963284
	Arrayed single-cell readout of pooled genetic perturbation libraries	2020	1.112.161	NHGRI	https://reporter.nih.gov/project-details/9960539
	Systematic identification of oncogenic KRAS synthetic lethal interactions	2019	499.996	NCI	https://reporter.nih.gov/project-details/9952702
	Comprehensive functional characterization and dissection of noncoding regulatory elements and human genetic variation	2020	1.496.387	NHGRI	https://reporter.nih.gov/project-details/9952404
	Center for Cell Circuits	2020	2.800.000	NHGRI	https://reporter.nih.gov/project-details/9952395
	Programmable RNA-targeting tools	2020	1.124.060	NHGRI	https://reporter.nih.gov/project-details/9951080
	Rapid ex vivo biosensor cultures to assess dependencies in gastroesophageal cancer	2020	566.213	NCI	https://reporter.nih.gov/project-details/9946259
	Discovery of compounds and genes that regulate cancer's epigenome, using combinatorial screening in a nanodrop-microwell platform	2020	29.860	NCI	https://reporter.nih.gov/project-details/9852879

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
	Comprehensive Characterization of Adaptive Regulatory Variation Linked to Human Disease	2019	124.916	NHGRI	https://reporter.nih.gov/project-details/9805238
	Characterizing TP53 and PPM1D mutations as resistance drivers to radiation therapy in Diffuse Intrinsic Pontine Gliomas	2019	497.259	NCI	https://reporter.nih.gov/project-details/9781662
	Expanding the Scope of Base Editing	2019	422.147	OD	https://reporter.nih.gov/project-details/9768957
	Comprehensive functional characterization and dissection of noncoding regulatory elements and human genetic variation	2019	1.497.668	NHGRI	https://reporter.nih.gov/project-details/9766882
	Massively-parallel functional interrogation of psychiatric genetics	2019	1.093.342	NIMH	https://reporter.nih.gov/project-details/9749919
	Arrayed single-cell readout of pooled genetic perturbation libraries	2019	1.120.845	NHGRI	https://reporter.nih.gov/project-details/9736763
	Programmable RNA-targeting tools	2019	1.140.080	NHGRI	https://reporter.nih.gov/project-details/9719879
	Comprehensive functional characterization and dissection of noncoding regulatory elements and human genetic variation	2018	933.353	NHGRI	https://reporter.nih.gov/project-details/9696513
	Center for Cell Circuits	2019	2.800.000	NHGRI	https://reporter.nih.gov/project-details/9692736
	Integrating Chemistry and Evolution to Illuminate Biology and Enable Novel Therapeutics	2019	692.434	NIGMS	https://reporter.nih.gov/project-details/9689014
	Discovery of compounds and genes that regulate cancer's epigenome, using combinatorial screening in a nanodrop-microwell platform	2019	61.610	NCI	https://reporter.nih.gov/project-details/9683440
	Expanding the Scope of Base Editing	2018	422.361	OD	https://reporter.nih.gov/project-details/9675825
	Systematic Mapping of the Functional Common Noncoding Variants in the TNFAIP3 Locus	2019	65.606	NIAID	https://reporter.nih.gov/project-details/9628643
	Continuous Evolution of Proteins with Novel Therapeutic Potential	2019	451.488	NIBIB	https://reporter.nih.gov/project-details/9620618
	Comprehensive functional characterization and dissection of noncoding regulatory elements and human genetic variation	2018	500.000	NHGRI	https://reporter.nih.gov/project-details/9564177
	Arrayed single-cell readout of pooled genetic perturbation libraries	2018	1.073.196	NHGRI	https://reporter.nih.gov/project-details/9553855
	Programmable RNA-targeting tools	2018	1.139.738	NHGRI	https://reporter.nih.gov/project-details/9546834
	Systematic identification of oncogenic KRAS synthetic lethal interactions	2018	807.776	NCI	https://reporter.nih.gov/project-details/9538605
	Characterizing TP53 and PPM1D mutations as resistance drivers to radiation therapy in Diffuse Intrinsic Pontine Gliomas	2018	507.552	NCI	https://reporter.nih.gov/project-details/9512814
	Massively-parallel functional interrogation of psychiatric genetics	2018	1.092.930	NIMH	https://reporter.nih.gov/project-details/9509556
	Center for Cell Circuits	2018	2.800.000	NHGRI	https://reporter.nih.gov/project-details/9493509
	Integrating Chemistry and Evolution to Illuminate Biology and Enable Novel Therapeutics	2017	618.244	NIGMS	https://reporter.nih.gov/project-details/9492988
	Continuous Evolution of Proteins with Novel Therapeutic Potential	2017	304.001	NIBIB	https://reporter.nih.gov/project-details/9484392
	Integrating Chemistry and Evolution to Illuminate Biology and Enable Novel Therapeutics	2018	692.783	NIGMS	https://reporter.nih.gov/project-details/9469527

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
	Systematic Mapping of the Functional Common Noncoding Variants in the TNFAIP3 Locus	2018	61.174	NIAID	https://reporter.nih.gov/project-details/9451927
	Epigenomic, transcriptional and cellular dissection of Alzheimer's variants	2017	1.527.396	NIA	https://reporter.nih.gov/project-details/9440479
	Continuous Evolution of Proteins with Novel Therapeutic Potential	2018	451.488	NIBIB	https://reporter.nih.gov/project-details/9419171
	Programmable RNA-targeting tools	2017	1.095.702	NHGRI	https://reporter.nih.gov/project-details/9379750
	Arrayed single-cell readout of pooled genetic perturbation libraries	2017	1.128.407	NHGRI	https://reporter.nih.gov/project-details/9379592
	Characterizing TP53 and PPM1D mutations as resistance drivers to radiation therapy in Diffuse Intrinsic Pontine Gliomas	2017	502.615	NCI	https://reporter.nih.gov/project-details/9368268
	Systematic identification of oncogenic KRAS synthetic lethal interactions	2017	807.776	NCI	https://reporter.nih.gov/project-details/9330127
	Massively-parallel functional interrogation of psychiatric genetics	2017	1.097.505	NIMH	https://reporter.nih.gov/project-details/9310141
	Center for Cell Circuits	2017	2.800.000	NHGRI	https://reporter.nih.gov/project-details/9278246
	Network-based prediction and validation of causal schizophrenia genes and variants	2017	475.347	NIMH	https://reporter.nih.gov/project-details/9264586
	Systematic Mapping of the Functional Common Noncoding Variants in the TNFAIP3 Locus	2017	57.066	NIAID	https://reporter.nih.gov/project-details/9258074
	Non-coding genetic variants that impact immune phenotypes and diseases	2017	870.349	NHGRI	https://reporter.nih.gov/project-details/9249624
	Comprehensive functional characterization and dissection of noncoding regulatory elements and human genetic variation	2017	654.000	NHGRI	https://reporter.nih.gov/project-details/9247640
	Systematic identification of oncogenic KRAS synthetic lethal interactions	2016	807.776	NCI	https://reporter.nih.gov/project-details/9150537
	Massively-parallel functional interrogation of psychiatric genetics	2016	1.061.900	NIMH	https://reporter.nih.gov/project-details/9147643
	Massively-parallel functional interrogation of psychiatric genetics	2016	1.061.900	OD	https://reporter.nih.gov/project-details/9147643
	Network-based prediction and validation of causal schizophrenia genes and variants	2016	424.175	NIMH	https://reporter.nih.gov/project-details/9108677
	Center for Cell Circuits	2016	3.700.000	NHGRI	https://reporter.nih.gov/project-details/9070877
	Non-coding genetic variants that impact immune phenotypes and diseases	2016	871.466	NHGRI	https://reporter.nih.gov/project-details/9052201
	Genome engineering tools for functional screening of non-coding elements	2016	25.020	NHGRI	https://reporter.nih.gov/project-details/8974432
	Systematic identification of oncogenic KRAS synthetic lethal interactions	2015	817.805	NCI	https://reporter.nih.gov/project-details/8966918
	Genome engineering tools for functional screening of non-coding elements	2015	99.937	NHGRI	https://reporter.nih.gov/project-details/8804084
CRISPR Therapeutics *Founded:* 2013 *Company type*: Public *Headquarters:* Boston, Massachusetts, U.S.					

Type of information	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Number of employees: 407 (as of December 31, 2023) *Operating revenue:* 443 million USD (as of 2023)					
Licensing	Development partnership	2021	$900 million	Vertex Pharmaceuticals	https://www.fiercebiotech.com/biotech/vertex-takes-lead-crispr-therapeutics-partnership-900m-upfront
Financing round	Series B	2016	$38 million	Institutional: New Leaf Venture Partners, Leaps by Bayer Corporate: Vertex Pharmaceuticals, Franklin Templeton Investments, Wellington Facilitator: Guggenheim Partners, VISCHER, Goodwin	https://www.fiercebiotech.com/biotech/crispr-therapeutics-adds-38m-to-series-b-pot-but-lags-behind-parker
Financing round	Series A and Series B	2014	$64 million	Institutional: SR One, New Enterprise Associates, Abingworth, Versant Ventures Institutional: Abingworth, Versant Ventures, New Enterprise Associates Corporate: Celgene	https://www.biospace.com/despite-patent-battle-worth-billions-crispr-raises-64-million-in-series-a-and-b-rounds
Financing round	Series A	2014	$25 million	Institutional: Versant Ventures	https://www.fiercebiotech.com/r-d/an-international-biotech-tackles-crispr-gene-editing-tech-25m-bankroll

Legend:
HHS = United States Department of Health and Human Services
NIA = National Institute on Aging
NCI = National Cancer Institute
NHGRI = National Human Genome Research Institute
NIMH = National Institute of Mental Health
OD = NIH Office of the Director
NIDDKD = National Institute of Diabetes and Digestive and Kidney Diseases
NINDS = National Institute of Neurological Disorders and Stroke
NIGMS = National Institute of General Medical Sciences
NIBIB = National Institute Of Biomedical Imaging And Bioengineering
NIAID = National Institute of Allergy and Infectious Diseases
*= Basic research that used CRISPR/Cas9 but not specifically for sickle cell disease or ß-thalassemia. However, findings may have contributed to the understanding needed for Exa-cel

Table A - 13: Vertex Pharmaceuticals key financial information from 2023 to 2009 (all monetary value in thousands USD)

Key financials & employees 2023-2009 for Vertex Pharmaceuticals															
Year of report (all published on the 31st of December)	**2023**	**2022**	**2021**	**2020**	**2019**	**2018**	**2017**	**2016**	**2015**	**2014**	**2013**	**2012**	**2011**	**2010**	**2009**
Source	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K
Operating revenue (Turnover)	9.869.200	8.930.700	7.574.400	6.205.683	4.162.821	3.047.597	2.488.652	1.702.177	1.032.336	580.415	1.211.975	1.527.042	1.410.626	143.370	101.889
P/L for period [=Net income]	3.619.600	3.322.000	2.342.100	2.711.647	1.176.810	2.096.896	263.484	-112.052	-556.334	-738.555	-445.028	-107.032	29.574	-754.626	-642.178
Profit margin (%)	44,38	47,39	36,05	50,23	33,51	19,70	-0,63	-3,96	-54,03	n.a.	-51,66	2,10	4,29	n.a.	n.a.
Number of employees	5.400	4.800	3.900	3.400	3.000	2.500	2.300	2.150	1.950	1.830	1.800	2.200	2.000	1.691	1.432
Key financials & employees 2009-1994 for Vertex Pharmaceuticals															
Year of report (all published on the 31st of December)	**2008**	**2007**	**2006**	**2005**	**2004**	**2003**	**2002**	**2001**	**2000**	**1999**	**1998**	**1997**	**1996**	**1995**	**1994**
Source	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	10-K	PROSP.	PROSP.	PROSP.	10-K	10-K
Operating revenue (Turnover)	175.504	199.012	216.356	160.890	102.717	69.141	94.770	85.297	153.282	108.887	62.566	49.714	18.910	27.534	23.145
P/L for period [=Net income]	-459.851	-391.279	-206.891	-203.417	-166.247	-196.767	-108.621	-66.233	-34.740	-41.154	-51.007	-19.342	-43.055	-21.528	-17.595
Profit margin (%)	n.a.	n.a.	-96,11	n.a.	n.a.	n.a.	n.a.	-94,06	-20,60	-37,80	-81,86	-38,87	n.a.	-78,19	-76,02
Number of employees	1.333	1.132	945	806	736	720	980	1.000	799	550	304	220	178	n.a.	n.a.

Table A - 14: 10 biggest shareholders of Vertex Pharmaceuticals (information extracted from ORBIS)

Current shareholders					
Name of firm	**Country ID**	**Type**	**Ownership**		**Information as of Date**
			Direct %	**Total %**	
Capital World Investors, Inc.	US	E	10.00	n.a.	03/2024
The Vanguard Group, Inc.	US	C	-	8.35	03/2024
State Street Corporation	US	E	-	4.65	03/2024
Blackrock Fund Advisors	US	E	-	3.36	03/2024
Fidelity Management & Research Company LLC	US	C	-	3.10	03/2024
Equitable Holdings, Inc.	US	A	-	2.75	03/2024
Blackrock Institutional Trust Company National Association	US	E	-	2.25	03/2024
Geode Capital Management LLC	US	F	-	2.25	03/2024
Capital Research Global Investors	SG	F	-	2.23	03/2024
J. P. Morgan Investment Management, Inc.	US	F	-	1.82	03/2024

Legend
E = Mutual and pension fund, nominee, trust, trustee
C = Corporate
A = Insurance company
F = Financial company

Table A - 15. Search strategy and search terms for chapter 7

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	Casgevy	n.a.	Yes	Earliest mention – 10/2024	Active substance, Medical specialty, Pharmacotherapeutic group, Therapeutic area, Class, Orphan designation, Categorization, Additional monitoring, Conditional approval, Accelerated assessment, PRIME: priority medicines, Marketing authorisation issued
https://adisinsight.springer.com/	Casgevy		Yes		Alternative names:
https://pubmed.ncbi.nlm.nih.gov/	Casgevy; Exagamglogene autotemcel; Autologous CRISPR-Cas9 modified CD34+ hHSPCs - CRISPR Therapeutics/Vertex Pharmaceuticals; Autologous CRISPR-Cas9 modified CD34+ human hematopoietic stem and progenitor cells - CRISPR Therapeutics/Vertex Pharmaceuticals; CRISPR/Cas9 gene-edited therapy - CRISPR Therapeutics/Vertex Pharmaceuticals; CTX-001; Exa-cel; Vertex Pharmaceutical Editas Medicines; The Broad Institute; CRISPR Therapeutics		Yes		Development history CRISPR/Cas9/Casgevy
https://clinicaltrials.gov/			Yes		Clinical trials using CRISPR/Cas9
https://euclinicaltrials.eu/			Yes		
https://eudract.ema.europa.eu/			Yes		
https://cordis.europa.eu/			Yes		
https://reporter.nih.gov/		Doudna; Doudna CRISPR; Doudna Cas; Emmanuelle Charpentier; Charpentier; Stuart Orkin; Orkin Cas9	Yes		Basic research for CRISPR/Cas9. Authors selected based on literature found on PubMed
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm		n.a.	Yes		Patent information and associated references
https://trialsearch.who.int/			No		n.a.
https://competition-cases.ec.europa.eu/search			No		
https://www.ihi.europa.eu/			No		
https://eismea.ec.europa.eu/index_en			No		
https://eit.europa.eu/			No		
https://eic.ec.europa.eu/index_en			No		
https://www.eib.org/en/index			No		
https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en			No		
https://www.sbir.gov/		Vertex Pharmaceutical; Editas Medicines; The Broad Institute; CRISPR Therapeutics	Yes		Project funding for companies involved in the development of Casgevy
https://www.nsf.gov/		n.a.	No		n.a.
https://www.ukri.org/			No		
https://foerderportal.bund.de/			No		
https://www.health-holland.com/			No		
https://www.bpifrance.com/			No		
https://www.inserm.fr/en/home/			No		
https://innovationsfonden.dk/da			No		
https://www.ucc.ie/en/apc/			No		
https://www.amractionfund.com/about			No		

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://reporter.nih.gov/			No		
https://www.gatesfoundation.org/			No		
https://www.google.com/			Yes		Patent deal information
https://www.forbes.com/			No		
https://www.reuters.com/			No		n.a.
https://www.science.org/			No		
https://www.cafepharma.com/			Yes		
https://www.livescience.com/			Yes		
https://www.biospace.com/			Yes		
https://www.bioworld.com/		AND funding OR financing OR M&A OR patent deal OR collaboration OR grant	Yes		
https://www.biopharmadive.com/			Yes		
https://pharmaphorum.com/			Yes		Collaborations, funding, financing, patent dispute, acquisitions
https://pharmatimes.com/			Yes		
https://pharmafile.com/			Yes		
https://www.fiercepharma.com/			Yes		
https://www.businesswire.com/			Yes		
https://www.businessinsider.com/			Yes		
https://www.statnews.com/			Yes		

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH