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# Dorocubicel + unexpanded CD34– cells (Zemcelpro) for the treatment of haematological malignancies in adults

Health Technology Assessment

Final Report

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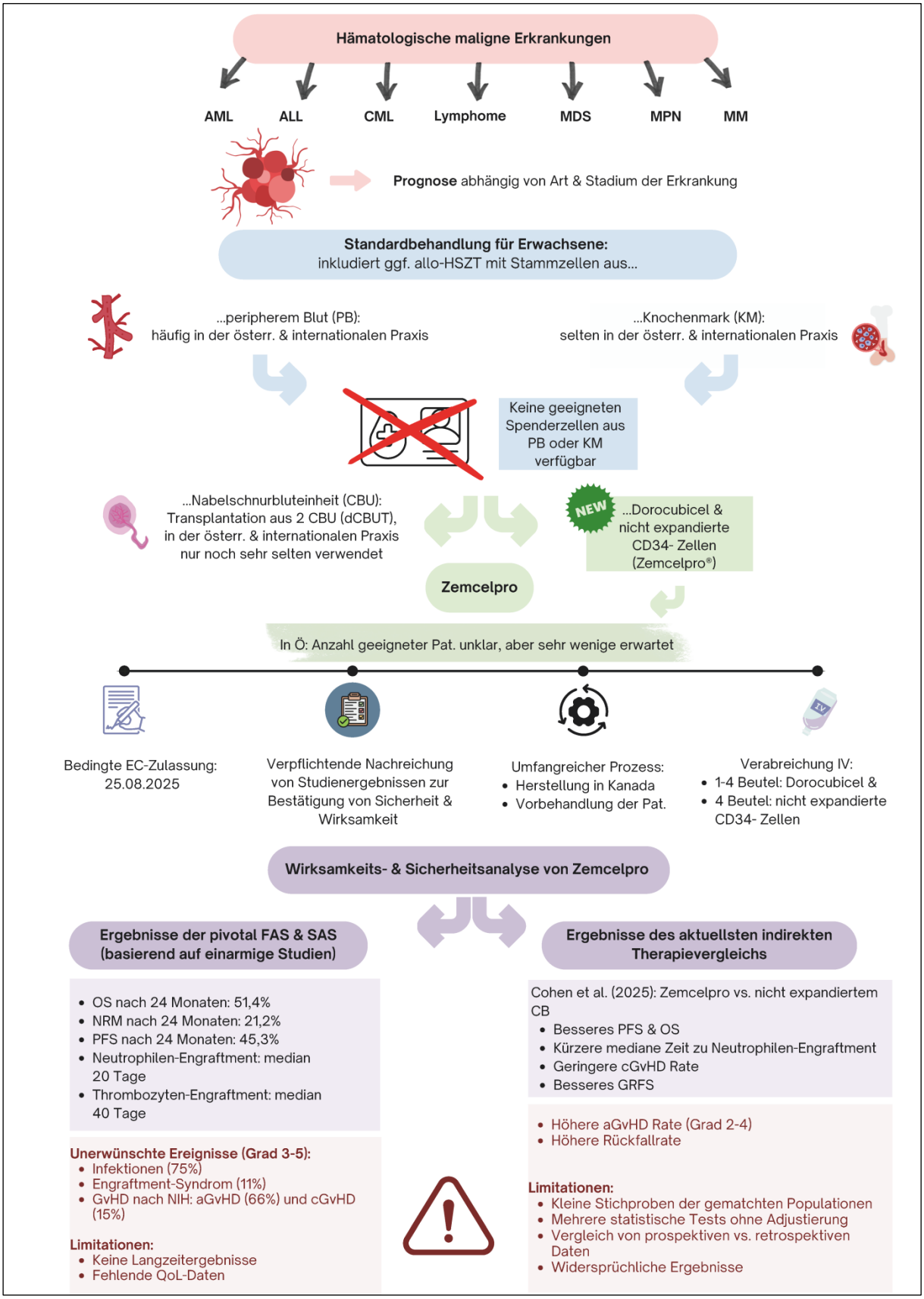
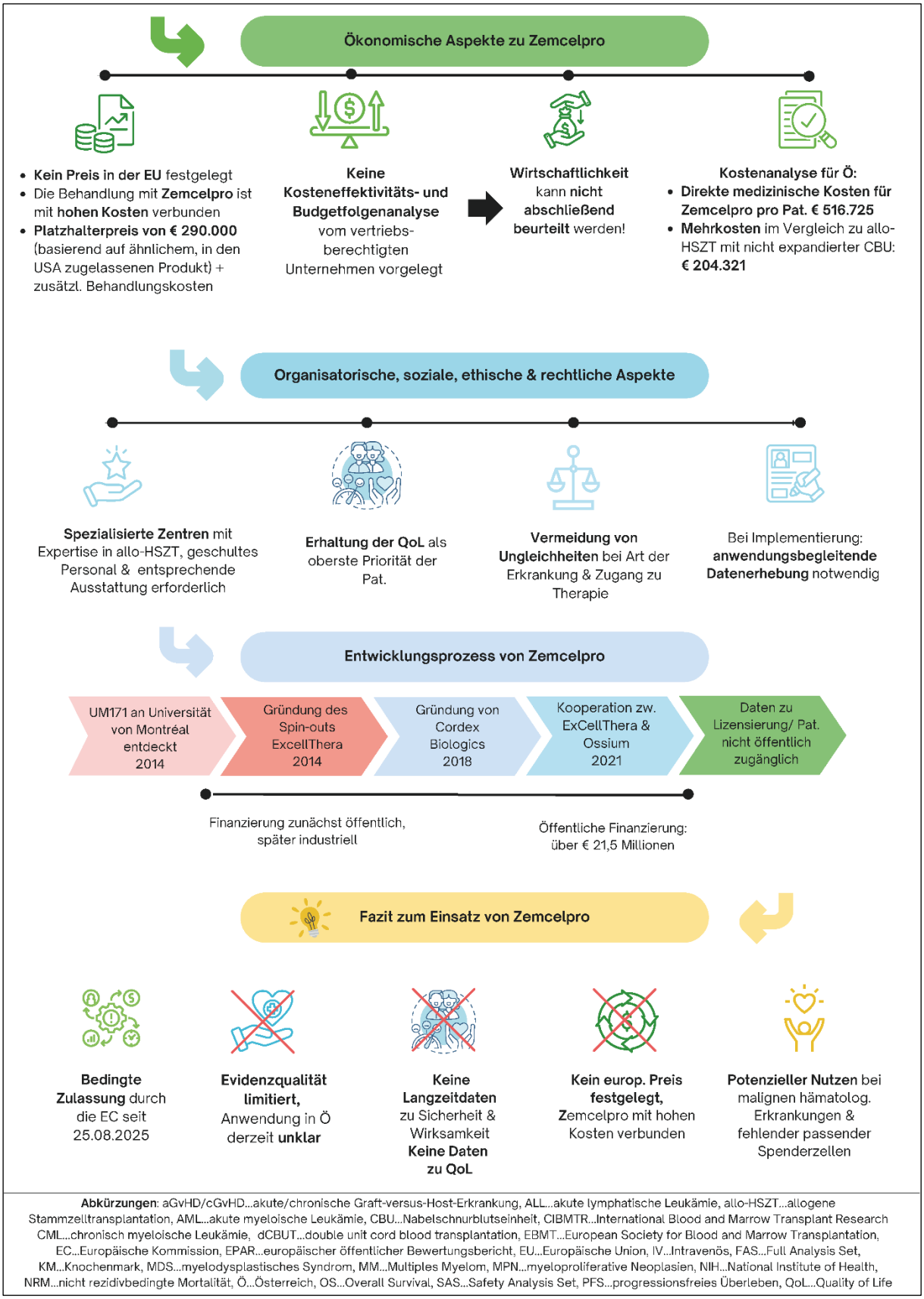





**Abkürzungen**: aGvHD/cGvHD...akute/chronische Graft-versus-Host-Erkrankung, ALL...akute lymphatische Leukämie, allo-HSZT...allogene Stammzelltransplantation, AML...akute myeloische Leukämie, CBU...Nabelschnurblutseinheit, CIBMTR...International Blood and Marrow Transplant Research CML...chronisch myeloische Leukämie, dCBUT...double unit cord blood transplantation, EBMT...European Society for Blood and Marrow Transplantation, EC...Europäische Kommission, EPAR...europäischer öffentlicher Bewertungsbericht, EU...Europäische Union, IV...Intravenös, FAS...Full Analysis Set, KM...Knochenmark, MDS...myelodysplastisches Syndrom, MM...Multiples Myelom, MPN...myeloproliferative Neoplasien, NIH...National Institute of Health, NRM...nicht rezidivbedingte Mortalität, Ö...Österreich, OS...Overall Survival, SAS...Safety Analysis Set, PFS...progressionsfreies Überleben, QoL...Quality of Life

# Zusammenfassung

Der vorliegende Health Technology Assessment (HTA)-Bericht evaluiert expandierte CD34+ Zellen/ Dorocubicel + nicht expandierte CD34– Zellen (Zemcelpro) zur Behandlung von erwachsenen Patient:innen mit hämatologischen malignen Erkrankungen, die eine allogene hämatopoetische Stammzelltransplantation (allo-HSZT) benötigen und keine passenden Spenderzellen haben.

## Beschreibung der Erkrankung und Behandlungsoptionen

Hämatologische maligne Erkrankungen sind Krebserkrankungen, die ihren Ursprung im Blut, im Knochenmark oder im lymphatischen System haben. Sie umfassen unter anderem akute und chronische myeloische Leukämie, akute lymphatische Leukämie, myelodysplastische Syndrome, andere myeloproliferative Neoplasien, multiple Myelome sowie Lymphome. Diese Erkrankungen machen etwa 6,5 % aller Krebserkrankungen aus. Die allo-HSZT stellt für viele dieser Erkrankungen die einzige potenziell kurative Behandlungsoption dar. Die Prognose variiert je nach Erkrankungstyp, Krankheitsstadium und verfügbaren Behandlungsoptionen. Patient:innen, die eine allo-HSZT benötigen, aber keinen Zugang zu geeigneten Spenderzellen haben, weisen eine besonders ungünstige Prognose auf.

In Österreich lebten im Jahr 2023 etwa 15.351 Menschen mit Non-Hodgkin-Lymphom, 10.826 mit Leukämie, 4.325 mit Hodgkin-Lymphom und 3.202 mit multiplem Myelom. Im Jahr 2024 wurden in Österreich 609 Stammzelltransplantationen durchgeführt, davon 270 allogene Transplantationen.

Gemäß den Leitlinien (National Comprehensive Cancer Network/NCCN, Handbuch der European Society for Blood and Marrow Transplantation/ESBMT, National Marrow Donor Program/NMDP) ist die bevorzugte Spenderquelle für eine allo-HSZT eine HLA-(humanes Leukozytenantigen)-kompatible Geschwisterspende, gefolgt von einer HLA-kompatiblen Fremdspende. Stammzellen werden hauptsächlich aus peripherem Blut und Knochenmark gewonnen. Etwa ein Drittel der Patient:innen findet jedoch weder kompatible verwandte noch unverwandte Spender:innen. Für diese Patient:innen stehen alternative Stammzellquellen zur Verfügung, darunter haploidentische Spender:innen (Haplo), nicht vollständig kompatible Fremdspender:innen sowie Nabelschnurblut. Nabelschnurbluttransplantationen wurden in Österreich in den letzten fünf Jahren nicht durchgeführt, da für alle Patient:innen geeignete Spender:innen gefunden werden konnten.

## Überblick über das neue Arzneimittel

Zemcelpro ist eine kryokonservierte allogene Stammzelltherapie, die aus zwei verschiedenen Zellkomponenten besteht, die aus derselben Nabelschnurbluteinheit gewonnen werden: (1) expandierte CD34+ Zellen (Dorocubicel), die *ex-vivo* unter Verwendung des Moleküls UM171 vermehrt werden, und (2) nicht expandierte CD34– Zellen, die CD3+ T-Zellen enthalten. Diese Kombination ermöglicht eine personalisierte Antitumorreaktion sowie eine Immunrekonstitution. Die Behandlung erfolgt als einmalige intravenöse Infusion und erfordert eine stationäre Aufnahme in einem spezialisierten Transplantationszentrum. Patient:innen erhalten zunächst eine myeloablative Konditionierungstherapie, gefolgt von der Zemcelpro-Infusion.

Zemcelpro erhielt im August 2025 eine bedingte Zulassung durch die Europäische Kommission für die Behandlung erwachsener Patient:innen mit hämatologischen Malignomen, die eine allo-HSZT nach myeloablativer Konditionierung benötigen und für die keine anderen Arten geeigneter Spenderzellen verfügbar sind. Die Zulassung stützt sich auf Studiendaten aus Kanada, sowie den USA und Niederlanden. Die US-amerikanische Arzneimittelzulassungsbehörde (Food and Drug Administration, FDA) hat Zemcelpro bisher nicht zugelassen.

Klinische Expert:innen schätzen, dass die Zahl der für Zemcelpro geeigneten Patient:innen in Österreich sehr gering sein wird, da in der Regel für alle Patient:innen, die eine allo-HSZT benötigen, geeignete Spender:innen gefunden werden können.

## Wirksamkeit und Sicherheit

Die Analyse der Wirksamkeit basierte auf einer gepoolten Analyse einer Untergruppe von Hochrisiko-Patient:innen mit akuter Leukämie oder Myelodysplastischem Syndrom, die für eine Transplantation mit einem kryokonservierten ECT-001-CB vorgesehen waren, das aus der Expansion einer kleinen Nabelschnurbluteinheit gewonnen wurde. Für die Analyse wurden zwei laufende Phase-2-Studien (pivotal full analysis set/FAS) mit 25 erwachsenen Patient:innen im Alter von 18 bis 70 Jahren berücksichtigt. Die mediane Nachbeobachtungszeit betrug 13,27 Monate. Die Gesamtüberlebensrate nach 12 Monaten lag bei 66,0 % und nach 24 Monaten bei 51,4 %. Die progressionsfreie Überlebensrate betrug 52,8 % nach 12 Monaten und 45,3 % nach 24 Monaten. Die Non-Relapse-Mortalität lag bei 21,2 % sowohl nach 12 als auch nach 24 Monaten. Die mediane Zeit bis zum Neutrophil-Engraftment betrug 20 Tage, jene bis zum Thrombozyten-Engraftment 40 Tage. Daten zur Lebensqualität wurden nicht erhoben, und Langzeitdaten über 24 Monate hinaus fehlen.

Die Sicherheitsanalyse umfasste 116 Patient:innen aus fünf Studien mit einer medianen Nachbeobachtungszeit von 22,49 Monaten. Nahezu alle Patient:innen (99,1 %) erlebten mindestens ein unerwünschtes Ereignis (aller Grade). Die häufigsten unerwünschten Ereignisse (Grad ≥3) waren Lymphopenie (46,6 %), Anämie (44,0 %), Neutropenie (35,3 %), Thrombozytopenie (31,9 %) und akute Graft-versus-Host-Erkrankung (graft-versus-host-disease, GVHD) (22,4 %). Eine akute GVHD aller Grade trat bei 66,4 % der Patient:innen auf, eine chronische bei 14,7 %. Insgesamt wurden 42 Todesfälle (36,2 %) berichtet, davon 26 aufgrund einer Krankheitsprogression oder eines Rezidivs und 15 aufgrund therapiebedingter Mortalität.

Die methodische Qualität der verfügbaren Studien wird durch ein einarmiges Studiendesign, kleine Stichprobengrößen, kurze Nachbeobachtungszeiträume und das Fehlen von Lebensqualitätsdaten erheblich eingeschränkt.

Darüber hinaus zeigten vier retrospektive indirekte Vergleiche mit nicht expandiertem Nabelschnurblut Vorteile für Zemcelpro hinsichtlich der Non-Relapse-Mortalität, des progressionsfreien Überlebens und der Zeit bis zum Neutrophil-Engraftment. Diese Vergleiche unterliegen jedoch erheblichen methodischen Limitationen, einschließlich kleiner Fallzahlen, fehlender Anpassung an multiples Testen und systematischer Verzerrungen durch den Vergleich prospektiver mit retrospektiver Daten.

## Ökonomische Aspekte

Der Hersteller hat weder eine Preisangabe noch eine gesundheitsökonomische Evaluation oder eine Budgetfolgenanalyse zu Zemcelpro für Österreich zum Zeitpunkt der Datenerhebung für diesen Bericht eingereicht. Auf Basis einer vereinfachten Kostenanalyse für den österreichischen Kontext, unter Verwendung eines Platzhalterpreises von € 290.000 (basierend auf dem US-Preis eines vergleichbaren Produkts, Omidubicel)[1], belaufen sich die direkten medizinischen Kosten pro Patient:in auf etwa € 516.725. Dies entspricht Mehrkosten von etwa € 204.321 im Vergleich zu einer allo-HSZT mit nicht expandiertem Nabelschnurblut (die Kosten betragen ungefähr € 312.404). Die Kosten für eine allo-HSZT mit peripherem Blut oder Knochenmark von einer nicht vollständig kompatiblen Spenderperson betragen ungefähr € 236.094.

Die Hauptkostentreiber sind der Erwerb von Zemcelpro (€ 290.000) sowie die Kosten für die Transplantationsprozedur, die Hospitalisierung und die Behandlung von Komplikationen (€ 226.725). Unter Berücksichtigung der bei 43,4 % der Patient:innen in den Studien erforderlichen Re-Hospitalisierungen steigen die Gesamtkosten auf etwa € 567.455 pro Patient:in.

Die Kostenanalyse unterliegt mehreren Limitationen, insbesondere aufgrund der Unsicherheit hinsichtlich des tatsächlichen europäischen Preises (nicht bekannt zum Zeitpunkt der Datenerhebung für diesen Bericht), der pauschalen Anwendung von LKF-Codes und des Ausschlusses verschiedener Kostenkomponenten wie Diagnostik und Langzeitbetreuung aus der Primäranalyse.

[1] Da der Preis zum Zeitpunkt der Erstellung dieses Berichts nicht bekannt war, könnte dieser Preis unterschätzt sein.

## Öffentliche Investition

Die Entwicklung von Zemcelpro begann an der Universität Montreal in Kanada mit der Forschung zum UM171-Molekül. Die Grundlagenforschung wurde überwiegend öffentlich finanziert. Im Jahr 2015 wurde das Spin-out-Unternehmen ExCellThera gegründet, dessen Tochtergesellschaft Cordex Biologics 2023 gegründet wurde. Insgesamt konnten über € 21,5 Millionen an direkter und indirekter öffentlicher Förderung identifiziert werden, die zur Entwicklung von Zemcelpro beigetragen haben. Der größte Förderanteil entfiel auf die Universität Montreal (€ 14,3 Millionen), gefolgt von ExCellThera (€ 6,6 Millionen) und dem Clinical Research Institute of Montreal (€ 511.421). Details zu Lizenzvereinbarungen zwischen der Universität Montreal und ExCellThera/Cordex Biologics sind nicht öffentlich verfügbar, da die beteiligten Unternehmen nicht börsennotiert sind.

## Soziale, organisatorische, ethische und rechtliche Aspekte

Zemcelpro könnte eine Versorgungslücke für Patient:innen ohne geeignete Spender:innen für Stammzellen aus peripherem Blut oder Knochenmark schließen, insbesondere für Patient:innen aus ethnischen Minderheiten mit geringerer Wahrscheinlichkeit, HLA-kompatible Fremdspender:innen zu finden. Die Wahrscheinlichkeit, eine HLA-kompatible Spende zu finden, liegt für die kaukasische Bevölkerung bei etwa 80 %, für andere ethnische Gruppen jedoch deutlich darunter. Angesichts zunehmender Migration nach Österreich könnte die Zahl der für Zemcelpro geeigneten Patient:innen in Zukunft steigen.

Die Implementierung von Zemcelpro in Österreich erfordert die Berücksichtigung komplexer internationaler Herstellungs- und Logistikprozesse. Die Herstellung erfolgt in Kanada und dauert vom Zeitpunkt der Auswahl der Nabelschnurbluteinheit bis zur Lieferung an das Transplantationszentrum etwa 45 Tage. In Österreich stehen fünf spezialisierte Zentren für allogene Stammzelltransplantationen zur Verfügung, die über die erforderliche Infrastruktur verfügen. Generell müssen im Rahmen einer allogener HSZT als auch bei der Anwendung von Zemcelpro ausreichend personelle und strukturelle Ressourcen zur Verfügung stehen, um die sichere Anwendung von Zemcelpro zu gewährleisten.

In Österreich fungiert das Österreichische Stammzellregister (ÖSZR) als zentrale Anlaufstelle für Fremdspendersuchen, während das Österreichische Stammzelltransplantationsregister (ASCTR) alle in Österreich durchgeführten Stammzelltransplantationen dokumentiert.

## Weitere Entwicklungen

Vier laufende klinische Studien zu Zemcelpro wurden identifiziert. Zwei davon (ECT-001-CB.002 und ECT-001-CB.004) sollen im Februar 2026 bzw. im Oktober 2027 abgeschlossen werden und weitere Daten zur Wirksamkeit und Sicherheit liefern, wie von der EMA im Rahmen der bedingten Zulassung gefordert. Zusätzlich sind zwei randomisierte kontrollierte Studien geplant, die bis 2030 abgeschlossen sein sollen. Darüber hinaus wurden zwei weitere Therapien in der Entwicklungspipeline für die Behandlung hämatologischer Malignome identifiziert (Orca-t, Smart101), mit erwarteten Zulassungsentscheidungen zwischen Jänner 2027 und Juni 2029. Das vergleichbare Produkt Omidubicel wurde 2023 von der FDA in den USA zugelassen, ist jedoch noch nicht in der Europäischen Union zugelassen.

## Schlussfolgerung

Zemcelpro könnte einen wichtigen ungedeckten medizinischen Bedarf für Patient:innen mit hämatologischen malignen Erkrankungen adressieren, insbesondere für ethnische Minderheiten mit geringerer Wahrscheinlichkeit, HLA-kompatible Spender:innen für Stammzellen aus peripherem Blut oder Knochenmark zu finden. Die derzeit verfügbare klinische Evidenz ist jedoch durch methodische Einschränkungen sowie fehlende Langzeit- und Lebensqualitätsdaten limitiert. Aus gesundheitsökonomischer Sicht ergeben sich aus den hohen Zusatzkosten erhebliche Budgetauswirkungen, wobei langfristige Einsparungen bei bestätigter Reduktion der chronischen GVHD möglich wären. Die Integration von Zemcelpro in die österreichische klinische Praxis bleibt unklar, da der Standard die allo-HSZT mit Stammzellen aus peripherem Blut oder Knochenmark vorsieht und der Vergleich mit doppeltem Nabelschnurblut

derzeit nicht valide beurteilbar ist. Interessengruppen sehen aufgrund begrenzter Daten Unsicherheiten hinsichtlich der Krankenhaus-Aufenthaltsdauer und der Nebenwirkungen. Zwei laufende klinische Studien, die bis 2026/2027 abgeschlossen werden sollen, werden entscheidende Daten zur Wirksamkeit, Sicherheit und Lebensqualität liefern und die Grundlage für eine umfassende Re-Evaluierung sowie für zukünftige Empfehlungen zur Rolle von Zemcelpro in Österreich bilden.

# Executive summary

This health technology assessment (HTA) evaluates expanded CD34+ cells/dorocubicel + unexpanded umbilical cord-derived CD34– cells (Zemcelpro) for the treatment of adult patients with haematological malignancies requiring an allogeneic haematopoietic stem cell transplantation (allo-HSCT) who do not have other suitable donor cell sources available.

## Disease background

Haematological malignancies encompass a variety of cancers that originate from the blood (leukaemias), bone marrow (myelomas), and lymphatic system (lymphomas). They account for approximately 6.5% of all cancers. In 2023, 15,351 people in Austria were living with non-Hodgkin lymphoma, 10,826 with leukaemia, 4,325 with Hodgkin lymphoma and 3,202 with multiple myeloma. Allo-HSCT is the only potentially curative treatment option for many subtypes. In 2024, 609 stem cell transplants (SCT) were performed in Austria, of which 270 were allogeneic (allo). The primary indications for allo-SCT were acute myeloid leukaemia, acute lymphoblastic leukaemia, and myelodysplastic syndrome. Patients who require allo-HSCT but cannot access a readily available suitable donor face a high unmet medical need.

According to the guidelines (National Comprehensive Cancer Network/NCCN, European Society for Blood and Marrow Transplantation Handbook/ESBMT, National Marrow Donor Programme/NMDP), the preferred allo-HSCT donor is an HLA-matched sibling donor (MSD), followed by a matched unrelated donor (MUD). Stem cells are primarily harvested from peripheral blood (PB) or bone marrow (BM). Approximately one-third of patients lack an MSD or MUD. Alternative donor sources include haploidentical (haplo), mismatched unrelated donors (MMUD), and umbilical cord blood (CB). However, no CB transplants have been performed in Austria over the past five years, as other suitable donors were identified for all patients.

## Overview of the new medicinal product

Zemcelpro is a cryopreserved stem cell therapy consisting of two different cell components derived from the same unit of CB: (1) expanded CD34+ cells (dorocubicel), which are expanded *ex vivo* using the small molecule UM171, and (2) unexpanded CD34– cells, which include CD3+ T-cells. This combination enables enhanced immune reconstitution and anti-tumour response. Treatment is administered as a single intravenous infusion and requires inpatient admission to a specialised transplant centre. Patients first receive myeloablative (MA) conditioning therapy.

Zemcelpro received conditional approval from the European Commission in August 2025 for the treatment of adult patients with haematological malignancies who require allo-HSCT after MA conditioning and for whom no other type of suitable donor cells is available. The approval is based on clinical data from a Canadian study and from an international study (USA and the Netherlands). The US Food and Drug Administration (FDA) has not yet approved Zemcelpro.

Austrian clinicians estimate that the number of patients eligible for Zemcelpro will be very low, as suitable donors can usually be identified for all patients who require allo-HSCT.

## Clinical effectiveness and safety

The efficacy assessment is based on a pooled analysis of a subset of patients with high-risk acute leukaemia or myelodysplasia intended to be transplanted with a cryopreserved ECT-001-CB derived from the expansion of a small CB unit. For analysis, two ongoing phase 2 studies (pivotal full analysis set/FAS) involving 25 adult patients aged 18-70 years were considered. The median follow-up was 13.27 months. The overall survival rate was 66.0% after 12 months and 51.4% after 24 months. The progression-free survival rate was 52.8% after 12 months and 45.3% after 24 months. The non-relapse mortality was 21.2% at both 12 and

24 months. The median time to neutrophil engraftment was 20 days, and to platelet engraftment was 40 days. Quality of life (QoL) data were not collected, and long-term data beyond 24 months are lacking.

The safety analysis included 116 patients from five studies, with a median follow-up of 22.49 months. Nearly all patients (99.1%) experienced at least one adverse event (AE) of all grades. The most common AEs (grade ≥3) were lymphopenia (46.6%), anaemia (44.0%), neutropenia (35.3%), thrombocytopenia (31.9%) and acute graft-versus-host disease (GVHD: 22.4%). Acute GVHD of all grades occurred in 66.4% of patients, while chronic GVHD occurred in 14.7%. A total of 42 deaths (36.2%) were reported, 26 of which were due to disease progression or recurrence and 15 of which were due to treatment-related mortality. The reported evidence is associated with substantial uncertainty due to the single-arm study design, the short follow-up period, and the absence of QoL measures.

Additionally, four retrospective indirect comparisons demonstrated the benefit of Zemcelpro over unexpanded CB in terms of NRM, PFS, and time to neutrophil engraftment. However, these comparisons are subject to significant methodological limitations, including small sample sizes, lack of adjustment for multiple testing, and systematic bias arising from comparisons between prospective and retrospective data sources.

## Economic aspects

The manufacturer did not submit any price proposal by the data cut-off for this report, health economic evaluation or budget impact analysis for Zemcelpro for Austria. Based on a simplified cost analysis for the Austrian context using a placeholder price of €290,000 (based on the US price of a comparable product, omidubicel)[2], the direct medical costs per patient amount to approximately €516,725. This corresponds to additional costs of approximately €204,321 compared to allo-HSCT using unexpanded CB, at approximately €312,404. Allo-HSCT with PB or BM from an alternative mismatched donor (haplo, MMUD) costs approximately €236,094. The main cost components are the Zemcelpro acquisition cost (€290,000) and the costs of the transplant procedure, hospitalisation and treatment of acute complications (€226,725). Subsequent re-hospitalisation, required by 43.4% of trial participants, would increase total costs to approximately €567,455 per patient.

The cost analysis is subject to several limitations, primarily due to the lack of an actual European price before data cut-off, the use of flat-rate averages with uncertain composition, and the exclusion of various cost components, such as diagnostics and long-term care.

## Public investment aspect

The development of Zemcelpro started at the University of Montreal, Canada, through basic research on the UM171 small molecule, which was predominantly publicly funded. In 2014, the spin-out company ExCellThera was founded; its subsidiary, Cordex Biologics, was established in 2022. Over €21.5 million in direct and indirect public funding was identified to have contributed to Zemcelpro's development, with the majority allocated to the University of Montreal (€14.3 million), followed by ExCellThera (€6.6 million) and the Clinical Research Institute of Montreal (€511,421). Licensing agreements between the University of Montreal and ExCellThera/Cordex Biologics are not publicly available as the companies are not listed on the stock exchange.

## Social, organisational, ethical and legal aspects

Zemcelpro could help address the high unmet need for patients without suitable donors for stem cells from peripheral blood or bone marrow, especially for patients from ethnic minorities. The probability of finding an HLA-compatible unrelated donor is around 80% in the Caucasian population but is significantly lower in other ethnic groups. Given the increasing number of migrants to Austria, the number of patients potentially eligible for Zemcelpro could increase in the future.

[2] As the price was not know at the time of conducting this report, this price could be underestimated.

Implementing Zemcelpro in Austria requires managing complex international manufacturing and logistics processes. Manufacturing is carried out in Canada, with approximately 45 days required from CBU selection to delivery at the transplant centre. Austria has five specialised centres for allo-HSCT with the necessary infrastructure. However, in general, with allo-HSCT, additional human and infrastructural resources must be allocated to ensure safe handling, administration, and post-treatment monitoring.

In Austria, the Austrian Stem Cell Donor Registry (ÖSZR) serves as the central contact point for unrelated donor searches, while the Austrian Stem Cell Transplant Registry (ASCTR) documents all stem cell transplants performed in Austria.

## Landscape overview

Four ongoing clinical trials of Zemcelpro have been identified. Two of these (ECT-001-CB.002 and ECT-001-CB.004), scheduled for completion in February 2026 and October 2027, respectively, are expected to provide additional efficacy and safety data required by the EMA for the conditional marketing authorisation. Two further randomised controlled trials are planned, with anticipated completion by 2030. In addition, two other therapies for the treatment of haematological malignancies were identified as in development: Orcat and Smart101, with regulatory decisions expected between January 2027 and June 2029. The comparable product omidubicel received FDA approval in 2023 but is not yet authorised in the European Union.

## Conclusion

Zemcelpro could address a significant unmet medical need for patients with haematological malignancies, particularly for ethnic minorities who are less likely to find HLA-compatible donors for stem cells from peripheral blood or bone marrow. However, the currently available clinical evidence is limited by methodological constraints and a lack of long-term and QoL data. From a health economic perspective, the high additional costs have a significant impact on the budget. However, long-term savings would be possible if a reduction in chronic GVHD were confirmed. The integration of Zemcelpro into Austrian clinical practice remains unclear, as the standard procedure is allo-HSCT using PB or BM stem cells, and comparisons with double umbilical CB are uncertain. Due to limited data, stakeholders are uncertain about the length of the hospital stay and potential side effects. Two ongoing clinical trials, scheduled for completion by 2026/2027, will provide crucial data on efficacy, safety and QoL and form the basis for comprehensive re-evaluation and future recommendations on the role of Zemcelpro in Austria.

# 1 Introduction

The objective of this report is to evaluate the clinical effectiveness and safety, as well as the economic and organisational aspects of Zemcelpro, for the treatment of adult patients with haematological malignancies requiring an allogeneic haematopoietic stem cell transplantation (allo-HSCT) following myeloablative conditioning for whom no other type of suitable donor cells is available [1]. Zemcelpro is a cell-based medicine composed of two distinct cell components: (1) the fraction of expanded CD34+ cells (dorocubicel) and (2) the fraction of unexpanded CD34– cells. In this health technology assessment (HTA) report, "Zemcelpro" is used as the primary designation, rather than the international non-proprietary name. This approach is adopted to enhance readability, as the proprietary name is more concise than the combined technical nomenclature of its two cellular components. Moreover, the European Public Assessment Report (EPAR) [2] consistently refers to the product "Zemcelpro".

Zemcelpro zur Behandlung von Erwachsenen mit hämatologischen malignen Erkrankungen, geeignet für allogene hämatopoetische Stammzelltransplantation

## 1.1 Disease background

Haematological malignancies are cancers originating from the blood, bone marrow (BM), or lymphatic system. Unlike solid tumours, haematological malignancies arise from abnormal differentiation of haematopoietic stem cells (HSC), typically caused by abnormal self-renewal, impaired differentiation, clonal expansion, and dysfunction of haematopoietic cell biology [3]. These malignancies account for about 6.5% of all cancers and are more common in older adults [4].

maligne Erkrankungen mit Ursprung im Blut, Knochenmark oder lymphat. System

While treatment approaches vary depending on the specific disease, allo-HSCT represents the only potentially curative option for many of these conditions. Diseases that most commonly require allo-HSCT include acute and chronic myeloid leukaemia (AML, CML), acute lymphoblastic leukaemia (ALL), myelodysplastic syndromes (MDS), other myeloproliferative neoplasms (MPN), multiple myeloma and lymphoma [5, 6]. The underlying haematologic malignancies are briefly described in the following section, without detailing individual subtypes. As the comprehensive characterisation of these diseases lies beyond the scope of this assessment and is not directly relevant for the evaluation of Zemcelpro, detailed descriptions of disease, pathogenesis, aetiology, risk factors, clinical presentation, and diagnostic procedures are not provided. Instead, reference is made to established medical guidelines and authoritative clinical sources.

unterschiedliche Behandlungsoptionen für Betroffene, potenzieller kurativer Ansatz ist allo-HSZT

### Overview of haematological malignancies

#### Acute myeloid leukaemia

Acute myeloid leukaemia (AML) is an acute blood cancer characterised by rapid accumulation of abnormal myeloid cells in the BM [7]. The abnormal cells grow and survive better than normal cells, crowding out and slowing the development of normal blood cells. AML is most common among adults aged 60 or older. Following diagnosis, AML requires prompt treatment initiation

AML ist durch schnelle Progression gekennzeichnet; betrifft vor allem Pat. >60 Jahre; ...

with intensive therapy consisting of induction, consolidation, and maintenance therapy. Patients with relapsed or refractory AML may undergo allo-HSCT or participate in clinical trials [7]. AML is the most frequent indication for allo-HSCT [8, 9].

... verschiedene Behandlungsoptionen, u. a. allo-HSZT

### Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is a fast-growing blood cancer characterised by infiltration of the BM and peripheral blood (PB) by immature lymphoid cells. There are two types of ALL, depending on the type of lymphoblast that develops into leukaemia: (1) B-cell ALL and (2) T-cell ALL, with B-cell ALL being the predominant subtype [10]. Treatment includes, as in AML, induction, consolidation, and maintenance therapy, and consists of chemotherapy, as well as allo-HSCT and CAR T-cell therapy [7]. Treatment may also include tyrosine kinase inhibitors (TKIs) blocking the protein (tyrosine kinase) that causes the leukaemia cells to grow and divide out of control [10]. Approximately 17% of allo-HSCT are performed for ALL [8, 9].

ALL mit schnellem Verlauf, B- oder T-Zellen betroffen

allo-HSZT als Behandlungsoption

ca. 17 % aller allo-HSZT bei ALL

### Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) is another subtype of leukaemia, characterised by a slowly progressive course [7]. Unlike acute leukaemia, many patients initially have no symptoms and may be diagnosed through routine blood tests. CML is characterised by specific genetic abnormalities that make it particularly responsive to targeted therapies. CML demonstrates responsiveness to targeted therapy, with oral TKIs serving as first-line treatment and producing good response rates in most patients. Allo-HSCT may be administered in cases not responding adequately to TKI therapy [11].

CML: langsamer und teils asymptomatischer Verlauf

Ursache oft genetisch

Standardtherapie: TKI, bei Nicht-Ansprechen allo-HSZT indiziert

### Lymphoma

Lymphoma represents a diverse group of malignancies originating from lymphocytes, broadly divided into Hodgkin lymphoma (HL), affecting about 18% of lymphoma and non-Hodgkin lymphoma (NHL), affecting about 82% of lymphoma) [7]. These malignancies can affect B-cells, T-cells, or natural killer cells at various stages of differentiation, typically manifesting in lymph nodes but potentially affecting any organ. For HL, combination chemotherapy is the most common treatment, with some patients receiving radiation therapy in addition. For relapsed and refractory disease, physicians may recommend HSCT [7]. For NHL, treatment options include watch-and-wait approach, chemotherapy with or without radiation therapy, drug therapy, immunotherapy, CAR T-cell therapy, and allo-HSCT [7].

Hodgkin- und Non-Hodgkin-Lymphome

unterschiedliche Behandlungsansätze, allo-HSZT möglich

### Multiple myeloma

Multiple myeloma is a very common haematological malignancy [11], arising from the malignant transformation of a single plasma B-cell [7]. Under normal conditions, plasma cells primarily produce antibodies and play a crucial role in the immune response. In myeloma, however, these cells produce abnormal monoclonal immunoglobulins rather than functional antibodies. Myeloma cells are predominantly found in the BM but may accumulate in other parts of the body, forming cell masses (plasmacytomas) that most often occur in bones, skin, muscles, or lungs. When myeloma cells form a single cell mass, the disease is termed solitary plasmacytoma; when it occurs in multiple areas, it is called multiple myeloma, which represents the majority of cases. Multiple myeloma is not curable, but substantial improvements in quality of life and survival have been achieved. Active disease treatment includes combination

multiples Myelom: Plasmazellenerkrankung

nicht heilbar, Kombinationstherapie (Chemo + auto-HSZT + Bestrahlung), vereinzelt allo-HSZT empfohlen

drug therapy, high-dose chemotherapy followed by auto-HSCT, CAR T-cell therapy, radiation therapy (in localised disease), and in selected cases also allo-SCT [12].

### Myelodysplastic syndromes

MDS charakterisiert durch klonale Hämatopoese und Zellmutationen

Myelodysplastic syndromes (MDS) are a group of clonal HSC disorders unified by distinct mutations in HSC, most frequently in genes involved in RNA splicing. MDS are characterised by ineffective and dysplastic haematopoiesis [13]. MDS are classified into primary MDS (where no underlying cause can be identified) and secondary MDS (treatment-related). Most diagnosed patients have primary MDS. Treatment depends on subtype, prognostic score, age, and overall health status. Patients require chronic blood and platelet transfusions, erythrocyte-stimulating agents (ESA) or chemotherapy. Allo-HSCT is the only curative treatment for MDS [14].

Behandlung abhängig vom Subtyp und Risiko

### Myeloproliferative neoplasms

verschiedene Subtypen bei MPNs

Myeloproliferative neoplasms (MPNs) are a group of blood cancers caused by genetic mutations in HSCs in the BM, leading to excessive production of one or more types of blood cells – red cells, white cells, or platelets [7]. Some MPNs grow slowly over time (called “indolent”), while others are more aggressive. Each type affects different blood cells. The three classic types include Polycythaemia vera (PV), Essential thrombocythemia (ET) and Myelofibrosis (MF). Different treatment options are available for patients with MPNs, depending on the subtype. MPN treatment options include JAK (Janus kinase-proteins) inhibitors [7], chemotherapy, immunotherapy, and radiation therapy. In MF, as in other haematological malignancies, allo-HSCT remains the only potentially curative treatment option [7].

Behandlungen bei MPN: JAK-Inhibitoren & allo-HSZT bei MF

## Prognosis

Prognose abhängig von Art und Stadium der spezifischen Erkrankung

Prognosis in haematological malignancies varies depending on the specific disease type, stage, molecular characteristics, and available treatment options [15]. Patients requiring allo-HSCT who lack access to suitable donor cells face a significant clinical challenge and dismal prognosis [2]. When allo-HSCT represents the only curative treatment option, the underlying disease is typically characterised by a rapid and aggressive progression. AML can progress rapidly, with overall 5-year survival rates ranging from 20-60% in adults, though prognosis varies based on age, cytogenetic profile, and molecular markers [16]. Among lymphomas, prognosis varies by subtype, with HL generally associated with more favourable outcomes than NHL [17]. For patients without suitable stem cell donors, outcomes are further compromised, underscoring the critical need to increase donor availability and expand access to allo-HSCT.

tendenziell schlechtere Prognose, wenn allo-HSZT indiziert

## Epidemiology

8,3 % der malignen Erkrankungen bei Männern, 7,2 % bei Frauen sind hämatologische Erkrankungen

Haematological malignancies constitute 8.3% of all malignancies in men and 7.2% in women [18]. According to Austrian statistical data from 2023, approximately 1,572 people were newly diagnosed with NHL, 1,295 with leukaemia, 565 with multiple myeloma, and 181 with HL, with men having higher incidence rates across these disease types. Prevalence data from 2023 show 15,351 people living with NHL, 10,826 with leukaemia, 4,325 with HL, and 3,202 with multiple myeloma in Austria. In the same year, leukaemia (including all subtypes) was the leading cause of death among haematological malignancies (823 deaths), followed by NHL (689 deaths), with mortality rates consistently higher in men than women across disease types [19].

Leukämie mit höchster Inzidenz, Prävalenz und Mortalität assoziiert

## 1.2 Standard of care in Austria

As outlined above, allo-HSCT represents a critical treatment option across multiple haematological malignancies, offering curative potential or serving as an important salvage option. In allo-HSCT, healthy blood stem cells are infused into the body to replace damaged or cancerous stem cells. HSCs are found in the BM, PB, and umbilical cord blood (CB), with PB being the most common source of HSCs for transplantation [20]. The success of allo-HSCT depends on identifying a suitable donor with adequate human leukocyte antigen (HLA) matching to minimise complications such as graft-versus-host disease (GVHD), while maintaining graft-versus-malignancy effects [20].

allo-HSZT: wichtige Behandlungsoption durch potenziellen kurativen Effekt

Stammzellen aus Knochenmark, peripherem Blut und Nabelschnurblut

According to the Austrian transplant report [5], 609 SCTs were performed in 2024, of which 270 were allogeneic transplants (93 from related donors and 177 from unrelated donors). The primary indications for transplantation were plasma cell diseases (241 transplants, mainly autologous), AML and ALL (162 transplants, mainly allogeneic), lymphoma (88 transplants mainly autologous), MPN/MDS (60 transplants, exclusively allogeneic), and CML (5 transplants, allogeneic). Details are presented in Chapter 1.2 in the Appendix.

Ö-Transplant Bericht: 270 allo-HSZT vor allem bei Plasmazellerkrankungen, AML, Lymphomen, MPN und MDS

### Stem cell types and HLA matching

For allo-HSCT, a suitable donor, who may be either related or unrelated to the patient [21, 22], is required. To identify potential donors, HLA-typing is performed [21], assessing genotypes for HLA proteins on cell surfaces that enable the immune system to distinguish the body's own cells from foreign cells [23]. HLA typing is conducted for both the patient and family members, as the likelihood of finding a compatible match is higher among relatives [21, 24]. In parallel, searches are carried out in registries of unrelated volunteer donors [24]. Both low-resolution (HLA-A, -B, -DRB1; 6/6 match) and high-resolution typing (adding HLA-C, -DQB1, -DPB1, 8/8 or 10/10 match) are used [21, 24]. A full match – either a matched related donor (MRD) or matched unrelated donor (MUD) – typically requires complete concordance of HLA-A, -B, -C and -DRB1 (8/8 match), and sometimes also HLA-DQB1 (10/10). A partial match (e.g., 7/8 or 9/10) occurs when one or two loci differ, while a haploidentical (haplo) match is defined by single haplotype matching in family donors as seen with parents or children, and in proportion of siblings [23]. For CB, minimum matching requirements are 4/6 (HLA-A, -B, -DRB1) or 4/8 (HLA-A, -B, -C, -DRB1) [24]. In general, full matches would be preferred due to lower risks of GVHD and transplant failure, but partial or haplo matches can be used when fully matched donors are unavailable [22].

Spender: in bei allo-HSZT benötigt

HLA-Typisierung, um Kompatibilität zu überprüfen

MRD/MUD; 8/8-10/10 bevorzugt; Haplo/CB als Alternativen

### Donor selection

The preferred donor for allo-HSCT is an HLA-matched sibling (MSD), followed by a MUD (see Figure 1-1). Given the increasing recipient age, younger MUD may frequently be preferred to an older matched sibling [6]. A 10/10 HLA-match (matching at HLA-A, -B, -C, -DRB1, and -DQB1) is the standard requirement for unrelated donor SCT. An 8/8 match (matching at HLA-A, -B, -C, and -DRB1) is often considered acceptable when a 10/10 match is not available for related donor transplants [9].

verwandte Spenderzellen bevorzugt

alternative Stammzellen oft notwendig: Haplo, MMUD, Nabelschnurblut

However, approximately one-third of patients lack either an MSD or MUD, and will need to look for a donor from three alternative HSC sources [25]:

- Haplo-match or a related donor with a partial HLA mismatch
- Mismatched unrelated donors (MMUD) – an unrelated donor with a partial HLA mismatch
- Umbilical CB – stem cells obtained from a banked cord blood unit (CBU)

MMAD: Vor-und Nachteile

The European Society for Blood and Marrow Transplantation (EBMT) recommendations for transplant indications combine these options into a single category of mismatched alternative donors (MMAD) [9]. Each alternative has specific advantages and limitations, with clinical practice increasingly favouring certain options over others.

höhere Toleranz bei HLA-Mismatch bei Nabelschnurblut

Umbilical CB transplantation was developed to address the limitations of HLA-matched BM and PB from unrelated donors. Advantages include greater tolerance for HLA mismatch, reduced risk of chronic GVHD, and immediate availability from established CB banks [22, 26].

Limitationen von Nabelschnurblut → häufigere Verwendung von Haplo

The primary limitation of CB transplantation is the relatively low cell dose available per unit, particularly for recipients with higher body weight. Furthermore, CB transplantation is associated with delayed haematopoietic engraftment, increased risk of graft failure, higher rates of infectious complications, and substantial procurement costs [22]. Consequently, unexpanded CB transplantations were performed less frequently in recent years. They were replaced mainly by haplo-transplantations using post-transplant cyclophosphamide to reduce the risk of GVHD and to enable safe transplantation from a partially HLA-matched donor [8]. Haplo-HSCT shares the advantages of CB transplantation while offering superior outcomes, lower costs, and a simpler process [26].

Nabelschnurblut-Option für Pat. ohne geeignete Spender:innen

Despite decreased utilisation, CB remains a relevant option for specific patient populations lacking other alternatives, including those without available haplo-relatives, patients requiring urgent transplantation when donor search time is limited. Recent data also suggests that CB may be a preferred stem cell source for patients with very high-risk leukaemias and some genetic and metabolic disorders in children; however, comparative studies with other alternative donors are lacking in the scientific literature [26]. Additional information on CB collection and storage is provided in Chapter 1.2 in the Appendix.

Spender:innenauswahl

The donor search algorithm begins with early HLA typing of the patient and family members, followed by simultaneous search for related and unrelated donors. If a suitable MSD is available, transplantation proceeds [24]. Without an MSD, a 10/10 MUD is preferred. If unavailable, preferred alternative donors are selected based on patient age and donor-specific antibodies, with three options:

MMUD (9/10 HLA match), haplo-donor (haplo, 9/10 match), or CB (minimum 4/6 match) [25]. Each alternative has specific HLA matching requirements, cell dose criteria, and clinical considerations for optimisation of transplant outcomes.

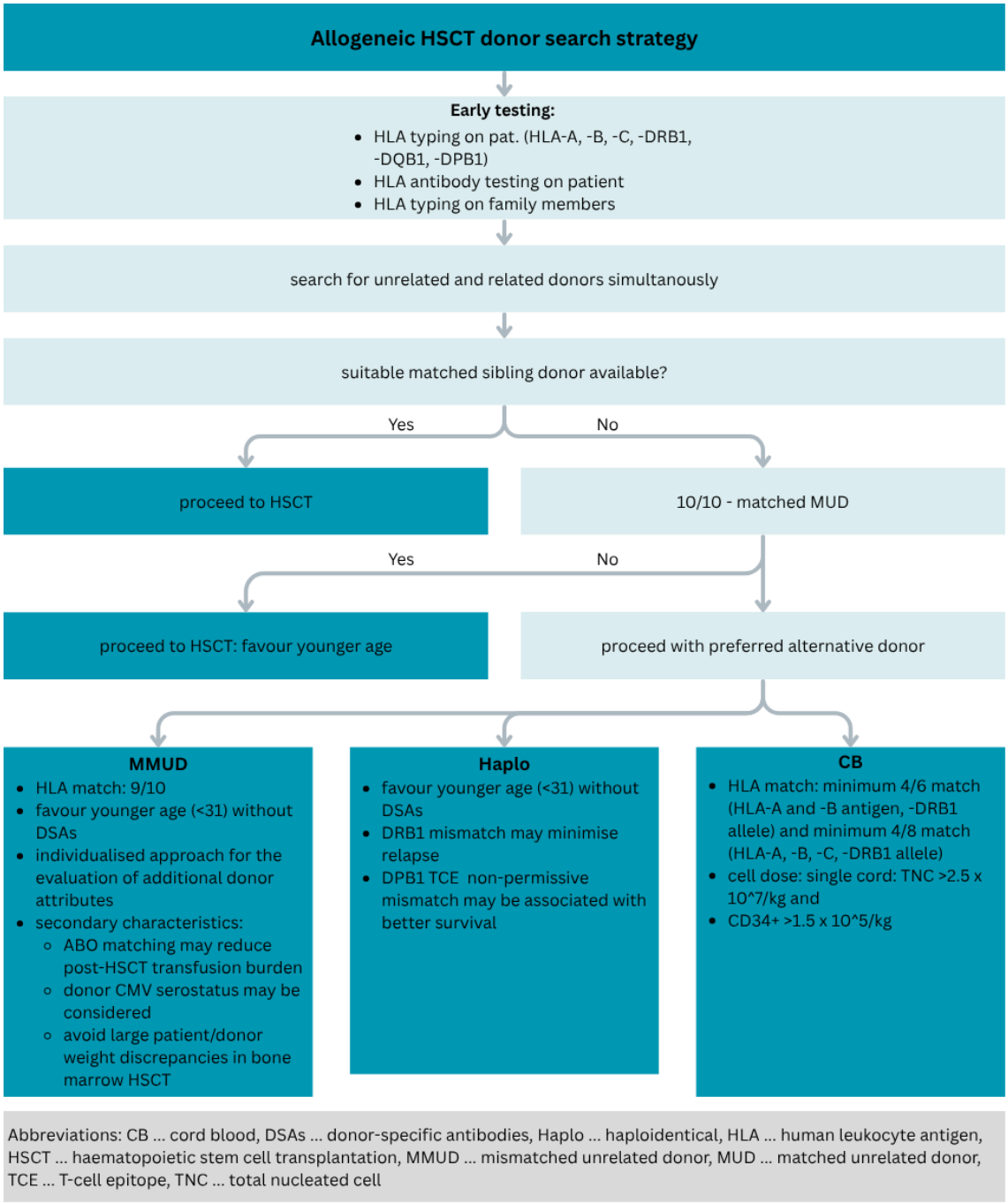



*Figure 1-1: Donor search and selection process [24, 25]*

## Haematopoietic stem cell transplantation process

Patients requiring allo-HSCT first undergo a pre-transplant evaluation to confirm the histologic diagnosis and define the disease status [22]. This includes physical examination, functional testing, imaging, and laboratory tests. The donor receives medication for haematopoietic cell mobilisation, typically filgrastim, a granulocyte colony-stimulating factor. In case of insufficient collection, the addition of plerixafor may be indicated. The minimum target is 4-5 x $10^6$ CD34 cells/kg.

Pat. durchlaufen eine Evaluierung vor Transplantation

Zellmobilisierung bei Spender:innen

Meanwhile, the recipient undergoes a conditioning regimen. The preferred regimen for AML, CML and MDS is myeloablative (MA) conditioning, whereas non-myeloablative (NMA) conditioning is preferred in lymphoma and multiple myeloma. MA regimens cause irreversible (or close to irreversible) pancytopenia. Additionally, haematopoietic cell support is required to rescue marrow function and prevent aplasia-related death (details are provided in the National Comprehensive Cancer Network/NCCN guideline [22]).

Empfänger:innen bekommen eine Konditionierungstherapie

Transplantation takes place in a qualified transplantation centre (an overview of Austrian centres is provided in Chapter 6). The recipient is admitted to the centre one week prior to transplantation and stays there for a minimum of three to four weeks [6]. After the transplantation, monitoring of GVHD, multi-organ dysfunction and infections is required, and regular follow-up visits are recommended [22]. The whole allo-HSCT process is displayed in Figure 1-2.

Transplantation in qualifizierten Zentren

gefolgt von engmaschiger Überwachung

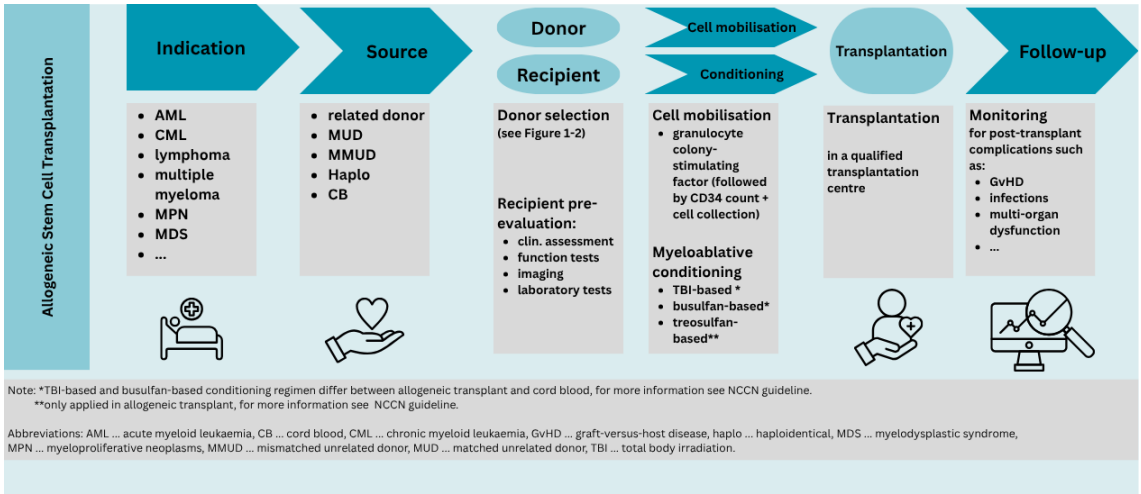



*Figure 1-2: Description of the whole allo-HSCT process [21]*

## 1.3 Medicinal product under evaluation

Zemcelpro: kryokonservierte Zelltherapie

The medicinal product under evaluation in this HTA is Zemcelpro, a cryopreserved allogeneic haematopoietic stem and progenitor cell therapy [1]. As reported above, it consists of two cell components derived from the same patient-specific umbilical CBU: expanded CD34+ cells (dorocubicel) and unexpanded CD34– cells (see Table 1-1).

*Table 1-1: Characteristics of the medicinal product [2]*

| | |
|---|---|
| INN | Dorocubicel |
| Product name | Zemcelpro |
| Active substance(s) | Dorocubicel and unexpanded CD34- cells |
| Anatomical Therapeutic Code | B05AX04 |
| Pharmacologic class | Allogeneic haematopoietic stem cell therapy |
| Manufacturer/MAH | Cordex Biologics International Limited |

*Abbreviations: INN … International non-proprietary name, MAH … marketing authorisation holder*

### Regulatory Status

EMA: Zulassung durch EC im August 2025

FDA: derzeit keine Zulassung

On 19 June 2025, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a conditional marketing authorisation for Zemcelpro for the treatment of adult patients with haematological malignancies requiring an allo-HSCT following MA conditioning for whom no other type of suitable donor cells is available [2]. Zemcelpro received a conditional marketing authorisation from the European Commission (EC) on 25 August 2025 [2]. The medicinal product was supported through EMA's PRIority MEdicines (PRIME) scheme and was designated as an orphan medicine. EMA regulatory information is summarised in Table 1-2. The U.S. Food and Drug Administration (FDA) has not (yet) approved Zemcelpro.

*Table 1-2: EMA regulatory information on Zemcelpro [2]*

| Regulatory information | Status |
|---|---|
| Orphan designation status medicinal product | Yes |
| Conditional marketing authorisation | Yes |
| Specific obligations of the conditional marketing authorisation | To confirm the efficacy and safety, the MAH shall submit the final results from Study ECT-001-CB.002 and CB.004 |
| Additional monitoring | Yes |
| Accelerated approval | No |
| Exceptional circumstances | No |
| ATMP | Yes |
| PRIME | Yes |
| Orphan medicinal product | Yes |
| First approved indication | treatment of adult patients with haematological malignancies requiring an allogeneic haematopoietic stem cell transplantation following myeloablative conditioning for whom no other type of suitable donor cells is available |

*Abbreviations: ATMP … Advanced Therapy Medicinal Product, HLA … Human leukocyte antigen, MAH … Marketing Authorisation Holder, PRIME … Priority Medicines*

The mechanism of action of Zemcelpro differs between the two cell components:

Wirkmechanismus:

- ***The UM171-expanded cell component (dorocubicel):*** The CD34+ fraction is expanded *ex-vivo* in the presence of UM171, a small molecule that enhances the expansion and maintenance of HSC [1]. This component promotes haematopoietic recovery and restoration of immune capabilities [2].

expandierte Zell-Komponente (dorocubicel): hämatologische Regeneration

- ***The unexpanded cell component:*** The CD34–fraction remains unexpanded and contains CD3+ T cells as the active component [1]. These cells support immune reconstitution and may provide graft-versus-leukaemia effects while potentially reducing the risk of graft rejection [2].

nicht expandierte Zell-Komponente: Immunrekonstitution

After the infusions, haematopoietic stem and progenitor cells from Zemcelpro migrate to the BM, where they proliferate, mature, and differentiate into all haematopoietic cell lineages. The resulting mature cells are released into the bloodstream, with some circulating in PB while others migrate to specific tissue sites, leading to partial or complete restoration of blood cell counts and function, including immune capabilities of BM-derived blood cells [1].

transplantierte Zellen gelangen in das Knochenmark und differenzieren sich in alle hämatolog. Zelllinien

## Posology and method of administration

The manufacturing process begins with the prescriber selecting an appropriate erythrodepleted CBU and the manufacturer purchasing and shipping the CBU to Canada. Selection criteria include minimal HLA matching requirements: at least 4/6 antigens (HLA-A, HLA-B, and HLA-DRB1 alleles), target matching (6/8 HLA-match with high-resolution typing), minimum cell dose requirements (pre-freeze CD34 cell count $\geq 0.5 \times 10^5$/kg and total nucleated cell count $\geq 1.5 \times 10^7$/kg) [1].

Herstellungsprozess startet mit CBU-Auswahl durch Zentrum und Transport durch Hersteller

Following manufacturing and quality control testing at the Canadian manufacturing site, each infusion bag is placed in a metallic cassette and transported cryopreserved to Europe, for delivery to the transplant centre. Zemcelpro has a shelf-life of 12 months when stored at ≤ –150°C. After thawing, the product must be administered within one hour at room temperature (15-30°) [1].

Aufbewahrung bei ≤ –150°C, Haltbarkeit 12 Monate

Treatment consists of a single dose for infusion containing a dispersion of expanded CD34+ cells in one to four infusion bags and unexpanded CD34– cells in four infusion bags. The target dose is 0.4 to $7.5 \times 10^6$ viable CD34+ cells/kg for the expanded CD34+ cell component (dorocubicel) and $\geq 0.52 \times 10^6$ viable CD3+ cells/kg for the unexpanded CD34– cell component [1].

1-4 Infusionsbeutel CD34+ Zellen + 4 Infusionsbeutel CD34– Zellen

The infusion starts with dorocubicel, followed by the unexpanded CD34– cells. The unexpanded component should be infused the same day as dorocubicel, but no later than the following day. If dorocubicel is not administered, the unexpanded component must not be infused to avoid immune reactions.

1. dorocubicel
2. nicht expandierte CD34- Zellen

## Requirements for pre-treatment diagnostic evaluation and/or monitoring

The administration of Zemcelpro consists of several steps, as presented in Figure 1-3. Before the administration of Zemcelpro, patients undergo pre-treatment conditioning [1]. Patients must receive appropriate myeloablative conditioning regimens with a transplant conditioning intensity score of 2.5

mehrstufiger Infusionsprozess, Start mit Dorocubicel, Vorkonditionierung erforderlich

and above before Zemcelpro is administered. Anti-thymocyte globulin is not recommended as it may interfere with CB cell engraftment.

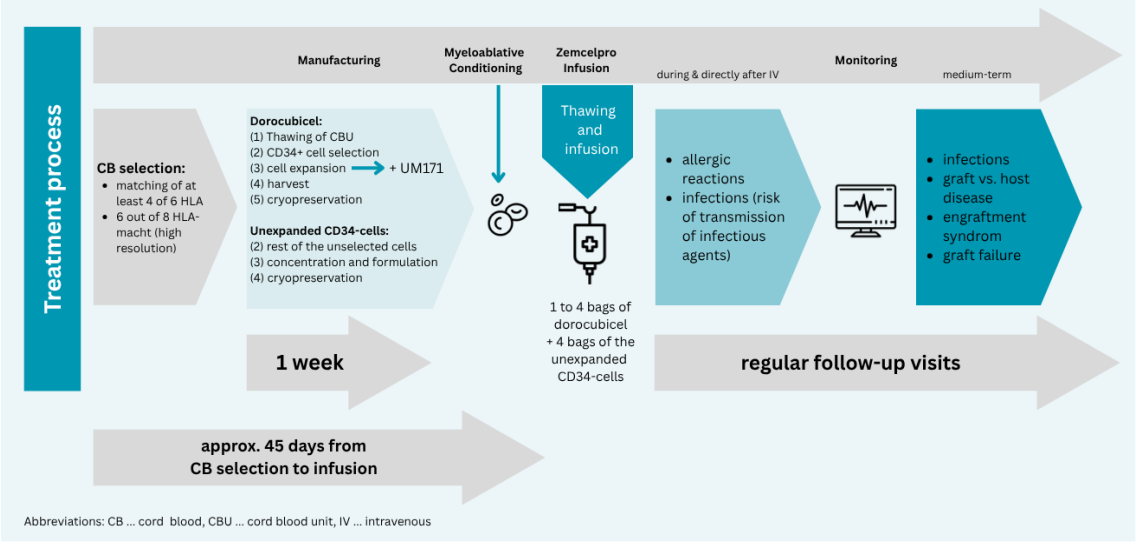



*Figure 1-3: Treatment process of Zemcelpro adapted from [1, 6]*

## Expected number of patients receiving Zemcelpro in Austria

EMA:
Indikation als „last resort" bei hämatologischen malignen Erkrankungen

According to EMA, the wording of the Zemcelpro indication reflects the last resort setting in patients with haematological malignancies. The target population includes only those patients who lack access to any suitable donor for stem cells from peripheral blood, or bone marrow or cord blood. The occurrence of such cases in clinical practice is expected to be very limited [2].

Transplantbericht:
für 90 % von 410 Pat. waren passende Spender:innen verfügbar

In 2024, 410 patients were registered in the Austrian Stem Cell Registry for an unrelated donor search. The number of newly registered patients increased by almost 7% compared with the previous year (2023: 384). As of March 31, 2025, at least one suitable unrelated donor had been identified for 90% of patients. For the remaining 10% (approximately 40 newly registered Austrian patients), no suitable unrelated donor was found [5].

letzte CB-Transplantation in Österreich 2019

potenzielle Verwendung von Zemcelpro – nur 1 CBU notwendig

According to Austrian clinical experts, all patients requiring allo-HSCT ultimately received one, though some procedures may have involved suboptimal HLA matching [6]. In these cases, transplantation with reduced HLA compatibility (MMUD and haplo) was still preferred over single CB transplantation alone. Notably, the last documented use of CB transplantation in Austria was in 2019 [5]. However, Zemcelpro may offer potential benefits over unexpanded CB transplants as instead of one to two CBUs, only one CBU might be necessary due to the increased numbers of stem cells, potentially improving the outcome of allo-HSCT.

# 2 Scope of assessment

This report aims to evaluate Zemcelpro (dorocubicel + unexpanded CD34– cells) for adults with haematological malignancies who need allogeneic haematopoietic stem cell therapy (allo-HSCT) and for whom no other suitable donor cells are available.

HTA: Evaluierung von Zemcelpro bei maligner hämat. Erkrankung bei Erwachsenen mit erforderlicher allo-HSZT

## 2.1 Research questions

The following research questions will be addressed in this report:

1. **Clinical domain:**

   In adult patients with haematological malignancies requiring allo-HSCT, is Zemcelpro more effective and safer than current standard treatments with respect to patient-relevant outcomes?

   klinische Domäne: Wirksamkeit und Sicherheit

2. **Non-clinical domains:**

   What are the economic, ethical, organisational, and social consequences of implementing Zemcelpro into the Austrian healthcare system?

   What were the key contributions of publicly funded research institutions and private companies in discovering and developing Zemcelpro as a therapy for disease, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

   nicht-klin. Domänen: ökonomische, ethische, organisatorische, soziale Konsequenzen, sowie öffentliche Beiträge zu Entwicklungskosten

## 2.2 Inclusion criteria

Inclusion criteria for relevant clinical studies are summarised in Table 2-1.

Einschlusskriterien für relevante klinische Studien

Regarding the non-clinical domains, relevant economic literature was included providing information on Zemcelpro prices, other direct medical costs, and health economic evaluations. In addition, relevant literature addressing organisational, ethical and social domain as well as literature on public investment, such as information on public grants, funding and contributions, was considered.

zusätzliche Literatur für nicht klin. Bereiche berücksichtigt

*Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain*

| Description of PICO elements | |
|---|---|
| P | Adults with haematological malignancies (including but not limited to leukaemia, lymphoma, and multiple myeloma) who need an allogeneic haematopoietic stem cell transplantation and for whom no other type of suitable donor cells is available |
| I | Zemcelpro: dorocubicel (expanded CD34+ cells) + unexpanded CD34– cells |
| C | Unexpanded cord blood unit/double cord blood unit (main comparator)<br>Other HLA-mismatched alternative donors: haplo and mismatched unrelated donors (Austrian clinical practice) |
| O | Efficacy:<br>■ Overall survival (OS)<br>■ Non-relapse mortality (NRM)<br>■ Progression-free survival (PFS)<br>■ Time to neutrophil engraftment<br>■ Time to platelet engraftment<br>■ Proportion reaching neutrophil engraftment by day 42<br>■ Proportion reaching platelet engraftment by day 100<br>PROs:<br>■ Quality of life (QoL)<br>Safety:<br>■ Transplant-related mortality (TRM)<br>■ (Severe/serious) adverse events<br>■ Treatment-emergent/-related adverse events<br>■ Graft-versus-host disease (GVHD)-free relapse-free survival (GRFS)<br>■ Chronic GVHD-free survival and relapse-free survival (CRFS) |
| Studies | Randomised controlled trials or meta-analyses<br>If not available: non-randomised controlled studies, indirect treatment comparisons, observational studies, single-arm trials |
| Languages | German, English |

*Abbreviations: CD34+ … cluster of differentiation 34 positive (cells), CD34– … cluster of differentiation 34 negative (cells), CRFS … chronic GVHD-free survival and relapse-free survival, GVHD … graft-versus-host disease, GRFS … GVHD-free relapse-free survival, haplo … haploidentical (donor), HLA … human leukocyte antigen, NRM … non-relapse mortality, OS … overall survival, PFS … progression-free survival, PICO … population, intervention, comparator, outcome, PROs … patient-reported outcomes, QoL … quality of life, TRM … transplant-related mortality*

# 3 Methods

Multi-Methoden-Ansatz: EUnetHTA-Leitfragen

Daten-Cut-off: 1. Oktober 2025

This health technology assessment (HTA) employed a multi-domain assessment approach, following the European Network for Health Technology Assessment (EUnetHTA) methodology (see guiding question in Chapter 3 of the Appendix) [27]. Methods were tailored to address the three research questions identified in Chapter 2, with a data cut-off on 1 October 2025.

## Systematic literature search and study selection

1 systematische Literatursuche in 4 Datenbanken: 179 Treffer

Suche nach laufenden Studien: 62 Treffer

kein Dossier vom Hersteller eingereicht

A systematic literature search was conducted on 16 September 2025, across four databases: the Cochrane Library, Embase, the International HTA Database, and Medline via Ovid. The search was restricted to English and German, excluding conference abstracts (see detailed search strategies in Chapter 3 in the Appendix). After removing duplicates, 179 citations were identified. Additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) yielded 62 potentially relevant hits. Since Zemcelpro received conditional approval from the European Medicines Agency (EMA), the European Public Assessment Report (EPAR) was also included in the HTA to capture regulatory data. The manufacturer did not submit a dossier.

Literaturauswahl für Wirksamkeits- und Sicherheitsanalyse

The study selection process followed a structured approach: two researchers (EM, NLR) initially screened abstracts based on the pre-defined criteria (see Table 2-1). Full texts were independently screened by the two reviewers, with disagreements resolved by a third reviewer (SGG). The study selection process is depicted in a PRISMA flow diagram in Figure 3.2 in the Appendix, Chapter 3.

## Clinical effectiveness and safety assessment

system. Datensynthese im 4-Augenprinzip

Data extraction was systematically performed by one reviewer (NLR) and cross-checked by a second reviewer (EM). Identified ITCs were critically appraised for methodological quality and relevance.

kein RoB-Tool angewendet

For the assessment of clinical effectiveness and safety, no formal risk of bias (RoB) tool was applied to the included single-arm study, following the methodological standards for single-arm trials issued by the Member State Coordination Group on Health Technology Assessment. In line with the Guidance on Validity of Clinical Studies, uncontrolled trials are inherently of limited value for evaluating relative effectiveness and therefore do not require a formal RoB assessment [28]. Instead, we conducted a structured descriptive evaluation examining the following:

deskriptive Bewertung der einarmigen Studie

- Study design appropriateness for the research question
- Population representativeness and external validity
- Outcome measurement validity and completeness
- Statistical analysis appropriateness
- Potential sources of bias specific to single-arm studies

keine GRADE-Bewertung

The evidence synthesis followed a narrative approach due to limited comparative data. Therefore, the strength of evidence was not assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [29].

## Economic evaluation methods

Preis-Infos von GÖG

To collect price information on Zemcelpro, the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) was contacted. In addition, the Pharmaceutical Pricing and Reimbursement Information (PPRI) network conducted a survey to gather data on the economic aspects of Zemcelpro, including pricing and managed entry agreements, across multiple European member states.

Umfrage im PPRI-Netzwerk (vertraulich)

zusätzliche Handsuche nach ökonomischen Analysen zu Zemcelpro

Regarding health economic evaluations of Zemcelpro, both submissions by the marketing authorisation holder (MAH) as well as published analyses would have been considered. For the latter, we screened the literature identified through systematic and additional manual searches via Google.

Alternative zur Budgetfolgenanalyse: Abschätzung der direkten medizinischen Kosten pro Pat. und Prozedur

Besides, according to the implementation regulation §4(2) of the Austrian Appraisal Board, a three-year budget impact analysis, including the gross drug budget impact and additional administration-related costs, should be conducted. Given the very small patient population and limited availability of economic data, a simplified cost analysis was conducted instead of a formal cost-effectiveness or budget impact analysis. Additionally, we accounted for anticipated cost variations through a scenario analysis. Overall, we have made the following assumptions in the cost analysis:

zahlreiche Annahmen getroffen: ...

- We derived the patient population estimates from published epidemiological data, which were validated by Austrian clinical experts.

... epidemiologische Daten (Expertenschätzungen)

- We considered a placeholder price for Zemcelpro based on the official US list price of a similar product, omidubicel, as no official European price is yet available[3].

... Platzhalterpreis notwendig

- For the cost calculations, we used inpatient treatment cost data from the Austrian procedure- and diagnosis-related groups (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue.

... Kostendaten: LKF-Katalog

- Minor cost categories, as well as costs related to diagnostics and long-term post-treatment management, were excluded from the primary analysis due to the individualised nature of diagnostic and monitoring procedures and the lack of available Austrian cost data. Nevertheless, we accounted for some costs descriptively in the scenario analysis.

... Diagnostik und Langzeitkosten in Primäranalyse nicht berücksichtigt

## Organisational, ethical and social assessment

Bewertung nach EUnetHTA-Methodik, 3 Quellen:

The assessment of organisational, ethical and social aspects utilised the EUnetHTA methodology. Data were gathered from three sources:

- Structured patient questionnaires (see Chapter 3.3 in the Appendix for details): Initially, we searched for eligible patients, carers and/or members of patient organisations in Austria. Since the indication is very specific, the search was expanded to the "DACH" region, additionally including Germany and Switzerland.

schriftliche Patient:innen-Befragungen

- Expert consultations with four leading clinicians (see Chapter 3.3 in the Appendix).

Expert:innen-Konsultationen,

- Systematic literature review and manual search findings.

& Literaturquellen

[3] There was no price submission by the MAH by the cut-off date of 1 October 2025.

## Development costs and public contributions

Entwicklungskosten und öffentliche Beiträge erhoben

The methodology for assessing development costs and public contributions involved several steps:

- Identifying product origins through searches for generic/ non-proprietary names and trade names.
- Searching for the earliest references to identify basic research and development support and research grants.
- Exploring databases on clinical trials and research funding.
- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching SEC reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.
- Funding amounts were converted to € using the conversion rates as of 25 September 2025, from the Austrian National Bank [30].

Identifizierung von: generischer oder (nicht) geschützter Bezeichnungen

Produktherkunft & Grundlagenforschung

Finanzierungsrunden, Fusionen & Übernahmen

Additionally, we compiled a landscape overview of other therapies, which are in the development for haematological malignancies, using the International Horizon Scanning Initiative (IHSI) database [31], supplemented by a review of other stem cell products in the pipeline identified through current literature.

zusätzlicher Überblick zu Therapien haematolog. maligner Erkrankungen in Entwicklung

# 4 Clinical effectiveness and safety

## 4.1 Characteristics of the included studies

Ultimately, five studies – one clinical study, three indirect treatment comparison (ITC) studies and the European Public Assessment Report (EPAR) were included for the synthesis of clinical effectiveness and safety.

5 Studien (davon 1 klin. Studie & 3 zu indirekten Therapievergleichen & EPAR)

### Studies identified through the systematic literature search

Through the systematic literature search, we identified one clinical phase 1/2 study (ECT-001-CB.001) evaluating the clinical efficacy and safety of Zemcelpro in adults with haematological malignancies requiring allogeneic haematopoietic stem cell transplantation (allo-HSCT) [32]. The main characteristics of the study are described in Table 4-1.

1 einarmige Phase-1/2-Studie durch system. Literaturrecherche identifiziert

*Table 4-1: Main characteristics of the ECT-001-CB.001 study [32]*

| Reference/ID | ECT-001-CB.001/UM0128171 |
|---|---|
| Study type and design | Phase 1/2, prospective, single-arm, multicentre, open-label study |
| Study population | Patients with haematological malignancies and an indication for allo-HSCT, who lacked a suitable HLA-matched donor |
| Study arms | Single-arm study:<br>■ Feasibility analysis: n=27<br>■ Phase 2: n=22 |
| Study duration, data cut-off and location | ■ Median study follow-up: 18 months (IQR: 12-22)<br>■ Data cut-off: 31 December 2018<br>■ Location: Canada |
| Study endpoints | ■ Primary endpoints: time to neutrophil engraftment; time to platelet engraftment; identification of the minimal pre-expansion CBU cell dose that ensures prompt engraftment<br>■ Secondary endpoints: correlation between neutrophil and platelet engraftment and CD34+ cell dose and CD34+ CD45RA- cell dose; incidence of acute and chronic GVHD; primary and late graft failure; incidence of back-up cord infusion and subsequent graft dominance; incidence of severe infections (≥ grade 3); TRM; OS; PFS; incidence of pre-engraftment syndrome or engraftment syndrome requiring therapy; hospitalisation events; immune reconstitution and HLA-match improvement. |
| Study protocol amendments | The study protocol of ECT-001-CB.001 underwent five amendments, with the final version (6.0) dated 15 May 2018. |
| Available documentation | ■ CSR: not provided<br>■ Registry entry: NCT02668315<br>■ Sponsoring status: sponsored |

*Abbreviations: allo-HSCT … allogeneic haematopoietic stem cell transplantation, CBU … cord blood unit, CD34+ … CD34-positive, CSR … clinical study report, GVHD … graft versus host disease, HLA … human leukocyte antigen, IQR … interquartile range, n … number of patients, NCT … National Clinical Trial, OS … overall survival, PFS … progression-free survival, TRM … transplant-related mortality*

## Supporting studies for European Medicines Agency approval

unterstützende Studien für die bedingte EMA-Zulassung

The European Medicines Agency (EMA) granted conditional approval for Zemcelpro based on an integrated summary of safety and efficacy, which included distinct populations. The complete regulatory assessment is available in the EMA's EPAR, which was identified through additional manual searches [2].

Wirksamkeitsanalyse basierend auf 2 laufenden klin. Studien: ECT-001-CB.002 & ECT-001-CB.004

The efficacy analysis of the EPAR incorporated data from two unpublished ongoing single-arm, open-label studies, ECT-001-CB.002 and ECT-001-CB.004 [2]. The main characteristics of these studies are presented in Table 4-2.

*Table 4-2: Main characteristics of ECT-001-CB.002 and ECT-001-CB.004 [2]*

| Reference/ID | ECT-001-CB.002 | ECT-001-CB.004 |
|---|---|---|
| Study type and design | Phase 2, single-arm, single-centre, open-label study | |
| Study population | Patients aged 18-70 years with high and very high-risk acute leukaemia or myelodysplasia | |
| Study arms | Single-arm study: UM171-expanded CB transplantation (n=30) | |
| Study duration, data cut-off and locations | ■ Median follow-up: 13.27 months (IQR: 0.92-38.18)<br>■ Primary completion date: October 2024<br>■ Study completion date: October 2027<br>■ Location: Canada | ■ Median follow-up: 13.27 months (IQR: 0.92-38.18)<br>■ Primary completion date (estimated): February 2026<br>■ Study completion date (estimated): February 2026<br>■ Location: the Netherlands, USA |
| Study endpoints | ■ Primary endpoints: TRM at 1 year; RFS at 2 years; OS at 2 years<br>■ Secondary endpoints: neutrophil engraftment; graft failure; platelet engraftment; incidence of acute GVHD; incidence of chronic GVHD; AEs grade ≥3; incidence of severe infectious complications; hospitalisation events; incidence of pre-engraftment/engraftment syndrome requiring therapy | ■ Primary endpoints: AEs 100 days post-transplant; AEs 2 years post-transplant; RFS at 1 year post-transplant; RFS at 2 years post-transplant<br>■ Secondary endpoints: time to neutrophil and platelet engraftment; incidence of TRM; incidence of GVHD; incidence of grade ≥3 infectious complications; incidence of pre-engraftment/ engraftment syndrome requiring therapy; GRFS and CRFS |
| Available documentation | ■ CSR: not provided<br>■ Registry entry: NCT03913026<br>■ Sponsoring status: sponsored | ■ CSR: not provided<br>■ Registry entry: NCT04103879<br>■ Sponsoring status: sponsored |

*Abbreviations: AE … adverse event, CB … cord blood, CRFS … chronic graft versus host disease-free and relapse-free survival, CSR … clinical study report, GRFS … graft versus host disease-free and relapse-free survival, GVHD … graft versus host disease, IQR … interquartile range, n … number, OS … overall survival, RFS … relapse-free survival, TRM … transplant-related mortality, USA … United States of America*

Sicherheitsanalyse basierend auf 5 klin. Studien

The safety analysis of the EPAR incorporated data from five single-arm, open-label studies: ECT-001-CB.001, ECT-001-CB.002, ECT-001-CB.003, ECT-001-CB.004 and ECT-001-CB.007 [2]. An overview of these studies is presented in Table 4-3.

*Table 4-3: Overview of the studies included in the safety analysis set from the EPAR [2]*

| Study (NCT number) | Description | Enrolment | (Estimated) completion date |
|---|---|---|---|
| ECT-001-CB.001 (NCT02668315) | Main characteristics of the study are described in Table 4-1. | Actual: 27 (infused: 26) | August 2018 |
| ECT-001-CB.002 (NCT03913026) | Main characteristics of the study are described in Table 4-2. | Actual: 30 (infused: 30) | October 2027 |
| ECT-001-CB.003 (NCT03441958) | Phase 1/2, open-label study of reduced intensity allogeneic transplant of Zemcelpro in patients with newly diagnosed high-risk multiple myeloma (after induction treatment). The clinical study investigates lower-to-intermediate-intensity conditioning regimens. | Actual: 20 (infused: 19) | October 2025 |
| ECT-001-CB.004 (NCT04103879) | Main characteristics of the study are described in Table 4-2. | Actual: 33 (infused: 30) | February 2026 |
| ECT-001-CB.007 (NCT04990323) | Phase 1/2, single-arm, single-centre, open-label study in paediatric and young adult patients (<21 years) with high-risk and very high-risk myeloid malignancies administered with Zemcelpro. | Actual: 13 (infused: 12) | June 2027 |

*Abbreviations: EPAR … European Public Assessment Report, NCT … National Clinical Trial*

## 4.1.1 Study population

### The efficacy analysis set

Wirksamkeitsanalyse der EMA (pivotal FAS): erwachsene Hochrisiko-Pat. mit akuter Leukämie/ Myelodysplasie im Alter von 18-70 Jahren (n=25), medianes FU: 13,27 Monate

The EMA's efficacy analysis (pivotal full analysis set, FAS) was based on a subgroup of patients from ECT-001-CB.002 and ECT-001-CB.004 studies, which enrolled adults aged 18 to 70 years with high-risk acute leukaemia and myelodysplasia. Patients were intended to be transplanted with cryopreserved Zemcelpro derived from the expansion of a small cord blood unit (CBU, containing $<1.5 \times 10^5$ CD34+ cells per kg or $<2.5 \times 10^7$ total nucleated cells/ TNC per kg pre-cryopreservation, before expansion). The analysis included 25 patients (infused: 24) with a median follow-up of 13.27 months (IQR: 0.92-38.18, data cut-off: 15 March 2024) [2]. The pivotal FAS formed the basis for the EMA approval and is therefore used for the effectiveness analysis in this HTA report. Key inclusion and exclusion criteria for these studies are summarised below.

*Table 4-4: Key eligibility criteria for ECT-001-CB.002 & ECT-001-CB.004 [2]*

| Eligibility criteria | Pivotal full efficacy analysis set: ECT-001-CB.002 + ECT-001-CB.004 |
|---|---|
| Inclusion criteria | ■ 18-70 years<br>■ High-risk acute leukaemia/myelodysplasia:<br>  ■ AML<br>  ■ ALL<br>  ■ MDS<br>■ KPS ≥70%<br>■ Adequate organ function<br>■ Adequate comorbidity<br>■ CB unit for expansion + back-up unit (≥4/6 or ≥4/8 HLA match)<br>■ CD34+ $>0.5\times10^5$/kg, TNC $>1.5\times10^7$/kg<br>■ Informed consent |

| Eligibility criteria | Pivotal full efficacy analysis set: ECT-001-CB.002 + ECT-001-CB.004 |
|---|---|
| Exclusion criteria | ■ Patients never treated with cytotoxic chemotherapy<br>■ Planned regimen without 12Gy TBI<br>■ Allogeneic myeloablative or autologous HSCT <6 months<br>■ Planned use of antithymocyte globulin in conditioning regimen<br>■ Planned use of HLA-matched CB (8/8), HLA antibodies against expanded CB<br>■ Uncontrolled infection<br>■ Malignancy other than indication <75% estimated 5-year survival<br>■ Seropositivity for HIV, hepatitis B/C with measurable viral load<br>■ Liver cirrhosis<br>■ Active CNS involvement, chloroma >2 cm<br>■ ≥50% blasts in marrow <1 month prior to conditioning, peripheral blasts >1,000/mm$^3$<br>■ Trial participation with investigational agents within 30 days<br>■ Pregnancy<br>■ Unwillingness to use contraception |

*Abbreviations: ALL … acute lymphoblastic leukaemia, allo-HSCT … allogeneic haematopoietic stem cell transplantation, AML … acute myeloid leukaemia, CB … cord blood, CD34 … cluster of differentiation 34 positive, CNS … central nervous system, Gy … gray, HIV … human immunodeficiency virus, HLA … human leukocyte antigen, HSCT … haematopoietic stem cell transplantation, KPS … Karnofsky performance status, MDS … myelodysplastic syndrome, mm … millimetre, TBI … total body irradiation, TNC … total nucleated cells*

### The safety analysis set

Sicherheitsanalyse der EMA (SAS): 116 Pat. → unterschiedliche Produktformen (z. B. kryokonserviert vs. frisch) & heterogene Pat.-Population

The EMA's safety analysis set (SAS) was based on a larger population comprising 116 patients from all five clinical studies: the published phase 1/2 study (ECT-001-CB.001) and four ongoing single-arm, open-label, clinical trials (ECT-001-CB.002, ECT-001-CB.003, ECT-001-CB.004 and ECT-001-CB.007), as described in the EPAR. The population in the SAS included both cryopreserved and fresh product formulations, small and standard-size CBU, and a diverse patient population – with respect to age, underlying disease, and myeloablative (MA) conditioning regimens – with a median follow-up of 22.49 months (range: 0.89-48.4 months, data cut-off: 15 March 2024) [2]. The SAS formed the basis for the EMA approval and is therefore used for the safety analysis in this HTA report. A detailed description of the inclusion and exclusion criteria for all studies can be found in Chapter 4.1 in the Appendix.

## 4.1.2 Baseline patient characteristics

pivotal FAS & SAS: Gemeinsamkeiten bzgl. Alter, Geschlecht, vorangegangener allogener Behandlung & Krankheitsklassifikation

The pivotal FAS and SAS population showed similar baseline characteristics, including comparable median ages (46 vs 44 years), a predominantly male population (72% vs 63.8%), and a similar proportion of patients having received prior allogeneic treatment (28% vs 26.7%). In both populations, the largest subgroup was patients with ALL (44% vs 24.1%) and AML (44% vs 43.1%) [2]. The key baseline demographics of the pivotal FAS and the SAS population are described in Table 4-5. Notably, the ECT-001-CB.007 study (part of the SAS) included children and adolescents aged 21 years and younger. Details of the key baseline characteristics of the ECT-001-CB.001 study are presented in the Appendix Chapter 4, since the study is non-regulatory and included solely to provide supportive evidence.

*Table 4-5: Key baseline demographics of the pivotal FAS (ECT-001-CB.002+ ECT-001-CB.004) and SAS (ECT-001-CB.001, ECT-001-CB.002, ECT-001-CB.003, ECT-001-CB.004 + ECT-001-CB.007) [2]*

| Parameter | Pivotal FAS (ECT-001-CB.002+ ECT-001-CB.004) | SAS (ECT-001-CB.001, ECT-001-CB.002, ECT-001-CB.003, ECT-001-CB.004 + ECT-001-CB.007) |
|---|---|---|
| N | 25 | 116 |
| Age [years], median (range) | 46 (24-64) | 44 (1-66) |
| Sex [f/m] (%) | | |
| Male | 18 (72%) | 74 (63.8%) |
| Female | 7 (28%) | 42 (36.2%) |
| Previous allogeneic treatment | 7 (28%) | 31 (26.7%) |
| Disease category (n[%]) | | |
| ALL | 11 (44%) | 28 (24.1%) |
| AML | 11 (44%) | 50 (43.1%) |
| MDS | 3 (12%) | 14 (12.1%) |
| Chronic myelogenous leukaemia: patients who progressed to blast crisis | 0 (0%) | 1 (0.9%) |
| Hodgkin lymphoma | 0 (0%) | 1 (0.9%) |
| Non-Hodgkin lymphoma, aggressive lymphoma: diffuse large B cell lymphoma | 0 (0%) | 2 (1.7%) |
| Adult T cell leukaemia/lymphoma | 0 (0%) | 1 (0.9%) |
| Chronic lymphocytic leukaemia and transformation to Hodgkin lymphoma | 0 (0%) | 1 (0.9%) |
| MM | NA | 18 (15.5%) |

*Abbreviations: ALL … acute lymphoblastic leukaemia, AML … acute myeloid leukaemia, FAS … full analysis set, MDS … myelodysplastic syndrome, MM … multiple myeloma, n … number, NA … not available, SAS … safety analysis set*

## 4.2 Outcomes

### Definitions and reporting of efficacy outcomes

mehrere Endpunkte zur Wirksamkeit v. Zemcelpro u. a.: OS, NRM, PFS

For the efficacy outcomes, in the pivotal FAS, neutrophil and platelet recovery – specifically, the proportions of patients achieving neutrophil engraftment by day 42 and platelet engraftment by day 100 – were evaluated. Additionally, overall survival (OS), non-relapse mortality (NRM), and progression-free survival (PFS) were investigated. Other efficacy endpoints included graft versus host disease-free and relapse-free survival (GRFS), chronic graft versus host disease-free survival and relapse-free survival (CRFS), and transplant-related mortality (TRM) [2].

### Definitions and reporting of safety outcomes

UE & SUE nach NCI-CTCAE

UE von Beginn der Konditionierung bis zur Entlassung aus dem Transplantationszentrum erfasst

For safety outcomes in the SAS, adverse events (AEs) were systematically assessed through ongoing monitoring and documentation of AEs and severe adverse events (SAEs) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The SAS recorded AEs from the initiation of the conditioning regimen through patient discharge from the transplant centre (i.e., up to approximately 3 months after transplantation, or around day 100), with follow-up assessments at 6, 12, and 24 months. Reporting was limited to AEs graded ≥3 or highly unusual grade 2. Grade 1 and grade 2 safety outcomes were not systematically reported. Studies ECT-001-CB.001, ECT-001-CB.002 and ECT-001-CB.003 reported all AEs irrespective of intent, whereas studies ECT-001-CB.004 and ECT-001-CB.007 restricted reporting to unintended events only [2]. For the detailed characteristics of the safety outcomes, see Appendix, Chapter 4.

## 4.3 Results on efficacy and safety

### 4.3.1 Clinical efficacy outcomes

Clinical efficacy outcomes for the pivotal FAS are detailed below and summarised in Table 4-6. Supportive efficacy results from the ECT-001-CB.001 study are presented in the Appendix, Chapter 4.

### Overall survival

OS (24 Monate): 51,4 %

Median OS was not reported because it was not reached at the data cut-off; the estimated OS at 12 months was 66.0% (95% CI: 49-82) and 51.4% (95% CI: 32-82) at 24 months. [2].

### Non-relapse mortality

NRM (12 & 24 Monate): 21,2 %

NRM rates were 21.2% (95% CI: 4-38) at both 12 and 24 months [2].

### Progression-free survival

PFS (24 Monate): 45,3 %

Although median PFS was not reached at the data cut-off, estimated PFS probabilities were 52.8% (95% CI: 36-78) at 12 months and 45.3% (95% CI: 28-74) at 24 months [2].

### Neutrophil and platelet recovery

Neutrophilenengraftment: median 20 Tage
Thrombozytenengraftment: median 40 Tage

The median time to neutrophil recovery was 20 days (range 10-39), and the median time to platelet recovery was 40 days (range 29-175). The proportion of patients achieving neutrophil engraftment by day 42 was 84% and platelet engraftment by day 100 was 79.2% [2].

### Graft versus host disease-free and relapse-free survival and chronic graft versus host disease-free and relapse-free survival

GRFS was 29.1% (CI: 15-55) at 12 months and not reported at 24 months. CRFS rates were 45.2% (CI:29-71) at 12 months and 30.2% (CI: 15-62) at 24 months [2].

### Other outcomes

Patient-reported outcomes, including quality of life (QoL) measures and long-term follow-up efficacy data were not reported.

kein Bericht zu QoL-Daten & Langzeitergebnissen

*Table 4-6: Efficacy results of the pivotal FAS [2]*

| Efficacy endpoints | | Pivotal FAS (n=25) |
|---|---|---|
| OS, Kaplan-Meier estimates (95% CI) – 12 months | | 66.0% (49-82) |
| OS, median | | NR |
| OS, Kaplan-Meier estimates (95% CI) – 24 months | | 51.4% (32-82) |
| NRM, cumulative incidence (95%CI) – 12 months | | 21.2% (4-38) |
| NRM, cumulative incidence (95%CI) – 24 months | | 21.2% (4-38) |
| PFS, Kaplan-Meier estimates (95% CI) – 12 months | | 52.8% (36-78) |
| PFS, median | | NR |
| PFS, Kaplan-Meier estimates (95% CI) – 24 months | | 45.3% (28-74) |
| Neutrophil engraftment | Evaluable patients, n | 25 |
| | Median time to neutrophil engraftment (days), median (range) for patients who have reached neutrophil engraftment | 20 (10-39) |
| | Median time to neutrophil engraftment (days), median (range) for all patients | 25 (10-42) |
| | Proportion achieving neutrophil engraftment by day 42, n (%) | 21 (84.0%) |
| Platelet engraftment | Evaluable patients, n | 24 |
| | Median time to platelet engraftment (days), median (range) for patients who have reached platelet engraftment | 40 (29-175) |
| | Median time to platelet engraftment (days), median (range) for all patients | 48 (29-175) |
| | Proportion achieving platelet engraftment by day 100, n (%) | 19 (79.2%) |
| Acute GVHD grade III–IV at 12 months, cumulative incidence (95%CI)[4] | | 28.5% (10-47) |
| Moderate to severe chronic GVHD at 24 months, cumulative incidence (95%CI)[4] | | 17.4% (0-38) |
| GRFS, Kaplan-Meier estimates (95% CI) – 12 months | | 29.1% (15-55) |
| GRFS, Kaplan-Meier estimates (95% CI) – 24 months | | NR |
| CRFS, Kaplan-Meier estimates (95% CI) – 12 months | | 45.2% (29-71) |
| CRFS, Kaplan-Meier estimates (95% CI) – 24 months | | 30.2% (15-62) |
| QoL | | Not reported |

*Abbreviations: CI … confidence interval, CRFS … chronic graft versus host disease-free and relapse-free survival, FAS … full analysis set, GRFS … graft versus host disease-free and relapse-free survival, GVHD … graft versus host disease, n … number, NR … not reached, NRM … non-relapse mortality, OS … overall survival, PFS … progression-free survival, QoL … quality of life*

[4] Reported as efficacy outcome.

### 4.3.2 Safety outcomes

The safety-related endpoints for the SAS are detailed below. All AE (grade ≥3) and adverse drug reactions (grade ≥3) after Zemcelpro administration (frequency ≥5%) are presented in the Appendix, Chapter 4.

#### Adverse events and serious adverse events

Nearly all patients (n=115/116, 99.1%) of the SAS population experienced at least one AE of any grade. The AEs were presented either by grade or by severity. Additionally, the acute chronic GVHD were reported using either CTCAE or National Institutes of Health (NIH) criteria.

99,1 % der Pat.: mind. 1 AE

The most frequently reported AEs grade ≥3 (≥5%) suspected to be related to Zemcelpro were lymphopenia (46.6%), anaemia (44.0%), neutropenia (35.3%), thrombocytopaenia (31.9%), acute GVHD (22.4%), leukopenia (20.3%), hypogammaglobulinaemia (18.1%), febrile neutropenia (15.5%), hypertension (12.9%), engraftment syndrome (11.2%), and pneumonia (11.2%). An overview is provided in the Appendix Chapter 4.

häufigste AE (Grad ≥3): Lymphopenie (46,6 %), Anämie (44,0 %) & Neutropenie (35,3 %)

Additionally, 61 patients (52.6%) reported at least one SAE [33]. The most frequently reported SAEs were acute GVHD (11.2%), pneumonia (5.2%), sepsis (5.2%) and transplant failures (5.2%) [2].

häufigste SAE: akuter GVHD (11,2%)

#### Adverse events of special interest

AEs of special interest included acute and chronic GVHD of all grades and occurred in 66.4% and 14.7% of patients respectively. Other AEs of special interest are presented in Table 4-7.

akuter & chronischer GVHD (alle Grade): 66,4 % bzw. 14,7 % der Pat.

*Table 4-7: AEs of special interest [2]*

| Adverse events (AEs) n (%) | | SAS (n=116) | | | |
|---|---|---|---|---|---|
| Grade | | 3 | 4 | 5 | All grades |
| Infections | | 61 (60.4) | 6 (5.9) | 7 (6.9) | 87 (75.0) |
| Engraftment syndrome | | 11 (9.5) | 2 (1.7) | 0 | 13 (11.2) |
| Cryptogenic organising pneumonia | | 0 | 3 (2.6) | 1 (0.9) | 4 (3.4) |
| Pneumonitis | | 1 (0.9) | 0 | 0 | 1 (0.9) |
| Pulmonary alveolar haemorrhage | | 0 | 1 (0.9) | 2 (1.7) | 3 (2.6) |
| Post-transplant lymphoproliferative disorder | | 1 (0.9) | 2 (1.7) | 0 | 3 (2.6) |
| GVHD | | | | | |
| Acute GVHD | Grade | 2 | 3 | 4 | All grades |
| | N (%) | 62 (53.4) | 14 (12.1) | 1 (0.9) | 77 (66.4) |
| Chronic GVHD | Grade | Mild | Moderate | Severe | All grades |
| | N (%) | 10 (8.6) | 7 (6.0) | 0 | 17 (14.7) |

*Abbreviations: AE … adverse event, GVHD … graft-versus-host-disease, n … number, SAS … safety analysis set*
*Notes: GVHD events were graded according to the NIH consensual criteria.*

### Deaths

Among the SAS population, 42 deaths (36.2%) were reported during a median study follow-up of 22.49 months (range: 0.89-48.4 months). The most frequent cause of death was disease progression or relapse (n=26), followed by non-relapse-related events (n=15). One additional death from pneumonia occurred around one year after study discontinuation because of transplant failure [2]. An overview of non-relapse-related deaths is presented in the Appendix, Chapter 4.

42 Todesfälle in der SAS-Population → hauptsächlich durch Krankheitsprogression/ Rezidiv

## 4.4 Quality of the evidence

### 4.4.1 Risk of bias

In accordance with the methodological standards for single-arm trials issued by the Member State Coordination Group on HTA (HTACG), no formal risk of bias (RoB) tool was used for ECT-001-CB.001, ECT-001-CB.002, ECT-001-CB.003, ECT-001-CB.004 and ECT-001-CB.007 studies. The Guidance on Validity of Clinical Studies states that uncontrolled trials are inherently limited in value for evaluating relative effectiveness and therefore do not require formal RoB assessment using standardised instruments [28].

keine formale RoB-Bewertung gemäß HTACG-Standards

In general, the single-arm, open-label design of the studies reflects the challenges posed by the small patient population and the disease severity of adult patients requiring allo-HSCT, and it represents a major limitation. Although not all haematological malignancies were covered in the efficacy analysis, the EMA deemed this acceptable because of the focus on the transplant procedure and justified extrapolating findings from the Canadian to the European population. The EMA further noted that all time-related endpoints were defined as time from infusion, which does not take into account the duration of the production of Zemcelpro [2].

Limitationen:
... einarmiges Design aufgrund kleiner Pat.-Population,

... Endpunktdefinition ohne Berücksichtigung der Produktionsdauer

Additionally, long-term follow-up data are missing, warranting a comprehensive assessment of sustained efficacy and late-onset toxicities [6], which is expected to be delivered as part of specific obligations for the conditional marketing authorisation [2]. Also, patient-reported outcomes, including QoL measures, were absent in all clinical studies.

...keine Daten zu Langzeit-Follow-up & QoL

### 4.4.2 Statistical analysis and inconsistencies

The efficacy analysis was based on the pivotal FAS comprising the ECT-001-CB.002 and ECT-001-CB.004 studies, whereas the safety analysis was based on the SAS, including the ECT-001-CB.001, ECT-001-CB.002, ECT-001-CB.003, ECT-001-CB.004 and ECT-001-CB.007 studies. The following chapter outlines the statistical analyses and inconsistencies across these studies.

statistische Analysen der für Wirksamkeit (pivotal FAS) & Sicherheit (SAS) herangezogenen Studien

### ECT-001-CB.001

In the ECT-001-CB.001 study [32], several methodological concerns were identified. The sample size was extended from 15 to 27 patients without a disclosed rationale, compromising transparency. While feasibility evaluations were conducted in all patients, primary and secondary endpoints were assessed in the per-protocol population rather than using intention-to-treat (ITT) analysis, which would have been more appropriate to avoid overestimating positive outcomes. Additionally, multiple statistical tests were performed on a heterogeneous patient population without correction for multiple comparisons, and post-hoc historical comparisons with transplant cohorts from the Canadian Hôpital Maisonneuve-Rosemont lacked pre-specification and matching criteria.

Stichprobenberechnung für n=15, erweitert auf n=27, post-hoc historische Vergleiche

### ECT-001-CB.002 and ECT-001-CB.004

For the ECT-001-CB.002 and ECT-001-CB.004 studies [33], no statistical analysis plan was published. However, a post-hoc pooled analysis of ECT-001-CB.002 and ECT-001-CB.004 (pivotal FAS) was conducted with no type I error control[5] and no pre-planning, which is a major issue. The EMA noted that with the methods used, some risks for resulting biases could be mitigated [2].

method. Limitationen: post-hoc Analyse ohne Matching, keine ITT-Analyse

### ECT-001-CB.003 and ECT-001-CB.007

For the ECT-001-CB.003 [35] and ECT-001-CB.007 studies [36], no statistical analysis plan was published; hence, no assessment, including potential methodological limitations, of the statistical analysis was possible.

keine statistischen Analysen für ECT-001-CB.003 & ECT-001-CB.007 verfügbar

## 4.5 Indirect treatment comparison

We have identified three indirect treatment comparison (ITC) studies and a single-arm study, including post-hoc analyses, comparing Zemcelpro with other types of allo-HSCT [32, 37-39].

3 indirekte Therapievergleiche & 1 einarmige Studie mit post-hoc-Analysen identifiziert

### 4.5.1 Description of studies

The study by Cohen et al. 2025 [37] was a retrospective cohort study comparing outcomes of the ECT-001-CB.001 study [32] to matched control cohorts from the European Society for Blood and Marrow Transplantation (EBMT) registry who received six different types of haematopoietic stem cell (HSC) sources: 1) unexpanded cord blood (CB), 2) peripheral blood (PB) from a 10/10 matched unrelated donor (MUD; UD), 3) BM from a 10/10 MUD, 4) 9/10 MUD, 5) T cell replete haploidentical (haplo) donor, and 6) HLA-matched sibling donor (MSD). EBMT controls were matched to Zemcelpro patients using exact and propensity score methods. The matching criteria included

Cohen et al. (2025): retrospektive Kohortenstudie mit EBMT-Kontrollen

[5] Type I errors are also known as “false positives” and occur in statistical hypothesis testing when a true null hypothesis is incorrectly rejected [34].

prior allo-HSCT, disease status at transplant, age, Karnofsky performance status and MA conditioning regimen.

Cohen et al. (2023): retrospektive gematchte Kohortenstudie mit CIBMTR-Kontrollen

Cohen et al. 2023 [38] performed an observational, retrospectively matched cohort study examining the long-term outcomes of allo-HSCT with either CB or PB in adults for haematologic malignancies. An independent matched-control analysis was conducted to compare outcomes of the ECT-001-CB.001 study [32] with two control cohorts from the Center for International Blood and Marrow Transplant Research (CIBMTR) research database: patients who received conventional single/double ≥ 4/6 HLA-matched CB, and those who underwent 8/8 MUD PB transplants. Matching used direct criteria (allo-HSCT number, malignancy type) and propensity scores based on age, previous allo-HSCT, comorbidity index, and performance status. The CIBMTR sought four CB and four PB controls per Zemcelpro patient using logistic regression-derived propensity scores.

Lagace et al. (2021): retrospektiver Vergleich, Fokus auf T-Zell-Wiederherstellung & Infektionsrate

The Lagace et al. 2021 study [39] retrospectively compared the Zemcelpro study (ECT-001-CB.001) with 12 patients who underwent transplantation with unexpanded CB (two patients received double CB, the rest single) following similar MA conditioning regimens at the same institution. This was a mechanistic study focusing on T cell reconstitution and infection rates. While sex, conditioning regimens, and cytomegalovirus status before transplant were similar between the cohorts, HLA matching was significantly higher in the Zemcelpro cohort.

Cohen et al. (2020): Vergleich der Zemcelpro-Kohorte mit anderen Transplantationen

Finally, in the Cohen 2020 study [32], post hoc analyses were conducted to compare outcomes for the Zemcelpro cohort with three cohorts transplanted at Hôpital Maisonneuve-Rosemont with HSCs from unexpanded CB, BM, or PB.

### 4.5.2 Results of the indirect treatment comparisons

Cohen et al. (2025): bei Zemcelpro u. a. kürzeres Neutrophilenengraftment

längeres GRFS & besseres PFS & OS

In the study by Cohen et al. (2025) [37], Zemcelpro demonstrated significantly shorter median time to neutrophil engraftment versus unexpanded CB. Compared to other stem cell sources, Zemcelpro showed a significantly shorter time to neutrophil engraftment versus MUD BM, but platelet engraftment was significantly delayed compared to MUD PB, MUD BM, UD, haplo, and MSD. The rate of severe or extensive chronic GVHD was lower in the Zemcelpro group versus MUD PB, MUD BM, and MSD. Although acute GVHD grade II–IV rate was higher in the Zemcelpro group compared to MUD BM, UD, haplo, and MSD, GRFS was longer for Zemcelpro versus MUD PB, UD, haplo, and MSD. Additionally, PFS and OS were superior with Zemcelpro compared to the haplo group. For detailed results, see Chapter 4.5 in the Appendix. An overview of the main results is presented in Table 4-8.

Cohen et al. (2023): signifikante Vorteile bei Überlebensendpunkten vs. Kontrollen: u. a. NRM (1 & 2 Jahre), PFS (2 Jahre), OS (1 Jahr) & GRFS (1 & 2 Jahre)

In the study by Cohen et al. (2023) [38], compared to CB, Zemcelpro demonstrated statistically significant improvements in NRM at one and two years, PFS at two years, OS at one year and GRFS at one and two years, and time to neutrophil engraftment. However, platelet recovery was statistically significantly slower with Zemcelpro versus CB. Comparison with MUD PB has shown a statistically significant difference favouring Zemcelpro in NRM at one and two years, PFS after two years, GRFS after one and two years and acute and chronic GVHD. Median neutrophil engraftment was slower, while median platelet recovery was faster in the Zemcelpro cohort versus MUD PB. See detailed results in Chapter 4.5 in the Appendix.

*Table 4-8: Overview of the results of Zemcelpro ITC with EBMT matched analysis [2]*

| Comparison of outcomes | Study 001[4] (n=22) | CBU (n=36) | 9/10 MMUD (n=62) | Haplo (n=59) |
|---|---|---|---|---|
| Effectiveness | | | | |
| OS[1] HR [95% CI] | 85.3% | 0.83 [0.32-2.15] | 0.48 [0.18-1.3] | 0.41 [0.19-0.92]* |
| NRM[1] HR [95% CI] | 4.4% | 0.22 [0.02-2.08] | 0.16 [0.02-1.19] | 0.13 [0.02-1.06] |
| PFS[1] HR [95% CI] | 72.3% | 0.74 [0.29-1.91] | 0.39 [0.14-1.07] | 0.42 [0.19-0.95]* |
| % neutrophil engraftment at D+42 | 100% | 91.7%* p<0.001 | 98.4% p=0.98 | 93.2% p=0.14 |
| Median time to neutrophil recovery (days) | 18 d | 22 d* p<0.001 | 17 d p=0.98 | 19 d p=0.09 |
| Median time to platelet recovery (days) | 43 d | 40 d p=0.41 | 16.5 d* p<0.0001 | 26 d* p<0.0001 |
| Safety | | | | |
| Grade III-IV acute GVHD[2] | 8.9% | 17.1% p=0.52 | 17% p=0.41 | 8.9% p=0.6 |
| Mod. to sev. chronic GVHD[3] | 0% | 16.3% p=0.07 | 7.3% p=0.21 | 12.5% p=0.10 |
| GRFS[1] HR [95% CI] | 63.6% | 0.55 [0.23-1.31] p=0.18 | 0.40 [0.16-0.98]* p=0.046 | 0.45 [0.2-1]* p=0.049 |

*Abbreviations: CBU … cord blood unit, CI … confidence interval, D+42 … day 42 post-transplant, EBMT … European Society for Blood and Marrow Transplantation, GRFS … graft-versus-host disease-free, relapse-free survival, GVHD … graft-versus-host disease, Haplo … haploidentical donor, HR … hazard ratio, Mod. to sev … moderate to severe, n … number, NRM … non-relapse mortality, OS … overall survival, PB … peripheral blood, PFS … progression-free survival, 9/10 MMUD … 9/10 HLA-mismatched unrelated donor*

*Notes:*

* *Statistical significance: green = advantage for Zemcelpro group; red = advantage for control group*

[1] *HR calculated over a 2-year follow-up period.*

[2] *Endpoints reported at 180 days. P-value are Gray test. Cox model (with cluster) cannot be used as there are not enough events in the ECT-001-CB group.*

[3] *Endpoints reported at 2 years. P-value are Gray test. Cox model (with cluster) cannot be used as there are not enough events in the ECT-001-CB group.*

[4] *Results for Study 001 presented in this table were derived from ECT-001-CB.001 CSR.*

Regressionsanalyse zeigt Reduktion NRM & GvHD bei Zemcelpro vs. Kontrollen

In addition, the regression analysis indicated that Zemcelpro cohort showed lower risk of NRM versus CB controls and reduced risk of GRFS events versus both CB and MUD PB controls (see Table 4-9).

*Table 4-9: Marginal cox regression analysis for Zemcelpro vs. CB and MUD PB controls in the study by Cohen et al., 2023 [38]*

| Outcomes Zemcelpro vs CB controls | HR (95% CI) | P-value |
|---|---|---|
| NRM | 0.13 (0.02-0.89) | 0.04 |
| GRFS | 0.37 (0.17-0.84) | 0.02 |
| **Outcomes Zemcelpro vs MUD PB controls** | **HR (95% CI)** | **P-value** |
| NRM | 0.20 (0.04-1.10) | 0.06 |
| GRFS | 0.27 (0.12-0.60) | <0.01 |

*Abbreviations: CB … cord blood, CI … confidence interval, GRFS … graft versus host disease-free and relapse-free survival, HR … hazard ratio, MUD … matched unrelated donor, NRM … non-relapse mortality, PB … peripheral blood*

In the Lagace et al. (2021) study [39], the time to engraftment of 500 neutrophils was similar between the two cohorts (17 and 20 days for the Zemcelpro and unexpanded CB cohorts, respectively, p=0.94). Both cohorts showed similar rates of acute and chronic GVHD. The median time to immunosuppression withdrawal was shorter in the Zemcelpro cohort than in the unexpanded CB group (5.9 vs 7.1, respectively; p=0.039). The Zemcelpro cohort had a lower frequency of severe infections at year 1 post-transplant, especially for grade 2-3 bacterial and viral infections, compared to the unexpanded CB cohorts.

Lagace et al. (2021): Zemcelpro vs. Kontrollen → u. a. vergleichbare akuter/chronischer GVHD,

weniger schwere Infektionen

Furthermore, post hoc analyses by Cohen et al. (2020) showed that the median time to neutrophil engraftment was significantly shorter in patients treated with Zemcelpro than in those receiving PB (p<0.001). A shorter time to neutrophil engraftment was also observed compared with BM (p=0.056) and unexpanded CB (p=0.092), although without statistical significance. For platelet recovery, the median time for Zemcelpro (42 days) was similar to that observed with unexpanded CB (40.5 days) but longer than that observed with BM (26.5 days) and PB (24 days) [32].

Cohen et al. (2020): Zemcelpro vs. Kontrollen → u. a. kürzere mediane Zeit zu Neutrophilenengraftment, vergleichbare mediane Zeit zu Thrombozytenengraftmen t

### 4.5.3 Limitations of the indirect treatment comparisons

The four retrospective indirect comparative analyses of Zemcelpro from the same ECT-001-CB.001 study share fundamental methodological limitations that undermine the strength of evidence for clinical superiority over alternative graft sources.

method. Limitationen der indirekten Therapievergleiche:

The most critical limitation is the sample size, since all comparisons included a low number of Zemcelpro patients matched to various control cohorts, with key outcomes represented by a limited number of events. Furthermore, there were multiple tests across numerous endpoints and multiple control groups without appropriate statistical correction, substantially inflating the risk of false findings.

... kleine Stichprobe,

... mehrere statistische Tests ohne Adjustierung

Moreover, the study designs introduce systematic bias by comparing prospective trials against retrospective registry or institutional data collected across diverse centres with variable practices, which cannot be overcome through propensity score matching. Substantial missing data in control groups and differential data collection methods introduce additional bias that remains unaddressed in the sensitivity analyses.

... systemat. Bias durch Vergleich von prospektiven vs. retrospektiven Daten

The confounding due to differences in HLA matching is inadequately controlled, which is concerning given that the Zemcelpro cohort achieved superior HLA matching compared to control cohorts.

... unkontrollierte Verzerrung durch HLA-Matching-Unterschiede

Most importantly, the findings are inconsistent. When data from different registries were analysed, some comparisons showed statistically significant results while others did not. This suggests that the findings may be artefacts of control selection rather than robust treatment effects. The repeated re-analysis and reporting of the same Zemcelpro cohort may overstate the level of supporting evidence, as the conclusions are based on a single, small, uncontrolled case series rather than independent datasets.

... widersprüchliche Ergebnisse deuten auf Artefakte statt echte therapeut. Effekte hin

# 5 Price comparisons, treatment costs and budget impact

The Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) found no official price information for Zemcelpro in the countries surveyed (14 EU member states, Norway and the United Kingdom (UK).

keine Preise zu Zemcelpro in Europa bekannt

Also, the marketing authorisation holder (MAH) did not submit any price proposal for Austria.

Unternehmen übermittelte keine Preisinformationen

## 5.1 Pharmacoeconomic model(s)

### 5.1.1 Submitted pharmacoeconomic model

The MAH did not submit a pharmacoeconomic model for the introduction of Zemcelpro in Austria.

kein gesök. Modell zu Zemcelpro für AT eingereicht

### 5.1.2 Published economic evaluations

The systematic literature search identified no published economic evaluations based on pharmacoeconomic models. Similarly, additional manual searches yielded no results.

auch keine publizierten gesök. Analysen zu Zemcelpro identifiziert

## 5.2 Budget impact analysis

### 5.2.1 Budget impact analysis submitted by the manufacturer

The MAH did not submit a budget impact analysis of Zemcelpro for the Austrian market.

keine Budgetfolgenanalyse zu Zemcelpro eingereicht

### 5.2.2 Austrian cost analysis

#### Eligible population and per-patient costs

According to the approved EMA indication, Zemcelpro is the last-resort therapy for patients requiring an allogeneic haematopoietic stem cell transplantation (allo-HSCT) who lack access to any type of suitable donor (including double cord [2]), a situation expected to occur only very rarely in Austria.

EMA-Indikation: letzte Therapieoption, bei fehlendem geeignetem Spender

The population potentially eligible for Zemcelpro treatment in Austria is estimated to be equivalent to patients who, in current clinical practice, undergo allo-HSCT using unexpanded umbilical cord blood (CB) from unrelated donors due to the unavailability of a matched or haploidentical (haplo) donor [40]. Based on literature reviews cited in the European Public Assessment Report (EPAR), 10-15% of patients lack access to HLA-matched unrelated donors or haploidentical donors [2]. However, the last recorded allo-HSCT using unexpanded CBU in Austria was in 2019 [5]. Nevertheless, given its

Nabelschnurblut als Stammzellquelle in Ö in seltenen Fällen, insbesondere bei ethnischen Minderheiten

greater permissiveness to HLA disparity [40, 41], clinical experts confirmed that CB remains a valuable alternative transplant option for patients lacking other alternatives, especially coming from racial and ethnic minority groups that face a lower likelihood of finding a well-matched unrelated donor [42]. Such cases do arise in Austrian clinical practice, albeit rarely [6].

Considering the small eligible patient population for the assessed product, the following cost analysis provides per-patient and per-procedure estimates of direct medical costs associated with allo-HSCT using Zemcelpro and the main comparator, an unexpanded CBU. For contextualisation, costs of allo-HSCT using conventional haematopoietic stem cell (HSC) sources – peripheral blood (PB) or bone marrow (BM) – from alternative mismatched donors (i.e., haplo and mismatched unrelated donors [MMUD]) are also presented [41].

Analyse:
Kosten pro Patient:in & Prozedur: Zemcelpro vs. CB & PB/BM

## Direct medical costs of Zemcelpro treatment

The total direct medical cost of Zemcelpro treatment is composed of these crucial cost categories:

- The acquisition cost of Zemcelpro (including the purchase of the CBU and subsequent processing).
- Costs of the allo-HSCT procedure, comprising inpatient hospitalisation, as well as myeloablative conditioning and prophylactic and supportive therapy for prevention of transplant complications.
- Costs related to long-term follow-up.

direkte medizinische Kosten sollten Zemcelpro-Preis, Konditionierung, Prophylaxe, Hospitalisierung & Follow-up-Kosten umfassen

Below, the direct medical costs of Zemcelpro treatment are presented per category.

### Acquisition costs

Another similar allogeneic CB-based product, omidubicel, which uses nicotinamide to expand CB-derived HSC, has been approved in the US. Its wholesale acquisition cost of $338,000 (€290,000, converted on 6 October 2025, using the European Central Bank's official exchange rate and rounded to the nearest thousand) serves as a placeholder price for Zemcelpro [43, 44].[6]

Platzhalterpreis:
$ 338.000 (€ 290.000) basierend auf US-Produkt Omidubicel

### Additional costs related to the allo-HSCT procedure

*Myeloablative conditioning (lymphodepleting chemotherapy)*

Patients treated with Zemcelpro must be pre-treated with lymphodepleting conditioning. Selected regimen should be of high or intermediate intensity, i.e., with a transplant conditioning intensity score (TCI) of 2.5 and above [1]. In study ECT-001-CB.001, two conditioning regimens were permitted [32]:

Konditionierung:
hohe/mittlere Intensität (TCI ≥2,5),
2 Regime zugelassen

1. Myeloablative (MA) regimen denoted as 12-13.2 Gy TBI consisting of cyclophosphamide 120 mg/kg, fludarabine 75 mg/m$^2$, and 12-13.2 Gy total body irradiation (TBI); administered to patients aged below 50 years (36% of patients).
2. Functionally myeloablative regimen denoted as Thiotepa-4GyTBI, consisting of cyclophosphamide 50 mg/kg, fludarabine 150 mg/m$^2$, thiotepa 10 mg/kg and 4 Gy TBI; administered to patients aged 50 and older and those contraindicated/unfit for TBI (64% of patients).

[6] There was no price submission by the MAH by the cut-off date of 1 October 2025.

*Prophylactic and supportive therapy*

prophylaktische Therapien:

All patients should receive prophylactic and supportive therapy for the prevention of transplant complications [1].

**1. Graft-versus-host disease prophylaxis**

GVHD-Prophylaxe: Tacrolimus + MMF

Prophylaxis of GVHD is recommended with a combination of tacrolimus and mycophenolate mofetil (MMF), based on the evidence from Zemcelpro clinical trials. The recommended administration is as follows [32]:

- Start of therapy: Day –3 before the transplant.
- Tacrolimus is administered at a full dose of 0.03 mg/kg intravenously daily until day +100; after that, in the absence of GVHD, the dose should be tapered by 10% per week (approximately) and discontinued by day +180.
- MMF is administered at a dose of 15 mg/kg intravenously every 8 hours until day +35; it is discontinued without taper.

**2. Supportive therapy**

G-CSF gegen Neutropenie

In the immediate post-transplant period, administration of granulocyte colony-stimulating factor (G-CSF) is recommended to minimise the risk of neutropenia and infection. The dosage is 5 µg/kg/day, starting 1-3 days post-transplant and continuing until the neutrophil count reaches 1,000 per microliter of blood.

unterstützende Therapie (SoC): Antiinfektiva, Transfusionen, Impfungen, Prämedikation

Patients treated with Zemcelpro also receive antibacterial, antifungal, antiviral, and anti-parasite prophylaxis, transfusional support, and post-transplant vaccination, as per the respective study protocols, as well as premedication for infusion-related reactions, including antipyretics, histamine antagonists, and corticosteroids [33]. These measures are part of the standard of care (SoC) for allo-HSCT and shall be administered in accordance with local institutional guidelines.

*Initial hospitalisation*

initiale Hospitalisierung: median 34 Tage (16-130), 7 % ICU (median 12 Tage)

All patients are hospitalised at the start of the conditioning regimen. The median duration of the initial hospitalisation in the Safety Analysis Set (SAS; hospitalisation data available for 83 patients[7]) was 34 days, ranging from 16 to 130 days. A total of 4/55 (7.1%) patients required a stay at the intensive care unit (ICU) during initial hospitalisation, with a median duration of 12 days [2].

LKF-Pauschale für allo-HSZT: € 182.746 für 90 Tage, inkl. Konditionierung, Prophylaxe & initiale Hospitalisierung

According to the performance and diagnosis-related groups (Leistungsorientierte Krankenantaltenfinanzierung, LKF) catalogue, the code MEL22.09 comprises costs for an allo-HSCT procedure with stem cells from an unrelated donor and high-dose/aplastic conditioning therapy. This code was selected for the cost analysis to account for additional treatments provided with standard allo-HSCT, including lymphodepleting conditioning, prophylactic and supportive care, and initial hospitalisation. The average flat rate for this code, assuming a maximum 90-day hospital stay, is €182,746.

Behandlung von GVHD im Krankenhaus: zusätzlich € 43.979 pauschal

In addition, as the acute GVHD of grade II–IV was reported in 77/116 (66.4%) of SAS patients [2], the cost of GVHD treatment with specific medications (antilymphocyte globulin/monoclonal antibodies), covered by the LKF code

[7] Of all participants in the SAS population (n=116), 83 participants provided data on hospitalisation, and data were not available for the remainder (i.e. for Study 003, n=18).

MEL22.21 with an average flat rate of €43,979, for hospitalisation ranging between 15 and 60 days, to the total cost.

Thus, the total direct medical cost of the allo-HSCT procedure amounts to €226,725.

Gesamtkosten allo-HSCT-Prozedur: € 226.725

### Long-term follow-up costs

Long-term follow-up after allo-HSCT is extensive, as there is a broad spectrum of long-term complications, ranging from organ-specific complications and infections to secondary malignancies. For example, it is estimated that 50-70% of patients treated with allo-HSCT develop chronic GVHD within ten years of treatment [45]. Depending on their severity, the long-term complications may necessitate additional hospitalisation. In Zemcelpro trials, 36/83 (43.4%) of the SAS with available hospitalisation data required subsequent re-hospitalisation. The mean (±SD) duration of the subsequent hospitalisations was 19.0 (±56.99) days. Of these, 27 patients were re-hospitalised within the first 100 days post-transplant, with a mean of 13.1 (±20.33) inpatient days [33]. Additionally, it is recommended that all patients receive individualised, risk-adapted, and multidisciplinary follow-up care, so that any complications that arise can be correctly diagnosed and appropriately treated [45]. Given the individualised nature of the follow-up procedures and the missing cost data, only the cost of subsequent re-hospitalisation is considered in our cost analysis.

Langzeit-Follow-up-Kosten nicht in Primäranalyse berücksichtigt

43 % Re-Hospitalisierung (Ø 19 Tage) – Kosten in Szenarioanalyse inkludiert

Based on the presented results, the overall direct medical costs of allo-HSCT procedure using Zemcelpro (without follow-up costs) amount to approximately €516,725 per patient (see Table 5-1).

Gesamtkosten Zemcelpro (ohne Follow-up-Kosten): ~€ 516.725 pro Patient:in

*Table 5-1: Cost of Zemcelpro allo-HSCT compared to allo-HSCT using unexpanded CBU and unrelated donor allo-HSCT using conventional graft sources (per patient and procedure)*

| Cost categories | Zemcelpro | Unexpanded CBU (main comparator) | Stem cells from PB or BM graft (unrelated donor) | Cost source |
|---|---|---|---|---|
| CBU acquisition | €290,000[8] | €75,334 (double CB) | - | Placeholder price [43, 44] |
| Costs related to allo-HSCT procedure | €226,725 | €237,070 | €236,094 | |
| Stem cell extraction from the source | included in the price | €10,345 | €10,345 | LKF data: MEL22.11, FB A, BDU: 10, BDO: 10 |
| Allo-HSCT procedure | €182,746 | €182,746 | €181,770 | LKF data: MEL22.09, average FB: A-D, BDU: 90, BDO: 90 |
| AEs: GVHD treatment | €43,979 | €43,979 | €43,979 | LKF data: MEL22.21, average FB: A-B, range of BD: 15-60 |
| Total direct medical costs of treatment | €516,725 | €312,404 | €236,094 | |

*Abbreviation: AE … adverse event, allo-HSCT … allogenic stem cell transplantation, BM … bone marrow, BD … Belegsdauer (duration inpatient stay), BDO … Belegsdauerobergrenze (maximal duration inpatient stay), BDU … Belegsdaueruntergrenze (minimal duration inpatient stay), CBU … cord blood unit, GVHD … Graft-versus-Host-Disease, LKF … Leistungsorientierte Krankenanstaltenfinanzierung (procedure and diagnosis-related group), MEL … Medizinische Einzelleistung (individual medical service), FB … Fallpauschale (flat rate), PB … peripheral blood*

[8] There was no price submission by the MAH by the cut-off date of 1 October 2025.

## Costs for the standard of care

### Standard allo-HSCT with unexpanded stem cells from cord blood

Kosten für allo-HSZT mit CBU (ohne Follow-up-Kosten): € 312.404

From a clinical perspective, the allo-HSCT procedure with Zemcelpro does not differ from standard CB transplantation, except for the additional *ex vivo* expansion of umbilical CB cells through the MAH. From a cost perspective, the CBU used for allo-HSCT is purchased from a CB bank, which stores the matching CBU selected by the clinicians. According to historical purchase data (year 2017/18), the average acquisition cost of unexpanded CBU used for Austrian patients was €37,667. As confirmed by clinical experts, for an adequate HSC dose, a double CBU is usually needed for adult patients. Therefore, the estimated cost of two CBUs was considered in the primary cost analysis. Further costs in a standard CB transplant arise from the need to extract stem cells from the CBU, corresponding to LKF code MEL22.11, with a flat rate of €10,345 per extraction. The resulting total direct medical cost of the allo-HSCT using unexpanded CB (without follow-up costs) is approximately €312,404 (see Table 5-1).

### Other alternative mismatched donors: allo-HSCT with stem cells from peripheral blood or bone marrow

direkte medizinische Kosten für PB/BM-Transplantation (ohne Follow-up-Kosten): € 236,094

The LKF coding does not differentiate the costs of allo-HSCT procedures by degree of HLA matching or graft source, but rather by conditioning regimen intensity and whether the donor is related or unrelated. Consequently, the costs of allo-HSCT procedures using stem cells from the PB or BM, which are the primary sources of HSC in Austria, do not differ from those of unexpanded CB allo-HSCTs. However, as patients are also allowed to receive reduced-intensity conditioning regimens, the average flat rate is slightly lower (€181,770). After adding the costs of the stem cell extraction procedure and eventual GVHD treatment, the total direct medical cost of allo-HSCT from an unrelated donor using PB or BM (without follow-up costs) amounts to an average of €236,094 (see Table 5-1).

## Scenario analysis

Szenarioanalyse für Zemcelpro-Kosten: Re-Hospitalisation (Ø 19 Tage, 13 Tage <100 Tage post-allo-HSZT) + € 50.730

In the scenario analysis, further costs arising from the need for subsequent hospitalisation were added, applying the mean duration of stay reported for the SAS population (43.4%) from Zemcelpro trials with available hospitalisation data, i.e., 19 days (13 days within the first 100 days post-transplant) [2]. The necessity for re-hospitalisation would increase the direct medical costs of Zemcelpro allo-HSCT by €50,730 (see Table 5-2).

*Table 5-2: Cost of Zemcelpro allo-HSCT per patient, including re-hospitalisation costs*

| Cost categories | Zemcelpro |
|---|---|
| CBU acquisition | €290,000 |
| Stem cell extraction from the source | included in the price |
| Allo-HSCT procedure | €182,746 |
| AEs: GVHD treatment | €43,979 |
| Subsequent re-hospitalisation | €50,730 |
| Total direct medical costs of treatment | €567,455 |

*Abbreviations: AE … adverse event, allo-HSCT … allogenic stem cell transplantation, CBU … cord blood unit, GVHD … Graft-versus-Host-Disease*

## Comparison of direct medical costs

Overall, the acquisition cost of Zemcelpro is essentially an additional cost item added to the average cost of a standard allo-HSCT procedure with an unrelated donor allograft. Consequently, allo-HSCT using Zemcelpro is associated with substantially higher direct medical costs, costing an estimated €204,321 more than unexpanded CB allo-HSCT.

Zemcelpro: + € 279.655 vs. Standard-CB-allo-HSZT

## Limitations

The presented cost analysis is subject to several limitations, primarily attributable to the uncertainties in Austrian costing data and the unavailability of detailed trial data on resource use.

Limitationen der Kostenanalyse

Firstly, there is uncertainty regarding the exact composition of the LKF code MEL22.09, which was used to account for the costs of the allo-HSCT procedure, including hospitalisation and myeloablative conditioning. On the one hand, uncertainty about ICU stay inclusion could lead to additional costs. On the other hand, the code accounts for the initial hospitalisation lasting up to 90 days. However, according to the Austrian clinical expert's experience in clinical practice, only very few patients require such an extended hospitalisation [46]. Hence, the cost of the allo-HSCT procedure was potentially overestimated in the cost analysis. In addition, according to clinical experts, the costs of the allo-HSCT with CBU might be higher compared to the allo-HSCT costs with PB or BM due to a longer hospital stay. Furthermore, GVHD treatment costs were applied uniformly across all treatments, although GVHD severity and duration can vary considerably.

potenzielle Überschätzung der allo-HSZT-Kosten aufgrund LKF-Pauschale

GVHD-Behandlungskosten pauschal angesetzt, trotz variabler Schweregrade und Dauer

Secondly, excluding multiple cost components might have affected the total direct medical costs. Costs of long-term post-transplant management were excluded due to the absence of long-term follow-up data and unified costing data for minor procedures such as diagnostics; consequently, the only follow-up costs considered arise from the need for re-hospitalisation, which was included in the scenario analysis. Considering specifically the costs for the main comparator, unexpanded CB allo-HSCT, the total costs might differ because the applied CBU acquisition costs were an average of historical billing data (2017/2018) [47]. Finally, standardised and widely accepted data on indirect healthcare costs are unavailable in Austria. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs.

ausgeschlossene Kostenkomponenten, z. B. Follow-up-Kosten, für kleinere Prozeduren

Preisschätzung für CBU-Einheit von 2017/2018

keine indirekten Kosten berücksichtigt

# 6 Extended perspectives

In the following chapter, relevant aspects for stakeholders are outlined, including structural and organisational requirements, current patient perspectives, as well as ethical and social considerations.

## 6.1 Stakeholder perspectives

keine Transplantation von Nabelschnurblut in Ö in den letzten Jahren

mögliche Zunahme der Patient:innenzahl durch ethnische Diversität durch Migration

As mentioned in previous chapters, allogeneic haematopoietic stem cell transplantation (allo-HSCT) with cord blood (CB) has not been utilised in Austria within the last few years. However, as migration increases population diversity, Zemcelpro may become more important for patients for whom no other type of suitable donor source can be found [6]. Healthcare providers consulted by the European Medicines Agency (EMA) estimated that the likelihood of finding an HLA-compatible unrelated donor (UD) in international registries for the Caucasian population is approximately 80%. In contrast, this rate is significantly lower in other ethnic populations [2]. This disparity must be factored into stakeholders' projections of future patient numbers, given ongoing migration patterns.

### Organisational aspects

Guideline der OeGHO: 4 Schritte der allo-HSZT

According to the guideline for SCTs by the Austrian Society for Haematology and Medical Oncology (Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie, OeGHO [48], the following five aspects need to be considered concerning the process of transferring stem cells (detailed description in Chapter 6 of the Appendix):

**1. Process and timeline for Zemcelpro administration**

Vorbereitung & Dauer ähnlich wie bei konventioneller allo-HSZT

The administration of Zemcelpro involves several steps, which are described and illustrated in detail in Chapter 1. The period from selecting the cord blood unit (CBU) to delivery at the transplant centre is approximately 45 days [49]. This is comparable to the duration of the process involving an UD, which clinical experts estimate at approximately five weeks [6].

**2. Manufacturing and logistics**

finale Selektion der CBU durch Transplantations-zentrum

The process of manufacturing and shipping Zemcelpro is complex. The selection of the erythrodepleted CBU for expansion is performed by the prescriber from a short list pre-identified by the manufacturer in accordance with the minimum requirements for human leukocyte antigen (HLA) matching and cell dose [49, 50]. Since the polymorphism of the classical HLA genes represents the most significant barrier among the factors influencing the outcome of allo-HSCT [51], matching for at least 4/6 HLA is recommended, with a target of 6/8 HLA matches [50]. Table 6-1 compares HLA matching and cell dose requirements for different CB transplantation approaches.

*Table 6-1: Comparison of HLA matching and cell dose between unexpanded CBU and Zemcelpro*

| | HLA matching | Cell dose |
|---|---|---|
| Single CBU [24] | minimum: 4/6 match (HLA-A and -B antigen, -DRB1 allele) and minimum 4/8 match (HLA-A, -B, -C, -DRB1 allele) | TNC >2.5 x 107/kg and CD34+ >1.5 x 105/kg |
| Double CBU [24] | | Each unit: TNC >1.5 x 107/kg and CD34+ >1.0 x 105/kg |
| Zemcelpro [1] | 4 of 6 antigens (HLA-A, -B, -DRB1 alleles), target matching (6 out of 8 HLA matching with high resolution typing) | 0.4 to 7.5 x 106 viable CD34+ cells/kg for dorocubicel and ≥0.52 x 106 viable CD3+ cells/kg for the unexpanded CD34– cell component |

*Abbreviations: CBU … cord blood unit, HLA … human leukocyte antigen, TNC … total nucleated cell*

Herstellung in Kanada → Versand → Transplantation in Ö

Following selection, the manufacturer purchases the CBU and produces Zemcelpro at a Good Manufacturing Practice (GMP)-approved site in Montréal, Canada. The manufacturer reports a success rate of approximately 97% for Zemcelpro, with failures attributed to the CBU rather than the process itself. Afterwards, the manufacturer performs quality assessment and quality control, and the finished product is shipped to Europe. Upon importation, Zemcelpro is received and released by a qualified person (an employee of Cordex Biologic International) before being sent to the transplant centre [49].

personelle & strukturelle Ressourcen müssen mobilisiert werden

The transplant centre is responsible for the myeloablative (MA) conditioning, administering the Zemcelpro infusion, and providing care [49]. Regarding the implementation of this new therapy in Austria and the associated organisational requirements, the respective responsibilities must be addressed [6]. However, it must be assumed that both staffing and structural resources are necessary for the efficient and safe administration of Zemcelpro and for ensuring the quality of the process.

### 3. Clinical practice requirements

laut Expert:innen kein sign. Unterschied im Ablauf in der klin. Praxis

Regarding the required previous physical examinations, pre-treatment MA conditioning, prophylactic and supportive therapy to prevent transplant complications, pre-medication, and hospitalisation duration, there is no significant difference compared to the standard procedure of allo-HSCT, according to Austrian clinical experts [6].

### 4. Infrastructure and expertise requirements

Behandlung in einem der 5 österr. Zentren für allo-HSZT

Zemcelpro must be administered in a qualified transplant centre with expertise in allo-HSCT by a physician with experience in the treatment of haematologic malignancies [50]. In Austria, there are five centres performing allo-HSCTs, as shown in Figure 6-1. The locations of the allogeneic transplant centres can be found in the transplantation annual report [5].

Pflege-Empfehlungen der ERQCC-Expertengruppe

Recommendations for the organisation of care in patients with haematological malignancies by the European Cancer Organisation Essential Requirements for Quality Cancer Care (ERQCC) experts group [52] can be found in the Appendix, Chapter 6.

### 5. Uncertainties concerning the implementation in Austrian

Unklarheiten besonders bzgl. Dauer der Hospitalisierung und Nebenwirkungen

From a stakeholders' perspective, several uncertainties remain regarding the implementation of Zemcelpro in Austria. Given the limited clinical data and small sample sizes, it is not possible to predict how the treatment will perform in real-world practice, particularly regarding the expected duration of hospitalisation. The same applies to the frequency and severity of adverse events (AEs) and serious adverse events (SAEs).

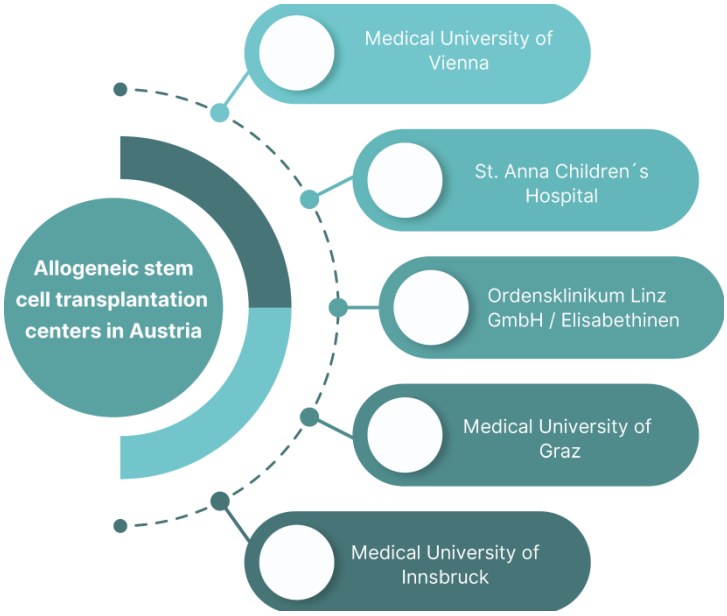



*Figure 6-1: Allogeneic transplantation centres in Austria [47]*

## 6.2 Patient's perspective

As part of this Health Technology Assessment (HTA), the patient's perspective was obtained through a questionnaire, as described in the methods section (Chapter 3). Two participants completed the patient questionnaire; both were representatives of a patient organisation. One participant is affected by a haematological disease, while the other participant has relatives who are affected. In their role as members of a patient organisation, both also provided insights from a collective perspective. The characteristics of the participants are described in Table 6-2.

2 Fragebögen wurden beantwortet: kollektive & persönliche Perspektive

*Table 6-2: Characteristics of participants of the structured patient questionnaires (n=2)*

| Patient characteristics | Total number of patients (n=2) |
|---|---|
| Sex | |
| Female | 1 |
| Male | 1 |
| Median age, years | 59.5 |
| Disease | |
| Multiple myeloma | 1 |
| Role | |
| Patient | 1 |
| Carer | 1 |
| Other | 0 |
| Member of a patient organisation | |
| Yes | 2 |

*Abbreviations: n…number*

Notably, including only two participants represents a limitation. Despite intensive efforts, no additional participants could be found. On the one hand, this could be due to the limited time available for identifying suitable persons. On the other hand, it should not be forgotten that those affected are going through a difficult phase in their lives and may not have the physical and mental resources to participate.

Limitation: es konnten nur 2 Personen befragt werden

## Patients' expectations and wishes regarding the new therapy

Based on published literature, maintaining quality of life (QoL) is a priority for patients with haematological malignancies, particularly as many live for extended periods with their disease. Preserving self-esteem and a sense of control, together with accurate assessments of physical and mental functioning, are therefore essential. In some instances, QoL considerations may even outweigh other clinical endpoints [52].

Erhalt der Lebensqualität als oberste Priorität

Moreover, a study conducted by Crawford et al. (2020) [53] analysed combined findings from a targeted literature review with patient-reported information shared on social media to further understand patient perspectives in haematologic cancers. The key points reported by patients included the perceived value of survival for achieving personal and/or life milestones, the emotional/psychological distress of their diagnosis, and the uncertainties about life expectancy and prognosis. Patients highlighted the importance of effective therapies capable of delaying disease progression and prolonging survival; however, these were considered in relation to their impact on QoL and potential disruption to daily life. Many patients voiced concerns about the limited availability of treatment options and their potential adverse events (AEs), and worried about the impact of their diagnosis and treatment on relationships and activities of daily living [53].

Schlüsselpunkte: Überleben, emotionaler/ psychologischer Aspekt der Diagnose, Unsicherheiten bzgl. Lebenserwartung & Prognose

These findings align with the expectations of the surveyed patients, who stated that they were not familiar with Zemcelpro but expressed a desire for a precise therapy administered under the supervision of medical experts. According to one patient, the new therapy should precisely and efficiently target the underlying disease, while minimising the risk of serious adverse events (SAEs) and AEs during administration, and, as far as possible, the likelihood of developing secondary conditions. The patient also emphasised the importance of having access to comprehensive information on efficacy, risks, and AEs of the treatment. Another important aspect mentioned was the possibility to consult a physician in case of questions or unclear symptoms. Overall, the main concerns regarding the new therapy were related to the infusion of foreign material into the body and the potential complications associated with it (e.g., graft versus host disease/GVHD). The second participant of the questionnaire was familiar with Zemcelpro and summarised the patients' expectations for a new therapy as "a cure as far as possible, combined with good tolerability and the prospect of returning to a normal life". Reported concerns included uncertainties regarding the medium- to long-term effectiveness and safety [54].

neue Therapie sollte möglichst Heilung bringen, bei guter Verträglichkeit

Information & Ansprechperson wichtig

Bedenken hinsichtlich Komplikationen

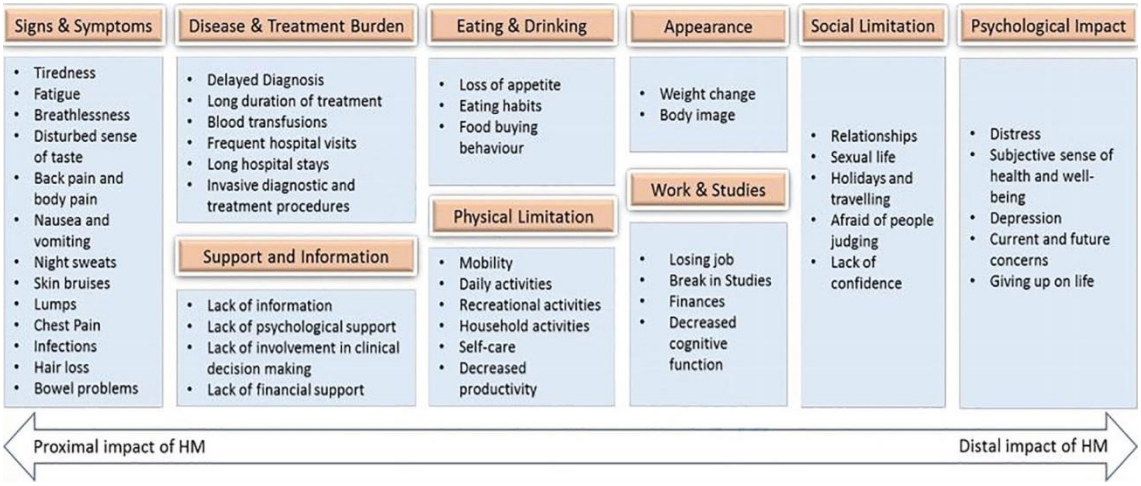
## 6.3 Further ethical and social aspects

### Impact of the disease and its treatment(s)

signifikante Auswirkung hämatol. maligner Erkrankungen auf Lebensqualität, Körperbild, berufliche Tätigkeit & finanzielle Situation

konzeptionelles Modell als Brücke zwischen Forschung & Praxis

Both haematological malignancies as well as their treatments have a significant impact on the health-related quality of life (HRQoL), particularly on issues such as body image, job role change and financial impact. Goswami et al. (2020) [55] identified HRQoL issues and symptoms in patients with haematological malignancies. Based on these data, they developed a conceptual framework showing relevant concepts, organised by type, with the proximal impact (i.e., areas directly impacted by the disease or the treatment) on the left and the distal impact (i.e., indirect and long-term effects of the disease and the treatment) on the right. The conceptual model, shown in Figure 6-2, may help healthcare providers successfully implement knowledge translation interventions in their practice. It can assist in gathering evidence on patients' HRQoL, identifying its proximal and distal impacts, and discussing tailored interventions with patients on an individual basis, acting as a bridge between research and practice [55].




*Abbreviations: HM … haematological malignancies; HRQoL … health-related quality of life*

*Figure 6-2: Conceptual model for impact on the health-related quality of life for patients with haematological malignancies [55]*

vielfältige Symptome durch Erkrankung & Therapie

The interviewed patient attributes their symptoms to the currently administered maintenance treatment, reporting bone pain, fatigue, increased susceptibility to infection, reduced libido, and occasional episodes of decreased performance and diarrhoea. Additionally, the other participant of the patient questionnaire mentioned symptoms such as weakness and a tendency to bleed [54].

### Social impact

psychische & soziale Herausforderungen bedürfen umfassender Unterstützung

In patients with haematological malignancies, psychological and social challenges are prevalent and require comprehensive support services [52, 55]. For instance, anxiety affects 45% of newly diagnosed lymphoma patients. Fear of recurrence, isolation, being a burden to others, and death are common. Distress disorder affects up to 27% of survivors and 44% of their partners, while

clinical depressive symptoms afflict 12% to 33% of patients with haematological malignancies. Notably, depressive symptoms at diagnosis have been linked to lower survival rates [52].

lebensbedrohliche Erkrankung „stellt das Leben der Pat. auf den Kopf"

This reflects the experiences described by the interviewed patients, who described the fear of recurrence, uncertainties about their own abilities, and the emotional challenges of coping with the reactions of their close family and friends. They also highlighted the importance of mindfulness and self-care. Additionally, they mentioned the impact the disease has on life planning and concerns about the future [54]. Published literature indicates that patients often set goals to deal with the uncertainty of their condition, with many focusing on their children or grandchildren [53]. Furthermore, one interviewed patient described how the disease "turns the patient's daily life upside down" due to the life-threatening nature and emphasised the significant emotional and physical burden experienced by patients and their relatives [54].

Ängste, Unsicherheiten

betrifft auch die Angehörigen

## Autonomy, justice and equity

Disparitäten im Zugang zu Behandlung: auch in Österreich

The treatment of haematological malignancies can be financially burdensome. On one hand, prolonged treatment periods and the use of novel, often expensive agents lead to reimbursement difficulties and unequal access to care [52]. According to Gribben et al. (2025) [52], disparities in access to treatment are particularly notable in Central and Eastern European nations. One interviewed patient highlighted regional disparities in patient care in Austria [54]. Such disparities are especially troubling given the recommendations by the ERQCC expert group, which outlines that fast and easy access to accurate diagnostic tests, clearly established referral pathways to specialised centres, centralised services, continuous monitoring of patient well-being; treatment strategies planned and agreed by a core multidisciplinary team; and involvement of patients and their families at all stages of decision-making are necessary [52].

finanzielle Auswirkungen durch Arbeitsunfähigkeit oder notwendige Reduktion der Arbeitszeit

On the other hand, both haematological malignancies and their treatments have a significant impact on job-role changes [55]. This has also been confirmed by an interviewed patient, who was forced to reduce his working hours and thus had financial losses. The other participant also states that pursuing employment is usually no longer possible, with the corresponding financial impact [54].

altersbezogene Ungleichheiten: schlechtere Outcomes für Ältere

In addition, age-related inequalities exist. Older patients with haematological malignancies can face significantly poorer outcomes compared to younger patients. This cannot be attributed solely to higher comorbidity rates in older individuals [52], but also to cancer-related complications and chemoresistance resulting in refractory cancer and cancer relapses [56].

genetische Vielfalt → ungleiche Spenderchancen

Equity issues arise because suitable donors are more difficult to obtain among ethnic groups with greater genetic diversity. While the likelihood of a patient finding an HLA-matched UD in public registries is variable, reaching 50% for patients of European ancestry, the rate drops significantly below 30% for minority ethnicities (Asian or Hispanic descent) and as low as 5-10% for some minorities (African descent). When an HLA-MSD is not available, the average delay between search initiation for an UD and transplantation is three to four months. Since nearly one-third of patients lack either an MSD or an MUD, alternative sources of stem cells are necessary [33]. Given the ongoing migration to Austria, there may be an increase in the number of patients for whom no other type of suitable donor can be found, potentially expanding the population for treatment with Zemcelpro.

potenziell mehr geeignete Pat. durch Migration

## 6.4 Registries and documentation of the application

In Austria, various registries are established for haematological malignancies, as listed in Table 6-3 [57, 58].

5 österreichische Register für hämatolog. maligne Erkrankungen

*Table 6-3: Registers for haematological diseases in Austria [57, 58]*

| Registry | Short title | Included diseases |
|---|---|---|
| Registry and Biobank for the collection of clinical data and biomaterial from adult ALL patients | AGMT_ALL Registry | ALL |
| Austrian Myeloid Registry | AGMT_aMYELOIDr | Myeloid diseases: AML, CML, MDS |
| AGMT Austrian CLL Registry | AGMT_CLL-Reg | CLL |
| Austrian Registry and Biobank of Peripheral T-cell Lymphomas (AGMT_PTCL Registry) | AGMT_PTCL Registry | Peripheral T-cell lymphomas |
| Austrian CML Registry | - | CML |

*Abbreviations: AGMT … Arbeitsgemeinschaft medikamentöser Tumortherapie, ALL … acute lymphoblastic leukaemia, AML … acute myeloid leukaemia, CLL … chronic lymphocytic leukaemia, CML … chronic myeloid leukaemia, MDS … myelodysplastic syndrome*

The Austrian stem cell registry (Österreichisches Stammzellregister, ÖSZR) serves as the central contact point for all national and international searches for UDs. It is linked to other donor registries worldwide and collaborates closely with Austrian donor and transplant centres. The ÖSZR manages search requests from national and international transplant centres, coordinates tissue-typing procedures, and oversees the activities of donor, collection, and SCT centres [47].

ÖSZR: zentrale Anlaufstelle für alle Fremdspendersuchen im In- & Ausland

As part of quality assurance, all allo-HSCTs performed in Austria are reported to the Austrian SCT registry, which is based at the Ordensklinikum Linz Elisabethinen hospital. It collects and reports transplantation data in compliance with the data protection regulations and submits these data to the EBMT [59].

ASCTR: Sammlung & Auswertung von Daten zur SZT in Ö

# 7 Development costs and public contributions

## 7.1 Own development costs, acquisitions and licences

Übersicht zu Entwicklungskosten

Table 7-1 provides a short overview of the development history and the public contributions associated with Zemcelpro. ExCellThera or Cordex Biologics have not published the total amount of research and development (R&D) expenses attributed to Zemcelpro. As this chapter relies on publicly accessible information wholly, any public funding amounts related to the development of Zemcelpro may be incomplete.

*Table 7-1: Zemcelpro overview*

| Originator | Developer | Information on acquisitions | Public contribution | Type of public funding |
|---|---|---|---|---|
| University of Montreal (PI Guy Sauvageau) | ExCellThera/Cordex Biologics (subsidiary of ExCellThera) | Spin-out in 2015: ExCellThera was founded with Guy Sauvageau (University of Montreal) as chairman | Over €21.5 million direct and indirect public funding | Basic and preclinical research<br>SME support |

*Abbreviations: PI … Principal Investigator, SME … Small and Medium-sized Enterprise*

### Basic research and clinical development

Entwicklungsgeschichte von Zemcelpro

The development of Zemcelpro emerged from research at the Université de Montréal (henceforth University of Montreal), as shown in Chapter 7 in the Appendix. The fundamental UM171 research as part of a stem cell therapy (SCT) for blood-cancer patients began to be pioneered by Guy Sauvageau and Anne Marinier at the Institute for Research in Immunology and Cancer (IRIC) of the University of Montreal and Josée Hébert, from the Hôpital Maisonneuve Rosemont, which over time informed the scientific groundwork that ultimately enabled the later development of Zemcelpro. In 2014, Sauvageau's team discovered the new molecule UM171, which can multiply stem cells in umbilical cord blood (CB). Following the discovery, Sauvageau and colleagues founded the spin-out ExCellThera in 2015 (with Sauvageau serving as chairman, founder, and chief scientific officer) to develop UM171 for human therapeutic use and thereafter Cordex Biologics in 2023 to develop and commercialise a therapy based on their findings [60-62].

## 7.2 Public contributions to drug development

etwa € 21,4 Millionen öffentliche Gelder flossen in die Grundlagenforschung und Subventionen für die Firma ExCellThera

Chapter 7 in the Appendix demonstrates public research funding for the academic institutions involved in the early scientific work (University of Montreal and IRIC) and the wholly subsidiary company (ExCellThera) that developed

Zemcelpro. Over €21.5 million[9] in direct and indirect public funding that led to the development of Zemcelpro were identified. These funding sources supported broad scientific programs rather than targeted product-specific development. The largest funding amount went to the University of Montreal with €14.3 million, followed by €6.6 million[9] for ExCellThera and €511,421[9] for the Clinical Research Institute of Montreal (see Chapter 7 in the Appendix for details).

Universität von Montreal veröffentlicht Förderungen nicht

No basic research funding amounts are available for many of the University of Montreal projects that contributed to the initial discovery of UM171 as this is not part of the public record.

Lizenzvereinbarungen nicht publiziert

No details of the initial licensing agreement between the University of Montreal and ExCellThera/Cordex Biologics are available, as neither company is publicly traded (and therefore has no mandatory reporting requirements).

Kooperation zwischen ExCellThera und Ossium

In 2021, ExCellThera and Ossium Health, a bioengineering company founded in 2016 for processing, banking, and deploying deceased-donor bone marrow (BM), announced a collaboration to evaluate and advance opportunities to treat blood cancers, improve organ tolerance, and repair radiation damage [63].

## Company structure and financials

Unternehmensgeschichte von ExCellThera und Cordex Biologics

ExCellThera was established as an independent private company in 2015 using early stage UM171 molecule licensed from the University of Montreal [61, 64]. In 2023, Cordex Biologics was founded as a wholly owned subsidiary of ExCellThera [62].

Funding information for ExCellThera and Cordex Biologics is not disclosed because both companies are not publicly traded. Therefore, no verified information is publicly available regarding their type or sources of funding.

## Patents

Patentlizenzierung/ -verkauf nicht öffentlich

No information regarding licensing deals between the University of Montreal and ExCellThera/Cordex Biologics could be identified. None of the parties involved have made the relevant licensing deals public.

[9] All funding amounts converted to € using the exchange rates from the Austrian National Bank from 25 September 2025

# 8 Landscape overview

## 8.1 Ongoing studies on Zemcelpro

4 laufende Studien zu Zemcelpro identifiziert

weitere Daten zu Wirksamkeit & Sicherheit v. Zemcelpro erwartet

Four ongoing clinical studies evaluating Zemcelpro were identified on ClinicalTrials.gov [60], two of which were sponsored by ExCellThera, the marketing authorisation holder (MAH) for Zemcelpro. The ongoing trials include ECT-001-CB.002 and ECT-001-CB.004, the studies that supported the marketing authorisation (MA) of Zemcelpro and will provide further data on efficacy and safety (see the following chapter). They are to be completed in October 2027 and February 2026, respectively. The ECT-001-CB.007 is another ongoing phase 1/2 study of Zemcelpro in paediatric and young adult (<21 years) patients with high-risk and very high-risk myeloid malignancies. The last one, ECT-001-CB.003, is a phase 1/2 study of reduced-intensity allogeneic transplant of Zemcelpro in newly diagnosed patients with high-risk multiple myeloma. Both ECT-001-CB.003 and ECT-001-CB.007 contributed to the Safety Analysis Set (SAS). Further details are provided in the Appendix (Chapter 8).

## 8.2 Specific obligations for Zemcelpro post-authorisation

Auflagen aus bedingter Zulassung durch EMA

Following the conditional MA of Zemcelpro by the European Medicines Agency (EMA), the MAH is required to complete specific obligations through ongoing clinical studies within a specific date as described in Table 8-1. This includes two randomised controlled trials (RCTs) with expected completion dates by 2030.

*Table 8-1: Specific obligations for Zemcelpro post-authorisation [2]*

| Description of the obligation | Study: study title | Due date |
|---|---|---|
| Submit the final results to confirm the efficacy and safety of Zemcelpro in adult patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available. | ECT-001-CB.002: A Phase II Open-label Study of ECT-001-Expanded Cord Blood Transplantation in Patients with High Risk Acute Leukemia/ Myelodysplasia. | 28 February 2026 |
| Submit the final results to confirm the efficacy and safety of Zemcelpro in adult patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available. | ECT-001-CB.004: A Phase II Open-Label Study of ECT-001-Expanded Cord Blood Transplantation in Patients with High and Very High-Risk Acute Leukemia/Myelodysplasia | 31 August 2026 |
| Submit the results of the subgroup analysis to confirm the efficacy and safety of Zemcelpro in patients aged 18-21 with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available. | ECT-001-CB.010: A Prospective Randomised Phase II Trial of Allogeneic SCT with ECT-001-CB Expanded Cord Blood Transplant Without Serotherapy Versus Other Stem Cell Source in Pediatric Patients with High risk/refractory/ relapsed Acute Myeloid Leukaemia | 30 June 2030 |
| Submit the results to confirm the efficacy and safety of Zemcelpro, and to further evaluate the dose parameters used in adult patients with high-risk and very high-risk acute leukaemia/MDS. | ECT-001-CB.011: A Multicenter, Prospective, Randomised, Open-Label Phase III Study of ECT-001-CB (ECT-001-Expanded Cord Blood) Transplantation versus Best Alternative Allogeneic Stem Cell Source Transplantation (Haplo, MMUD) in Patients with High-Risk Acute Leukaemia/Myelodysplasia | 30 June 2030 |

| Description of the obligation | Study: study title | Due date |
|---|---|---|
| Submit the results of a prospective, non-interventional study based on data from a registry, and evaluate dose parameters collected for Zemcelpro lot manufactured for each patient enrolled in the study to confirm the efficacy and safety of Zemcelpro in adult patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available. | Registry | 30 June 2031 |

*Abbreviations: haplo … haploidentical, HSCT … haematopoietic stem cell transplantation, MDS … myelodysplastic syndrome, MMUD … mismatched unrelated donor, SCT … stem cel transplantation*

## 8.3 Treatments in development

Through the International Horizon Scanning Initiative (IHSI) database [65], we identified two distinct therapies in development (Orca-t, Smart101) for a similar indication as Zemcelpro - the treatment of haematological malignancy. Additionally, we identified omidubicel (Omisirge), a therapy comparable to Zemcelpro, approved by the FDA in 2023 but not yet available in the EU [44]. The drug is indicated for use in adults and paediatric patients aged 12 years and older with haematologic malignancies who are planned for umbilical CB transplantation.

2 Therapien in der Pipeline oder vor der Zulassung für die Behandlung von hämatologischen Malignomen, die eine allo-HSZT erfordern

The expected European Commission (EC) decision time for MA is as follows: Orca-t (January 2027), Smart101 (June 2029). There is no expected EC decision for omidubicel. See Chapter 8 in the Appendix for details.

die erste erwartete Zulassung von den Therapien ist im Januar 2026

# 9 Discussion

This health technology assessment (HTA) report evaluates Zemcelpro, an orphan stem cell medicine comprising two cell components: dorocubicel (UM171-expanded CD34+ cells) and unexpanded CD34– cells. Zemcelpro was approved on August 25th 2025, through a conditional marketing authorisation (MA) for the treatment of adults with haematological malignancies requiring an allogeneic haematopoietic stem cell transplantation (allo-HSCT) and for whom no other type of suitable donor cells are available [2].

Zemcelpro als neue Zelltherapie bei Pat. mit hämatolog. malignen Erkrankung mit erforderlicher allo-HSZT

Based on the European Medicines Agency (EMA) approval, treatment guidelines and clinical experts' input, the following key research questions were defined for this report:

Forschungsfragen:

1. **Clinical domain:** In adult patients with haematological malignancies, is Zemcelpro more effective and safer compared to the current standard treatment regarding patient-relevant outcomes in Austria?
2. **Non-clinical domain:**
   What are the economic, ethical, organisational and social consequences of implementing Zemcelpro into the Austrian healthcare system?
   What were the key contributions of publicly funded research institutions and private companies in discovering and developing Zemcelpro, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to marketing authorisation?

1. Wirksamkeit & Sicherheit von Zemcelpro vs. Standardtherapie

2. Implementierungsfolgen im Ö Gesundheitssystem & Beitrag öffentlicher Forschungsgelder

Haematological malignancies such as acute and chronic myeloid leukaemia (AML, CML), acute lymphoblastic leukaemia (ALL), myelodysplastic syndromes (MDS), other myeloproliferative neoplasms (MPNs), multiple myeloma and lymphoma often require allo-HSCT as the only potentially curative treatment option. However, donor identification remains challenging. While stem cells from peripheral blood (PB) and bone marrow (BM) are the primary sources, cord blood units (CBU) are an alternative. Although the use of CBU in Austria is limited by both suboptimal HLA matching and low stem cell dose, Zemcelpro addresses the issue of low cell numbers through expansion technology. The increased cell number is expected to enhance engraftment potential and thereby improve tolerance to HLA mismatches [7, 22, 24].

allo-HSZT als einziger kurativer Behandlungsansatz

CBU in Ö selten verwendet – Zemcelpro = expandierte Zellen mit potenziell besserem Engraftment

Nevertheless, Austrian clinical experts identified allo-HSCT with unexpanded CBU as the primary comparator in the population eligible for Zemcelpro, alongside other HLA-mismatched alternative donors (haplo and mismatched unrelated donors/MMUD) [22].

Hauptvergleich zu Zemcelpro: allo-HSZT mit nicht expandiertem CBU

The pivotal full analysis set (FAS) and the safety analysis set (SAS), as detailed in the European Public Assessment Report (EPAR) [2], served as the foundation for our efficacy and safety assessment.

Pivotal FAS & SAS: Wirksamkeit & Sicherheit von Zemcelpro

The pivotal FAS population included patients with high-risk acute leukaemia and myelodysplasia – a population with a poor prognosis [2]. The main results at 12 months included overall survival (OS: 66%), non-relapse mortality (NRM: 21%), progression-free survival (PFS: 53%), graft versus host disease-free and relapse-free survival (GRFS: 29%), and chronic graft versus host disease-free and relapse-free survival (CRFS: 45.2%) [2]. Neutrophil engraftment occurred in 84% of patients within 42 days, and platelet engraftment in 79% by day 100, which represents only modest improvement in engraftment time [46]. Furthermore, long-term efficacy data beyond 24 months were not available, and quality of life (QoL) data were not reported.

unterschiedlicher Krankheitsschweregrad in pivotal FAS und ECT-001-CB.001-Studie

bessere Ergebnisse zum Überleben in der ECT-001-CB.001-Studie

Additionally, subgroup analyses [2] showed that 5/8 HLA matching was associated with faster engraftment than ≥6/8 HLA matching, but with slower platelet engraftment. Also, NRM at 24 months was higher in 5/8 HLA-matched recipients (23.79% vs 4.37%). In fact, NRM events occurred only among participants treated with intermediate-intensity conditioning regimens. NRM events were also increased in older patients (≥40 years), resulting in lower OS, PFS, GRFS, and CRFS. Lastly, AML patients demonstrated OS, PFS, and GRFS lower than in patients with other disease types. These results suggest that HLA matching, disease type and age impact the response to Zemcelpro.

unterschiedliche Ergebnisse zur Regeneration von Thrombozyten

The SAS population included a larger and more diverse population and showed that the most frequent grade ≥3 adverse events (AEs) comprised lymphopenia (46.6%), anaemia (44.0%), neutropenia (35.3%), thrombocytopenia (31.9%) and acute graft versus host disease (GVHD: 22.4%). All grades of acute and chronic GVHD arose in 66.4% and 14.7%, respectively. In addition, 42 deaths occurred (36.2%), with the majority due to disease progression or relapse (n= 26) and 15 deaths due to non-relapse mortality [2].

Sicherheit: häufigste AEs (Grad ≥3): Lymphopenie (46,6 %), Anämie (44,0 %) & Neutropenie (35,3 %)

42 Todesfälle

The study base for Zemcelpro faces several methodological limitations, including the study design, the ongoing status of the pivotal studies, small sample size, short follow-up periods, and post-hoc analysis with no type I error control and no pre-planning. Furthermore, time to neutrophil engraftment used as a primary endpoint has not been established as a predictive marker for OS, PFS, or NRM [2]. In addition, defining time-related endpoints from the infusion is problematic, as it excludes the manufacturing, shipment, and administration periods, potentially underestimating the total time to treatment benefit [2]. Additional concerns arise from heterogeneity across studies, as populations varied in age, disease type, and conditioning regimens, including the safety population, which combined patients from five different studies with varying protocols and product formulations.

limitierte vergleichende Wirksamkeitsaussagen aufgrund des Studiendesigns

multiple Analysen ohne Vorplanung & Kontrolle

Heterogenität in den Populationen

Besides, four retrospective indirect treatment comparisons (ITCs) evaluated Zemcelpro against conventional HSC sources [32, 37-39]. Regarding the main comparator, the unexpanded CB, the beneficial effects of Zemcelpro were demonstrated by a statistically significant improvement in NRM and PFS at 2 years [38], and by faster neutrophil engraftment [37]. Moreover, GRFS was statistically significantly higher [38], and time to immunosuppression withdrawal was shorter in the Zemcelpro cohort vs the unexpanded CB group [39].

4 retrospektive indirekte Vergleiche

Vergleich mit nicht expandiertem Nabelschnurblut

Additionally, the ITCs showed a statistically significant improvement in OS, PFS and GRFS at 2 years compared with haplo donors [37]. However, clinical experts highlighted that the small sample size in the ITC constitutes an important limitation, particularly since haplo donors represent a common donor type in clinical practice. As a result, the findings in the haplo-group should be interpreted with caution, as they may underestimate real-world outcomes and, consequently, overestimate the effect of Zemcelpro [46].

indirekter Vergleich mit haploidentischer Spende

The presented findings suggest that Zemcelpro addresses limitations of other stem cell sources, especially of unexpanded CB, by enhancing engraftment through increased stem cell number and thereby improving tolerance to HLA mismatches. Nevertheless, the clinical experts noted that some patients produce HLA antibodies – often the reason for a lack of suitable donors – making them unlikely candidates for Zemcelpro, as HLA mismatches would trigger rejection [46]. Besides, the superior GRFS with Zemcelpro suggests improved safety of the intervention and potential QoL benefits.

Zemcelpro unwahrscheinliche Option für Pat. mit vielen HLA-Antikörpern

methodische Limitationen der indirekten Vergleiche

The presented ITC results should be interpreted with caution and are of uncertain value, as they are characterised by substantial methodological limitations. For example, correction for multiple testing, systematic baseline imbalances between the matched groups, and inconsistent findings across registry comparisons. Critically, all comparisons involved prospective Zemcelpro data versus retrospective registry controls, introducing systematic bias. Moreover, substantial missing data in the control groups and differential data-collection methods further compromise the validity of these comparisons [32, 37-39].

Anwendbarkeit auf Ö Kontext

Moreover, the applicability of the available evidence of Zemcelpro to the Austrian clinical context requires consideration of several contextual factors:

Population

- Regarding the patient population, the pivotal FAS only enrolled patients with high-risk acute leukaemia or MDS. Hence, the applicability to the broader Austrian population with diverse haematological malignancies remains unclear.

unzureichende Evidenz für Pat. ≥65 Jahre

- In addition, generalisability concerns include insufficient evidence for patients aged ≥65 years.

keine Daten zur Lebensqualität

- Furthermore, the small sample size limits the weight of the evidence, while long-term follow-up data are absent. Also, QoL data were not reported. These concerns significantly constrain the generalisability and clinical applicability of the findings.

Herstellungsdauer: 45 Tage

- Regarding the intervention, the duration of the Zemcelpro production process needs to be considered, as it takes approximately 45 days from CBU selection to the manipulated CBU infusion (with a 4% manufacturing failure rate) [34], comparable to the duration of the process involving an UD, which clinical experts estimate at approximately five weeks . However, in the studies, production time was not considered, as outcomes were assessed from the infusion onwards [2].

MMUD oder Haplo in Ö bevorzugt

- As confirmed by Austrian clinical experts, Austria's HSCT centres primarily utilise mismatched unrelated and haplo donors for allo-HSCT and rarely use unexpanded CB. In contrast, some ITCs compared Zemcelpro only to unexpanded CB [32] or matched donors (PB 10/10) [38]. Given Austria's clinical practice, comparisons with haplo or MUD are of limited relevance, as these donors are consistently preferred when available. Therefore, only the comparison with unexpanded CB represents a clinically meaningful benchmark for Zemcelpro.

Zweittransplantation mit Zemcelpro fraglich

- According to Austrian clinical experts, Zemcelpro's use in second transplantation is questionable, as another MA conditioning – required for Zemcelpro – is typically not feasibly, limiting the applicability in relapsed patients [6].

A detailed overview of the applicability of the evidence to the Austrian context is provided in the Appendix, Chapter 9.

keine Daten zu Preis, Kosteneffektivität und Budgetfolgen liegen für Ö vor ...

Considering economic aspects, the MAH did not submit a price proposal (before data cut-off for this report), a health economic evaluation, or a budget impact analysis for Austria. In addition, no pharmacoeconomic evaluation of Zemcelpro was identified by a systematic or manual search. According to the conducted cost analysis for Austria, the per-patient direct medical costs associated with Zemcelpro allo-HSCT

were estimated at €516,725, representing an incremental cost of €204,321 compared to unexpanded CB allo-HSCT. However, the presented cost analysis is subject to several limitations. Most importantly, the Zemcelpro acquisition cost of €290,000[10] is a surrogate price derived from the wholesale acquisition cost of a similar product approved by the US Food and Drug Administration (omidubicel) [43, 44]. Accounting for 56% of the total Zemcelpro allo-HSCT cost, it essentially represents an add-on to the average hospital cost of a standard allo-HSCT procedure. No savings relative to the standard of care could be considered due to the absence of modelling of long-term effects. Nevertheless, it can be hypothesised that further savings might materialise with improved long-term outcomes, partially offsetting the initial acquisition cost.

...
Zemcelpro Platzhalterpreis basierend auf einem ähnlichen Produkt (Omidubicel)

Kosten insgesamt: € 516.725 (Add-on-Kosten von € 290.000)

Further limitations of the presented cost analysis arise primarily from the unavailability of needed costing data and long-term follow-up data concerning resource use. A detailed breakdown of the limitations is presented in Chapter 5.2.2.

Hauptlimitationen: fehlende Kostendaten & keine Follow-up-Daten Ressourcenverbrauch

From a healthcare burden perspective, the length of hospitalisation for transplantation is recognised as the major driver of total allo-HSCT costs [57]. In the Zemcelpro SAS population, the median duration of initial hospitalisation was 34 days, including a median 12-day intensive care unit (ICU) admission, required by 7.1% of patients. Re-hospitalisation, with a mean duration of 19 days (13.1 in the first 100 days post-transplant), was required in 43.4% of patients. A large US analysis of more than 68,000 hospitalisations of adult patients who underwent allo-HSCT showed that the stem cell source is a significant predictor for the length of a hospital stay, with CB being associated with a significantly longer median hospital stay (37 days) compared to BM (27 days) and PB (25 days) [66]. This finding was corroborated by another US study of adult allo-HSCT recipients, which documented the longest hospitalisation within 100 days post-transplantation for CB-transplanted patients (39.3 days vs 32.7 days for BM and 26.2 days for PB; $p < 0.01$). However, in the late recovery period (years 1-5), CB was associated with a lower long-term healthcare burden compared to other stem cell sources, mainly due to a lower incidence of chronic GVHD [67]. While the median duration of initial hospitalisation reported for the Zemcelpro SAS population aligns with the overall length of hospital stay associated with standard CB allo-HSCT in these studies, it is unclear whether the re-hospitalisations are captured comparably, preventing firm conclusions about the relative costs of Zemcelpro allo-HSCT attributable to hospitalisation. Nevertheless, as long-term healthcare burden is driven primarily by chronic GVHD, Zemcelpro could result in savings in the extended post-transplant period.

Krankenhausaufenthalt = Hauptkostenfaktor für allo-HSZT

Zemcelpro: 34 Tage initial, 43 % Rehospitalisierung

Krankenhaustage Stammzellquellen-Vergleich: CB (37-39T) > KM (27-33T) > PB (25-26T), jedoch CB möglicherweise langfristig günstiger (weniger chronische GvHD)

Zemcelpro: potenzielle Kosteneinsparungen post-Transplantation

Even if the patient number for Zemcelpro is expected to be very low in Austria, the market share could increase in the future if Zemcelpro demonstrates more robust additional benefits over the standard of care. Hence, with estimated direct medical costs of €516,725 per patient (excluding re-hospitalisation costs), treating even five to ten patients annually would result in €2.5-5 million in healthcare expenditure.

eventuell in Zukunft mehr Pat. für Zemcelpro zu erwarten: Budgetfolgen bei 5-10 Pat.: € 2,5-5 Mio.

[10] As the price was not known at the time of conducting this report, this price could be underestimated.

Unklarheiten aber vergleichbar mit allo-HSZT

mögliche Zunahme der Anzahl von Pat. durch Migration

From a stakeholders' perspective, several uncertainties remain regarding the implementation of Zemcelpro in Austria. Given the limited clinical data and small sample sizes, it is not possible to predict how the treatment will perform in real-world practice, particularly with regard to the expected duration of hospitalisation, as well as the frequency and severity of AEs and serious adverse events (SAEs). Otherwise, no significant differences in infrastructure and expertise requirements are expected compared to conventional HSCT. However, personal and structural resources must be mobilised. A relevant issue for stakeholders is the potential increase in Austrian patient numbers driven by ongoing migration patterns and ethnic diversity.

Erhalt der Lebensqualität als Priorität für Pat.

From a patient's perspective, maintaining QoL emerged as a priority, with key expectations for new therapies including precise and efficient disease targeting, minimising SAEs, and offering the prospect of returning to an everyday life. Both the disease and its treatments have a significant impact on HRQoL, body image, employment, finances, and the lives of their relatives. Hence, the life-threatening nature of the disease creates substantial psychological and social challenges requiring support services. These insights were provided by only two participants who completed the patient questionnaire, yet their responses underscore the difficulties patients face when living with haematological malignancies.

Disparitäten im Zugang zur Behandlung: geringere Spender-Kompatibilität bei bestimmten ethnischen Gruppen

Besides, significant equity concerns exist regarding access to treatment. Disparities in treatment access persist across Central and Eastern European nations, including access within Austria. HLA-compatible donor availability is significantly reduced in specific ethnic populations. Populations with greater genetic diversity are significantly less likely to identify suitable donors. As mentioned above, given the ongoing migration to Austria and increasing population diversity, the number of patients for whom no other type of suitable donor can be found may expand, potentially increasing the eligible population for Zemcelpro treatment.

Zemcelpro Beispiel für Forschung & Entwicklung an Universitäten → spätere Kommerzialisierung

The history of Zemcelpro's development demonstrates a clear progression from publicly funded academic research at the University of Montreal to successful commercialisation through the spin-out, ExCellThera, and its subsidiary, Cordex Biologics. With roughly €21.5 million identified in public direct and indirect research funding, Zemcelpro demonstrates that public investment in basic research, as well as in small- and medium-sized enterprise support, leads to new therapies.

klinische Beurteilung von Zemcelpro nicht vollumfänglich möglich

Overall, Zemcelpro may address an unmet medical need for patients with haematological malignancies requiring allo-HSCT without a suitable donor for stem cells from PB or BM, especially for ethnic minorities with a reduced likelihood of identifying HLA-compatible donors. However, several methodological limitations in the available clinical evidence, such as single-arm study designs and small sample sizes, as well as critical evidence gaps, such as missing long-term and QoL data, limit a comprehensive clinical evaluation.

From a health economic perspective, the high additional costs of Zemcelpro compared to standard allo-HSCT pose a significant budget impact, though potential long-term savings may be achieved if reduced chronic GVHD is confirmed. However, it remains unclear how Zemcelpro could be used in Austria, as standard clinical practice includes allo-HSCT with stem cells from PB and BM. In addition, Zemcelpro's benefit remains uncertain compared to double CBU, which is also rarely used in Austria. If Zemcelpro is administered in Austria in the future, adequate infrastructure for its delivery is already in place, given the existing transplant centres. However, implementation would require consideration of complex international manufacturing logistics, and the administrative resources required to coordinate between transplant and company responsibilities.

Zemcelpro: hohe Zusatzkosten vs. Standard-allo-HSCT

Anwendbarkeit in Ö unklar (Standard: PB/BM)

bei Implementierung: komplexe Logistik erforderlich

Finally, there are four ongoing trials, of which two are expected to be completed in February 2026 and October 2027 and will thus provide further data on effectiveness, safety, and QoL, as required by the EMA [2]. These studies will be necessary for further robust clinical and economic evaluations, enabling definitive recommendations regarding Zemcelpro's role in Austrian clinical practice.

2/4 laufende Studien zu fehlenden Daten bis Februar 2026 bzw. Oktober 2027 erwartet

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# Abbreviations

AE.....adverse event
AGMT.....Arbeitsgemeinschaft medikamentöse Tumortherapie
ALL.....acute lymphatic leukaemia, acute lymphoblastic leukaemia
allo-HSCT.....allogeneic haematopoietic stem cell transplant
AML.....acute myeloid leukaemia
ASCTR.....Austrian stem cell transplantation registry, Österreichisches Stamm-zelltransplantationsregister
ATC.....Anatomical Therapeutic Chemical
ATMP.....Advanced Therapy Medicinal Product
BM.....bone marrow
CAR.....chimeric antigen receptor
CBU.....cord blood unit
CD34+.....cluster of differentiation 34 positive
CHMP.....Committee for Medicinal Product for Human Use
CI.....confidence interval
CIBMTR.....International Blood and Marrow Transplant Research
CML.....chronic myeloid leukaemia, chronic myeloid leukaemia
CNS.....central nervous system
CRFS.....chronic graft versus host disease-free and relapse-free survival
CSR.....clinical study report
DACH.....Germany, Austria, Switzerland
EBMT.....European Society for Blood and Marrow Transplantation
EPAR.....European Assessment Report, European Public Assessment Report
ERQCC.....European Cancer Organisation Essential requirements for Quality Cancer Care
EU.....European Union
EUnetHTA...European Network for Health Technology Assessment
FAS.....full analysis set
FB.....Fallpauschale, flat rate
FDA.....U.S. Food and Drug Administration
G-CSF.....granulocyte colony stimulating factor
GMP.....Good Manufacturing Practice
GRADE.....Grading of Recommendations Assessment
GVHD.....graft-versus-host-disease
Gy.....Gray
HL.....Hodgkin lymphoma
HM.....haematological malignancies
HR.....hazard ratio
HRQoL.....health-related quality-of-life
HSC.....haematopoietic stem cell
HSC:.....haematopoietic stem cells
HTA.....Health Technology Assessment, Health Technology Assessmenr
HTACG.....Memeber State Coordination Group on HTA
ICU.....intensive care unit
IHSI.....International Horizon Scanning Initiative
INN.....international non-proprietory name
IRIC.....Institute for Research in Immunology and Cancer
ITC.....indirect treatment comparison
ITT.....intention-to-treat
JAK.....Janus kinase-proteins
KPS.....Karnofsky performance status
LKF.....Leistungsorientierte Krankenanstaltenfinanzierung
MA.....myeloablative
MAH.....marketing authorisation holder
MDS.....myelodysplastic syndrome
MEL.....Medizinische Einzelleistung, indicidual medical service
mm.....millimitre
MMF.....mycophenolate mofetil
MPN.....myeloproliferative neoplasms
MSD.....matched sibling donor
n.....number
NA.....not available
NCCN.....National Comprehensive Cancer Network
NCT.....National Clinical Trial
NHL.....non-Hodgkin lymphoma

NR .....not reached
NRM.....non-relapse mortality
OeGHO .....Österreichische Gesellschaft für Hämatologie/Medizinische Onkologie, Austrian Society for Haematology and Medical Oncology
OS .....overall survival
ÖSZR .....Austrian stem cell registry, Österreichisches Stammzellregister
PB .....peripheral blood
PFS .....progression-free survival
PI .....Principal Investigator
PICO .....population, intervention, comparison, outcome
PPRI.....Pharmaceutical Pricing and Reimbursement
PRIME .....PRIority MEdicines
PROs .....patient-reported outcomes
QoL .....quality-of-life
R&D .....Research & Development
RFS .....relapse-free survival
RoB.....risk of bias
SAS.....safety analysis set
SD.....standard deviation
SEC .....Securities and Exchange Commission
SME.....small and medium-sized enterprise
SUE .....schwerwiegendes unerwünschtes Ereignis
SZT .....Stammzelltransplantation
TBI .....total body irradiation
TNC .....total nucleated cell
TRM.....transplant-related mortality
UK.....United Kingdom
USA.....United States of America
WAC.....wholesale aquisition cost
WHO-ICTRP .....World Health Organization International Clinical Trials Registry Platform

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