European Union Risk Management Plan (RMP) Zemcelpro (dorocubicel)

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Abbreviations

Abbreviation	Definition/Description
aGVHD	Acute Graft versus host disease
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ASIR	Age-Standardized Incidence Rate
ATG	Anti-T-Cell Globulins
BMI	Body-Mass Index
CB	Cord blood
CBU	Cord blood unit
cGVHD	Chronic Graft versus host disease
CH	Clonal haematopoiesis
CSR	Clinical Study Report
DCF	Data Collection Form
DDL	Donor-derived leukemias
DDM	Donor-derived malignancies
DMSO	Dimethyl sulfoxide
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
EMA	European Medicines Agency
ES	Engraftment syndrome
GVHD	Graft versus host disease
haplo	haploidentical
HBV	Hepatitis B virus
hERG	Human ether-à-go-go-related gene
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HLA	Human leukocyte antigen
HSCs	Haematopoietic stem cells
HSCT	Haematopoietic stem cell transplantation
ICSR	Individual Case Safety Report
IV	Intravenous
MAH	Marketing Authorization Holder
MDS	Myelodysplastic Syndrome

Abbreviation	Definition/Description
MM	Multiple Myeloma
MMUD	Mismatched unrelated donor
MSD	Matched sibling donor
MUD	Matched Unrelated Donor
NA	Not applicable
NCI	US National Cancer Institute
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PI	Principal investigator
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RIC	reduced-intensity conditioning
RMM	Risk Minimization Measure
RMP	Risk Management Plan
R/R	Relapsed or refractory
SmPC	Summary of Product Characteristics
TBI	Total body irradiation
TRM	Transplant related mortality
ULN	Upper limit of normal
US	United States

Part I: Product(s) Overview

Product(s) Overview

Active substance(s) (INN or common name)	Company code for Zemcelpro: ECT-001-CB Zemcelpro consists of two components: • Dorocubicel i.e. expanded CD34+ cells: Common name: Haematopoietic stem cells and blood progenitors umbilical cord-derived expanded with (1R,4R)-N1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine dihydrobromide dihydrate) Internal code: ECT-001-CB-DP1 INN: dorocubicel • Unexpanded CD34- cells: Common name: unexpanded CD34- cells from which the CD3+ cells are the active fraction Internal code: ECT-001-CB-DP2 INN: none
Pharmacotherapeutic group(s) (ATC Code)	Stem cells from umbilical cord blood (B05AX04)
Marketing Authorization Applicant	Cordex Biologics International Limited.
Medicinal products to which this RMP refers	1
Invented name(s)	Zemcelpro™
Marketing authorization procedure	Centralised
Brief description of the product	Chemical class Somatic cell therapy medicinal products
	Summary of mode of action Zemcelpro is a personalised cell therapy product manufactured by expanding allogeneic umbilical cord blood-derived haematopoietic stem cells (HSCs) *ex vivo*. The ECT-001 expansion technology combines the use of the small molecule UM171 as a reagent, which preserves HSCs functions and prevents their differentiation *in vitro*, and a fed-batch culture system, which leads to the reduction of endogenously produced negative regulators of stem cell function.
	Important information about its composition Zemcelpro consists of haematopoietic progenitor cells, monocytes, lymphocytes, and granulocytes from human cord blood. The starting raw material will be an erythrodepleted donor-screened cord blood unit (CBU) commercially acquired from CBU banks (accredited, designated, authorised or licensed by a competent authority). For each patient, a CBU will be selected prior to transplant, based on order of preference for donor source prioritization, by the treating physician while respecting minimal requirement for human

	leukocyte antigen (HLA) matching, Total Nucleated Cells per kg and CD34+ cells per kg. Zemcelpro has the following excipients ingredients: dimethyl sulfoxide (DMSO), human albumin solution, sodium chloride, potassium chloride, sodium gluconate, sodium acetates, and magnesium chloride.
Hyperlink to the Product Information	NA
Indication(s) (global)	Current: NA
	Proposed: 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.
Dosages	Current: NA
	Proposed: A single dose for infusion containing a dispersion for infusion of expanded CD34+ cells in up to four infusion bags and four bags of unexpanded CD34 cells.
Pharmaceutical form(s) and strengths	Current: Dispersion for intravenous (IV) infusion. Zemcelpro consists of two components, expanded CD34+ cells (dorocubicel) and unexpanded CD34- cells, provided as a cellular dispersion for infusion. Each fraction is contained in four cryobags of 20 mL • Expanded CD34+ cells (dorocubicel): up to four bags containing at least 0.23 x 10^6 viable CD34+ cells per mL suspended in a cryopreservation solution are infused to patient. The cell suspension is colourless to slightly yellow. • Unexpanded CD34- cells: four bags containing at least 0.53 x 10^6 viable CD3+ cells per mL suspended in a cryopreservation solution are infused to patient. The cell suspension is reddish. The cryopreservation medium of both components contains DMSO.
	Proposed: NA
Is/will the product be subject to additional monitoring?	Yes

Part II: Safety specification

SI Epidemiology of the indication(s) and target population(s)

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.

Incidence

Haematological malignancies represent a heterogeneous group of neoplasms with regard to aetiology and molecular biology. They are myeloid and lymphatic tumours caused by disruption of normal haematopoietic function and are classified into several common subtypes, generally consisting of leukaemia, multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL) (Swerdlow et al 2017).

Based on a recent overview of the most recent national statistics worldwide, incident cases of haematological malignancies have been increasing since 1990, reaching 1343.85 thousand in 2019. As the number of cancer cases increases, the spectrum of haematological malignancies is also changing. For example, the incidence of leukaemia is declining globally, but it is still rising in developed regions (such as France, Spain, Slovenia, and Cyprus). Countries and regions differ in the types of haematological malignancies on account of differences resulting from different socioeconomic development stages. For specific leukaemia subtypes, the incident cases of acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia, and chronic lymphocytic leukaemia increased to 124.33 thousand, 153.32 thousand, 65.8 thousand, and 103.47 thousand in 2019, respectively, while the proportion of other subtypes of leukaemia decreased significantly due to the precision of classification in the past three decades (Zhang et al 2023).

The European Society for Blood and Marrow Transplantation (EBMT) reported that 19,806 allogeneic haematopoietic stem cell transplantations (HSCT) were performed in Europe in 2021, myeloid and lymphoid malignancies being the most common indications accounting for 86% of allogeneic HSCTs (Passweg et al 2023). Depending on the regional variations in ethnic diversity, up to 15% of patients who have a clear indication for HSCT have no access to a readily available suitable donor including haploidentical (haplo), mismatched unrelated donor (MMUD) or cord blood (CB) (Sanz et al 2020). This issue is particularly acute for minorities who are poorly represented in international donor registries (Dumont-Lagace et al 2022). Given these challenges, *ex vivo* expansion of long-term HSCs from small CB units represents a potentially appealing solution to address the unmet medical need. Indeed, a goal of expansion is to increase the therapeutic availability of CB units so that physicians can gain access to more than the 5% CB units stored in CB bank (Barker et al 2019).

Demographics of the population and risk factors for the disease

People over the age of 70 are at high risk of developing haematologic malignancies, about 80% of all age groups. Among all age groups, the highest incidence rates of leukaemia, MM, NHL, and HL were 95+ group, 85-89 group, 95+ group, and 90-94 group, respectively, with rates of 116.18, 23.55, 103.62, and 10.29 per 100,000 population in 2019. The male-to-female ratio for leukemia, MM, and NHL continued to increase from 1990 to 2019 (Zhang et al 2023). AML is the most frequent acute leukemia in adults with an incidence of 3 to 4 per 100,000 persons per year. The median age at diagnosis ranges from 66 to 71 years (Nagel et al 2017). Median age at ALL diagnosis in adults was 53 years (range 18-95 years) (Lennmyr et al 2019).

The predominance of males in haematological malignancies has been observed throughout the world, with male-to-female age-standardized incidence rate (ASIR) ratios of 1.3:1 for leukaemia, 1.4:1 for MM, 1.6:1 for NHL, and 1.5:1 for HL. Notably, the gender differences varied by age. The male-to-female ratios of haematological malignancies continue to decline from certain ages until females are dominant, with the peak age for leukaemia approaching 70 to 74 years, MM at 25 to 29 years, and lymphoma at 55 to 59 years (Zhang et al 2023).

The regions with the largest increasing trend in the ASIR of leukaemia, MM, NHL, and HL were Central Europe, Eastern Europe, East Asia, and Caribbean, respectively (Zhang et al 2023). For geographical regions, the highest ASIR of leukemia in 2019 appeared in Western Europe (16.87 per 100,000 population), North America (10.69 per 100,000 population), and Australasia (10.46 per 100,000 population) (Zhang et al 2023).

A range of disorders affecting the lymphatic system and immune response, including most notably human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS), organ transplantations, but also less severe states of immune perturbation such as autoimmune and chronic inflammatory conditions and infections, constitute risk factors for developing several subtypes of haematological malignancies. Other risk factors include smoking, high-dose radiation exposure, history of radiotherapy and chemotherapy (for treating solid tumors), chromosomal abnormalities related diseases (e.g. Down syndrome), and chemicals such as formaldehyde and benzene (Mohammadi 2016, Zhang et al 2021).

HSCT is the preferred and recommended treatment for a subset of patients with high-risk and relapsed or refractory (R/R) haematological malignancies (Snowden et al 2022). Out of 8,326 procedures performed in in the United States (US) in 2020, 90% of allogeneic HSCTs were for haematological malignancies. The most frequent indications were AML (39%), ALL (16%) and myelodysplastic syndrome (MDS) (14%) (Auletta et al 2023). Similar data have been reported by the EBMT (Passweg et al 2023). About 86% of allogeneic HSCT recipients were adults aged 18 years and over, 18% were aged 50-59 years, 28% were aged 60-69 years and 10% were aged 70 years and over. Even though the number of transplants and proportion of each disease group has been relatively stable over the past decade, the number of HSCT performed has increased in the 60-69 and 70 years and over age groups (Auletta et al 2023). Over the last decade, relative proportions of patients by race and ethnicity receiving allogeneic HSCT have remained fairly constant. In 2020, the racial/ethnic distribution of allogeneic HCT recipients was 69% non-Hispanic White, 15% Hispanic, and 9% non-Hispanic Black or African American (Auletta et al 2023).

The main existing treatment options

Conventional treatment of haematological malignancies involves induction therapy followed by one to three courses of consolidation. Usually, chemotherapy, targeted therapy, killer cells, and HSCT are used for treatment. Allogeneic HSCT following myeloablative conditioning is the only potential curative therapy for several haematological malignancies such as certain types of AML, ALL, MDS, lymphoma and other blood diseases (D'Souza et al 2020). Conditioning that is the preparative regimen consisting of chemotherapy with or without total body irradiation (TBI) is administered to the patients undergoing HSCT before the infusion of the stem cell grafts (Gagelmann and Kroger 2021). Patient-specific factors, including age, disease risk, coexisting medical conditions and performance status, are often taken into account when determining the appropriate treatment. The primary determinant for selecting one therapeutic approach over another namely chemotherapy or HSCT in the clinical management of haematological malignancies is the disease risk because long-term overall survival (OS) varies substantially depending on baseline demographic and clinical variables, cytogenetic and molecular abnormalities, and measurable residual disease (DeFilipp et al 2023, Dholaria et al 2020, DeFilipp et al 2019, Hoezler et al 2016, Armand et al 2014). Moreover, disease type and status at the time of transplantation are the strongest determinants of post-HSCT survival (Armand et al 2014). Where conventional chemotherapy and HSCT may be too aggressive for particular patients, immunotherapy could present an alternative treatment (Kaleka and Schiller 2022).

Mortality and morbidity inherent to allogeneic HSCT

In order to perform an allogeneic HSCT, the preferred choice of donor is an HLA-matched sibling donor (MSD). However, as families have become smaller and each sibling has only a 25% chance of being HLA matched, the most commonly used donor nowadays is a matched unrelated donor (MUD). Unfortunately, the probability of identifying an HLA matched donor is dependent on ethnicity as HLAs from Northern European ancestry are more commonly represented in the donor registry. Approximately one third of patients will not have an HLA identical donor (MSD or MUD) and this number increases depending on ethnic background. These patients require an alternative donor transplant (Zhu et al 2021). Three alternative options exist, all of which involve HLA mismatched donors: i) haplo donors typically using a

sibling, a parent or a child who is 50% HLA matched, ii) MMUD who are usually mismatched at 1 HLA locus and iii) CB, each option with their advantages and disadvantages (Hwang et al 2022).

Historically, stem cell transplants from mismatched donors (i.e., haplo and MMUD) increase the risk of transplant related mortality (TRM) because of the higher risk of graft-versus-host disease (GVHD) and infectious complications, leading to decreased survival (Lee et al 2007). GVHD is a common immune complication after HSCT occurring in approximately 50% of patients which can affect almost any organ and manifests as skin rash, vomiting, diarrhoea, liver inflammation, dry mouth, dry eyes, skin thickening and obstruction and small airways in the lungs. Moderate to severe GVHD translates into increased morbidity and mortality. The recent use of posttransplant cyclophosphamide (PTCy) in haplo and MMUD transplants has significantly reduced the incidence of severe GvHD previously seen with these mismatched transplants (Leick and Chen 2022; Al Hamed et al 2023; Brissot et al 2019). However, HLA matched donors remain the gold standard source for HSCT with the best overall results (Nagler et al 2023, Al Hamed et al 2023).

Choosing the best option between standard (MSD, MUD) and alternative donors (CB, haplo, MMUD) is decided on a case-by-case manner as certain patient disease conditions would favour one type of transplant (e.g. very high risk acute leukaemia favours use of CB transplants which is most effective to prevent relapse), while other conditions (e.g. more benign aplastic anaemia favours the use of MSD which has the least incidence of complications). In addition to the clinical disease being treated, physicians assess variables that positively or negatively affect the outcome of HSCT and make every effort to choose the best one. These include: source of HSC (bone marrow versus peripheral blood which is typically linked to greater T cell dose, more GVHD), HLA-mismatch (bad for GVHD, could be good from disease control), donor age (an older donor has been shown to result in inferior OS, increases risk of non-relapse mortality and acute GVHD (Mehta et al 2023), seropositivity for cytomegalovirus of donor and recipient, ABO mismatch (delays red blood cell engraftment), donor and recipient weight), anti-HLA antibodies (graft rejection), donor history of pregnancy (increases GVHD), etc.

Conventional allogeneic CB grafts are much smaller than adult-derived bone marrow and peripheral blood ones and very often do not meet the recommended minimal cell dose requirements to ensure an adequate engraftment in the adult (Dehn et al 2019, Politikos et al 2020). This low cell dose negatively affects the speed of blood count recovery leading to more infections and a higher risk of graft failure and TRM (Eapen et al 2014). To counteract this problem, physicians frequently select larger CB units which represent at best 5% of the units stored in the international banks for a 70 kg patient (Barker et al 2019). While allowing for safe reconstitution, the current practice of selecting these larger units that suffer from suboptimal HLA matching compared to smaller CB units that fail to meet the minimal criteria for clinical acceptability is somewhat counterproductive as each HLA mismatch increases transplant-related mortality by ~5%–10% (Yokoyama et al 2020; Eapen et al 2014).

Important co-morbidities

Patients are typically diagnosed at old age and may have other comorbid diseases that have to be taken into account for optimal treatment and care. Comorbid diseases may constitute risk factors for the development of subtypes of haematological malignancies, and/or determinants of complications and death (Mohammadi 2016).

A German study provided reference data for pre-existing comorbidities from a large set of adult ALL. The most frequent comorbidities were infections (17%), prior malignancies (16%), type 2 diabetes (16%), cardiac (14%) and moderate pulmonary disease (12%), obesity (11%) and mild liver disease (10%). Arrhythmias, cardiac disease, prior malignancies and diabetes increased with age while infections or obesity were not strongly correlated to age. Overall, this analysis revealed a high incidence of comorbidities in older >55 years (57-92%) and even in younger adults 18-55 years (46%) (Wermann et al 2018).

Comorbidities in AML patients have been shown to increase with age. In a large US retrospective study of comorbidities in AML compared to matched noncancer controls, AML patients had more comorbidities (67.9% vs. 61.2% with at least 1 comorbidity) and also had higher mean National Cancer Institute (NCI) co-morbidity index scores (1.81 vs. 1.63, P < .01). The most common co-morbidities among the overall AML cohort included type 2 diabetes without complications (31.3%), chronic obstructive pulmonary disease (28.2%), and congestive heart failure (21.5%). R/R AML patients were younger, had lower NCI comorbidity

scores, lower incidence rates of events of interest (such as infectious, haematologic, haemorrhagic, cardiovascular, cerebrovascular, hepatic, and renal events), and a longer follow-up time compared to non-R/R AML (Dhopeshwarkar et al 2019). Another population-based study including all newly diagnosed MDS patients found that 67% of patients had at least one relevant co-morbidity. The most common comorbidities at the time of diagnosis were cardiovascular disease (30.9%), (previous) malignancy (24.4%), chronic lung disease (17.2%), and diabetes mellitus (17.2%) (Rozema et al 2021).

SII Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

The final drug product (Zemcelpro) combines two cell components: dorocubicel, consisting of ex vivo UM171-expanded CD34+ cells, and unexpanded CD34- cells both derived from a single umbilical cord blood unit. The UM171 material is a novel small molecule almost completely removed from the drug product during final formulation. The residual amount of UM171 detected in translational and validation runs was determined to be less than 1 µg per bag of formulated drug product. This amount represents a potential exposure of UM171 of approximately 8 ng/kg for a 70 kg adult. The nonclinical program for Zemcelpro focused exclusively on the safety of the UM171 molecule itself and the safety of the UM171-expanded CD34+ cells. Non-clinical studies were not performed on the unexpanded CD34- cells since these cells are minimally manipulated and its cellular composition very closely resembles that of an unmanipulated UCB.

Toxicity

Engraftment and safety of dorocubicel was assessed during the primary or secondary immune reconstitution of immunocompromised NSG mice transplanted for up to 28 weeks with up to $5x10^6$ cells. At these dose levels (equivalent to up to 2.5 x 10^8 cells/kg, i.e., far above the human dose considering the high proportion of CD34+ cells in these expanded grafts), human engraftment in mice was very high, achieving levels in the range of 40-50% during the primary transplant experiments, and 0.3 to 22.9% in secondary mice. No signs of toxicity were noted.

The safety of the raw material UM171, which is used ex vivo to expand CD34+ cells to make dorocubicel, was assessed through single-dose toxicity studies in rats, and repeated-dose toxicity studies in cynomolgus monkeys. These studies showed that UM171 is not associated with any toxicity and was well tolerated when administered intravenously to rats or to cynomolgus monkeys at a dose of 1 mg/kg (0.161 mg/kg in HED) and 230 µg/kg (0.065 mg/kg in HED), respectively, which represent 20,000 and 8,000 times higher doses than the residual amount of UM171 present in the final formulated dorocubicel.

Carcinogenicity and mutagenicity

Genotoxicity assays and carcinogenicity studies in rodent models with dorocubicel were not performed. The oncogenic potential of UM171 and UM171-expanded cells is also expected to be extremely low. Two Good Laboratory Practice (GLP) studies assessing the carcinogenic and genotoxic potential of the UM171 molecule (Ames test and micronucleus assay) revealed UM171 shows no carcinogenic or genotoxic property even at very high concentrations, much higher than its use in the manufacture of UM171-expanded cells in its residual levels. In addition to a lack of tumourigenicity observed during the in vivo studies in NSG mice, in vitro cytogenetic analysis of UM171-expanded cells did not reveal any abnormal chromosomal changes in the cells.

Reproductive toxicity

Allogeneic stem cell transplant recipients have a very high chance of becoming infertile due to the high dose chemotherapy with or without radiotherapy necessary for stem cell transplantation. Use of dorocubicel is not recommended in pregnant women, and no studies on reproductive and developmental toxicity of the UM171-expanded cells were performed. No non-clinical reproductive safety studies were conducted with dorocubicel.

Juvenile animal studies

Juvenile toxicity studies were not conducted with dorocubicel.

Safety Pharmacology

Safety pharmacology assessment of UM171 was performed to determine whether UM171 interferes with the human ether-à-go-go-related gene (hERG) potassium ion channel. Human embryonic kidney (HEK) 293 cells transfected with the hERG gene were exposed for 5 minutes to 0.1, 1.0 and 10 µM of UM171. UM171 did not affect the current across the cell membrane indicating non hERG channel blocking potential.

No further non-clinical studies are planned at this time.

SIII Clinical trial exposure

Clinical trial exposure to Zemcelpro is summarized overall in Table 1, by age and sex in Table 2, and by ethnic origin in Table 3. As of 31-Mar-2025, 116 patients have been exposed to Zemcelpro in Cordex Biologics-sponsored clinical trials.

Table 1: Cumulative Subject Exposure in the Development Program

Treatment	Number of Subjects
Zemcelpro	119*

* Includes 3 patients under Compassionate Use protocols approved by Health Canada

Table 2: Cumulative Subject Exposure to Zemcelpro in all Clinical Studies by Age and Sex

Data from ongoing and completed studies as of 31-Mar-2025.

Number of Subjects			
Age Range (Yr)	**Male**	**Female**	**Total**
<18	[redacted]	[redacted]	8
18 – 65	67	38	105
>65 – 75	[redacted]	[redacted]	2
>75	0	0	0
Total	**74**	**42**	**116**

Table 3: Cumulative Subject Exposure to Zemcelpro in all Clinical Studies by Racial Group

Data from ongoing and completed studies as of 31-Mar-2025.

Number of Subjects			
Racial Group	**Male**	**Female**	**Total**
Caucasian	54	32	86
Black or African American	[redacted]	[redacted]	7
Asian	[redacted]	[redacted]	3
Other	11	6	17
Unknown	2	1	3
Total	**74**	**42**	**116**

SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 4 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Severe allergic or anaphylactic reactions	To ensure general safety of patients with known severe hypersensitivity to any of the excipients or to the conditioning drugs.	No	Hypersensitivity to the active substance or to any of the excipients (e.g. DMSO) is contraindicated in the EU Summary of Product Characteristics (SmPC). Contraindications of the conditioning regimen must also be considered. Hypersensitivity reactions are included as an important potential risk in this RMP (see Module SVIII).
Current renal or hepatic impairment	To ensure general safety of patients with renal or hepatic impairment.	No	Patients are usually required to have adequate renal or hepatic function to be eligible for an allogeneic HCTC. Clinical studies of Zemcelpro did not include subjects with significant renal or hepatic impairment to determine whether their clinical outcomes could be affected. Hence, administration of Zemcelpro to such patients should be cautious.
Pregnant women or nursing (breast feeding) mothers	To ensure the safety of pregnant women or nursing (breast feeding) mothers and their child.	Yes	Information on the use of Zemcelpro in pregnant women or nursing (breast feeding) mothers is provided in the EU SmPC including advice that it should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Elderly patients (≥ 65 years)	To ensure general safety of elderly patients.	Yes	Clinical studies of Zemcelpro did not include sufficient number of subjects aged 65 years and over to determine whether they respond differently than younger subjects. In general, administration of Zemcelpro to patients > 65 years should be cautious, reflecting their greater frequency of decreased

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Paediatric Patients	To ensure the safety of children. Further research is required to better understand the risk factors and outcomes regarding sequelae and survival after treatment.	No	Zemcelpro is not yet indicated for treatment in children. This therapy is currently under the approval process in adult patients.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Required pre-HSCT conditioning regimens that include chemotherapy and irradiation that could impact vital organ functions could also complicate adverse reaction reports.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 5: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women and breastfeeding women	Not included in the Zemcelpro clinical development program.
Patients with relevant comorbidities	
Patients with hepatic impairment	Patients with liver cirrhosis, with bilirubin >2 x upper limit of normal (ULN) unless felt to be related to Gilbert's disease or haemolysis; aspartate aminotransferase and alanine transaminase >2.5 x ULN; alkaline phosphatase >5 x ULN; and those with abnormal laboratory result that is considered by the principal investigator (PI) capable of altering patient's condition or study outcome were not included in the Zemcelpro clinical development program.
Patients with renal impairment	Patients with impaired renal function (e.g., creatinine clearance <50-60 mL/minute) were excluded from the Zemcelpro studies. No other specific exclusion regarding renal function. Patients with abnormal laboratory result that is considered by the PI capable of altering patient's condition or study outcome were not included in the Zemcelpro clinical development program.

Type of special population	Exposure
Patients with cardiovascular impairment	Patients with impaired cardiac function (e.g., left ventricular ejection fraction <40%, fractional shortening >22%) with uncontrolled arrhythmia or symptomatic cardiac disease or suspicion of cardiac amyloidosis were not included in the Zemcelpro clinical development program.
Patients with respiratory impairment	Patients with impaired respiratory function (e.g., forced vital capacity or forced expiratory volume in 1 second or diffusing capacity corrected for haemoglobin ≤50% of predicted) were not included in the Zemcelpro clinical development program.
Immunocompromised patients	No specific exclusion with exception of HIV positive.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the Zemcelpro clinical development program. The clinical trial programs of Zemcelpro recruited patients with malignant haematological diseases requiring an allogeneic haematopoietic stem cell transplantation.
Population with relevant different ethnic origin	The study population included the following racial classifications: • American Indian or Alaska Native [redacted]% • Black or African American [redacted]% • Asian [redacted]% • Native Hawaiian or Other Pacific Islander [redacted]% • White 81.1% • Other 5.4%.
Subpopulations carrying relevant genetic polymorphisms	No specific exclusion from the Zemcelpro clinical development program.
Other	
Elderly patients (≥75 years)	Only 2 patients between 65 and 75 years were included in the Zemcelpro clinical development program. There is no experience with patients of 75 years and older.
Paediatric Patients	Patients have been included in the Zemcelpro ongoing clinical paediatric development program, of whom 7 were <18 years old.

SV Post-authorisation experience

Zemcelpro has not yet been marketed in any country.

SVI Additional EU requirements for the safety specification

Zemcelpro has no potential for abuse as it is not associated with abuse-related activity and is not active in the central nervous system.

SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following identified risks are considered not important.

- Graft failure/delayed immune reconstitution
- Graft versus host disease (chronic and acute)
- Pulmonary alveolar haemorrhages
- Pneumonitis (idiopathic pneumonia syndrome and cryptogenic organizing pneumonia)
- Severe infections
- Post-transplant lymphoproliferative disorder
- Engraftment syndrome

These risks are expected in the context of an allogenic stem cell transplantation and are already adequately covered in the SmPC and do not require any additional risk minimisation measures.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Following a comprehensive review of the Zemcelpro safety data and based on clinical experience with allogeneic HSCT, these are important potential risks:

- Important potential risks: Clonal haematopoiesis, risks associated with the donor such as hereditary genetic disorders or malignancies from the donor.

Further details on the safety concerns are provided in section SVII.3.1.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns and/or reclassification/removal of important identified risks, important potential risks or missing information.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Details for important identified and potential risks are provided in Table 6.

Table 6: Important Potential Risks

Clonal haematopoiesis	
Potential mechanisms	Clonal haematopoiesis (CH) is the result of over-representation of blood cells derived from a single clone and evolves over a very long period of time. Throughout life, all somatic cells continuously accumulate mutations, and HSCs are no exception, acquiring ~10 mutations per year. The combination of the total numbers of mutations accumulated and the initial HSC pool size accounts for CH. Because it takes time to accumulate a sufficient number of mutations and then for those mutations to show biological expansion in humans, CH is rare before the age of 70 years (Jaiswal and Ebert 2019, Challen and Goodell 2020).

Evidence source(s) and strength of evidence	The source of information is scientific literature.
Characterisation of the risk	The potential health implications of CH are broad. It is associated with blood cancers, cardiovascular disease, and overall mortality (Jaiswal and Ebert 2019, Weeks and Ebert 2023). Furthermore, the interaction of CH with other risk factors, such as having type 2 diabetes or elevated serum levels of C-reactive protein, may be synergistic for adverse outcomes. Many of the most commonly seen mutations in CH are also recurrent drivers of AML, MDS, myeloproliferative neoplasms, and certain lymphomas, thus individuals with CH might develop hematological malignancies. Any mutations that occur in HSCs can also potentially alter the immune response or baseline inflammatory state (Jaiswal and Ebert 2019, von Bonin et al 2021, Weeks and Ebert 2023). CH patients are described to be enriched in illnesses like hemophagocytic lymphohistiocytosis, severe COVID-19, anti-neutrophil antibody-associated vasculitis. Also, all aspects of cellular therapies, from cell harvest to cell processing and product/graft function might be affected (von Bonin et al 2021).
Risk factors and risk groups	Risk factors: • Aging (Jaiswal and Ebert 2019, Challen and Goodell 2020, von Bonin et al 2021); • Smoking (Jaiswal and Ebert 2019, von Bonin et al 2021); • Genetic predispositions (Jaiswal and Ebert 2019); • Microbiome (Jaiswal and Ebert 2019); • Cytostatic therapy (von Bonin et al 2021) • Extrinsic factors such as some aspect of the transplantation process that promotes clonal expansion (Challen and Goodell 2020). Risk groups: • Elderly patients (Jaiswal and Ebert 2019, Challen and Goodell 2020); • Patients with blood malignancies (Jaiswal and Ebert 2019).
Preventability	CH screening might help in the donor selection process (von Bonin et al 2021). Since patients undergoing cell therapy are heavily pretreated and therefore have an elevated risk for the presence of CH (von Bonin et al 2021, Weeks and Ebert 2023), strategies for pretreatment reduction or cytostatic and radiation better selection might help prevention. Patients with high-risk CH may be monitored more frequently (Weeks and Ebert 2023).
Impact on the risk-benefit balance of the product	The risk of CH is not supported by the limited current clinical experience with Zemcelpro. Therefore, the risk of CH is not expected to meaningfully impact the benefit-risk profile of Zemcelpro.
Public health impact	Considering the possibility to identify and manage patients at risk, the risk of clonal haematopoiesis with Zemcelpro treatment is considered to have a moderate to low impact on public health.

SVII.3.2. Presentation of the missing information

Details for missing information are provided in Table 7.

Table 7: Missing Information

Use in patients over 65 years of age	
Population in need of further characterisation	Subjects > 65 years of age were not excluded from the Zemcelpro clinical program but an insufficient number (n = 2) were enrolled to enable a full evaluation of the safety and efficacy in this population. UCB seems to be a viable alternate donor stem cell source for elderly patients over the age of 60. However, transplantation is not widely used to treat older patients (e.g., in US fewer than one-third of patients aged 60–70 ever undergo a transplant, and only 7% of those aged 70–80 are transplanted). Although prospective randomized (or otherwise controlled) trials are lacking, retrospective comparisons suggest that if older patients are transplanted, their outcome appears to be superior to what would be expected if treated with continued chemotherapy (Appelbaum 2021). Many retrospective and registry studies have shown comparable outcomes among matched unrelated, umbilical cord, and haploidentical donors amongst elderly patients and cord blood transplants can be safe even amongst those in their 70s (Hagen et al 2021).

SVIII Summary of the safety concerns

Safety Concerns	
Important potential risks	• Clonal haematopoiesis
Missing information	• Use in patients over 65 years of age

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance (PV) activities

Routine pharmacovigilance activities will be carried out for all safety concerns included in the Zemcelpro safety specification described above.

The robust pharmacovigilance system established by Cordex Biologics enables collection and analysis of safety data from multiple sources including spontaneous notification, literature, regulatory authorities, commercial partners as well as detection and management of signals and risks. When safety information is received, it is triaged and entered into a safety database. Individual case safety reports are reviewed by a safety physician on a case-by-case basis for completeness and accuracy and to assess the seriousness, causal relationship between an adverse event and the drug, as well as the expectedness. If relevant information is missing, Cordex Biologics will conduct follow-up investigations to collect additional data such as outcome, concomitant medications, concurrent disease(s), etc.

After Zemcelpro is marketed, aggregate safety data will be reviewed periodically and compared to the previous period, taking into account the accumulated safety knowledge for the product to identify any safety signals or trends. If a signal is detected, Cordex Biologics will assess the data in order to validate the signal taking into account previous awareness, strength of the evidence, as well as clinical relevance.

Routine pharmacovigilance activities including expedited reporting of adverse reactions and signal detection are considered sufficient to identify and/or further characterise safety concerns associated with Zemcelpro.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are required.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Post-authorization efficacy studies for Zemcelpro are described in Table 8.

Table 8: Ongoing and planned Post-authorisation efficacy studies

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study 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 (Canada)*	• To confirm low TRM of ECT-001-expanded cord blood (CB) transplant defined as ≤20% at Day 100 and 1-year post-transplant • To evaluate relapse free survival at 1- and 2-years post-transplant	• Open-label efficacy and safety study transplantation in adult patients with high-risk acute leukemia/myelodysplasia	Final Clinical Study Report	28 February 2026
Study 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 (USA/EU)*	• To examine the safety and feasibility of infusing a single ECT-001-expanded cord blood in patients with high and very high-risk acute leukemia/myelodysplasia • To evaluate relapse free survival at 1- and 2-years post-transplant in a group of patients with high risk acute leukemia/myelodysplasia	• Open-label efficacy and safety study transplantation in adult patients with high-risk acute leukemia/myelodysplasia	Final Clinical Study Report	31 August 2026

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
ECT-001-CB.010 *A Prospective Randomized Phase II Trial of Allogeneic SCT with ECT-001-CB Expanded Cord Blood Transplant without Serotherapy versus other Stem Cell Source in Paediatric Patients with High Risk/Refractory/Relapsed Acute Myeloid Leukaemia (CAML Study)*	• To evaluate the efficacy of stem cell transplant using Zemcelpro without serotherapy compared to other stem cell sources in paediatric patients and young adult patients with high risk/refractory/relapsed AML	• Randomized efficacy and safety study in children and young adults	Protocol Submission Final Clinical Study Report	16 December 2025 30 June 2030
ECT-001-CB.011 *A Multicentre, Prospective, Randomized, Open-Label Phase III Study of Dorocubicel (ECT-001-Expanded Cord Blood) Transplantation versus Best Available Allogeneic Stem Cell Source Transplantation in Adult Patients with High-Risk Acute Leukaemia/Myelodysplasia.*	• To evaluate the efficacy, safety and to report dose parameters of Zemcelpro • To determine whether, in patients with high-risk and very high-risk acute leukaemia/MDS, Zemcelpro improves EFS (relapse-free treatment failure free survival) at 2-years from the date of randomization over best alternative allogeneic HSC source	• Randomized efficacy and safety study in adults	Protocol submission Final Clinical Study Report	16 December 2025 30 June 2030
ECT-001-CB.012 *Prospective registry study in a real-world setting in Europe assessing the effectiveness and safety of Zemcelpro® in patients with haematological malignancies requiring an allogeneic stem cell transplantation following myeloablative*	• To evaluate the clinical outcomes of this product for the approved indication (time to neutrophil engraftment and platelet recovery, relapse; progression-free survival; overall survival) • To evaluate the safety of patients with haematological malignancies treated with Zemcelpro in a real-world	• Real-world effectiveness and safety of Zemcelpro	Protocol submission Start of data collection End of data collection	16 December 2025 2026 (when Zemcelpro is commercially available) 2030 (upon follow-up completion of at least 30 patients)

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
conditioning for whom no other type of suitable donor cells is available	setting in the authorized indication • To report the dose parameters of Zemcelpro		Final Clinical Study Report	31 December 2031

Part V: Risk minimisation measures

V.1 Routine risk minimisation measures (RMMs)

Important risks of Zemcelpro, together with measures to minimise such risks, are outlined below.

The routine risk minimization measures identified for this medicinal product are:

- Specific Information, such as warnings, precautions, and advice on correct use, in the proposed Product Information addressed to patients and healthcare professionals;
- Clinical settings in which the product is administrated;
- Pack size;
- The medicine's legal status - the product is supplied to the patient with prescription.

Together, these measures constitute routine risk minimisation measures.

Table 8. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks	
Clonal haematopoiesis	**Routine risk communication:** Product information (SmPC, Package Leaflet) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Clinical setting: IV product that can only be administered in a qualified transplant centre under the direction of and supervised by a healthcare professional experienced in HSCT **Other risk minimization measures beyond the Product Information:** Pack size: not applicable Legal status: prescription only medicine
Missing information	
Use in patients over 65 years of age	**Routine risk communication:** Product information (SmPC, Package Leaflet) Section 4.2 Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** Clinical setting: IV product that can only be administered in a qualified transplant centre under the direction of and supervised by a healthcare professional experienced in HSCT **Other risk minimization measures beyond the Product Information:** Pack size: not applicable Legal status: prescription only medicine

V.2 Additional risk minimisation measures

The routine risk minimisation activities as described in Part V.1 are considered sufficient to manage the safety concerns of Zemcelpro. No additional RMM are needed.

V.3 Summary of risk minimisation measures by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important potential risks		
Clonal haematopoiesis	**Routine risk minimization measures:** Clinical setting: IV product that can only be administered in a qualified transplant centre under the direction of and supervised by a healthcare professional experienced in HSCT Pack size: not applicable Legal status: prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in patients over 65 years of age	**Routine risk minimization measures:** SmPC Section 4.2 Pack size: not applicable Legal status: prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan for Zemcelpro™

This is a summary of the RMP for Zemcelpro. The RMP details important risks of Zemcelpro, how these risks can be minimised, and how more information will be obtained about Zemcelpro's risks and uncertainties (missing information).

Zemcelpro's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zemcelpro should be used.

This summary of the RMP for Zemcelpro should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zemcelpro's RMP.

I. The medicine and what it is used for

Zemcelpro is authorised for the 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 (see SmPC for the full indication). It contains dorocubicel as the active substance and it is given by as an intravenous infusion in specialised hospital setting.

Further information about the evaluation of Zemcelpro's benefits can be found in Zemcelpro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Zemcelpro, together with measures to minimise such risks and the proposed studies for learning more about Zemcelpro's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Zemcelpro, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Zemcelpro is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Zemcelpro are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zemcelpro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important potential risks	• Clonal haematopoiesis
Missing information	• Use in patients over 65 years of age

II.B Summary of important risks

Important potential risk: Clonal haematopoiesis	
Evidence for linking the risk to the medicine	The source of information is scientific literature.
Risk factors and risk groups	Risk factors: • Aging (Jaiswal and Ebert 2019, Challen and Goodell 2020, von Bonin et al 2021); • Smoking (Jaiswal and Ebert 2019, von Bonin et al 2021); • Genetic predispositions (Jaiswal and Ebert 2019); • Microbiome (Jaiswal and Ebert 2019); • Cytostatic therapy (von Bonin et al 2021) • Extrinsic factors such as some aspect of the transplantation process that promotes clonal expansion (Challen and Goodell 2020). Risk groups: • Elderly patients (Jaiswal and Ebert 2019, Challen and Goodell 2020); • Patients with blood malignancies (Jaiswal and Ebert 2019).
Risk minimisation measures	Routine risk minimisation measures: • Clinical setting: IV product that can only be administered in a qualified transplant centre under the direction of and supervised by a healthcare professional experienced in HSCT • Pack size: Not applicable • Legal status: Product subject to medical prescription Additional risk minimisation measures: • None
Additional pharmacovigilance activities	None

Missing information: Use in patients over 65 years of age	
Risk minimisation measures	Routine risk minimisation measures: • Text in product information (SmPC and package leaflet) • Clinical setting: IV product that can only be administered in a qualified transplant centre under the direction of and supervised by a healthcare professional experienced in HSCT • Pack size: Not applicable • Legal status: Product subject to medical prescription Additional risk minimisation measures: • None
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation or specific obligation.

Study name	Purpose of the study
Study 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 (Canada)	• To confirm low TRM of ECT-001-expanded cord blood (CB) transplant defined as ≤20% at Day 100 and 1-year post-transplant • To evaluate relapse free survival at 1- and 2-years post-transplant
Study 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 (USA/EU)	• To examine the safety and feasibility of infusing a single ECT-001-expanded cord blood in patients with high and very high-risk acute leukemia/myelodysplasia • To evaluate relapse free survival at 1- and 2-years post-transplant in a group of patients with high risk acute leukemia/myelodysplasia
Study ECT-001-CB.010: A Prospective Randomized Phase II Trial of Allogeneic SCT with ECT-001-CB Expanded Cord Blood Transplant without Serotherapy versus other Stem Cell Source in Paediatric Patients with High Risk/Refractory/Relapsed Acute Myeloid Leukaemia (CAML Study)	• To evaluate the efficacy of stem cell transplant using Zemcelpro without serotherapy compared to other stem cell sources in paediatric patients and young adult patients with high risk/refractory/relapsed AML
Study ECT-001-CB.011: A Multicentre, Prospective, Randomized, Open-Label Phase III Study of Dorocubicel (ECT-001-Expanded Cord Blood) Transplantation versus Best Available Allogeneic Stem Cell Source Transplantation in Adult Patients with High-Risk Acute Leukaemia/Myelodysplasia.	• To evaluate the efficacy, safety and dose parameters of Zemcelpro • To determine whether, in patients with high-risk and very high-risk acute leukaemia/MDS, Zemcelpro improves EFS (relapse-free treatment failure free survival) at 2-years from the date of randomization over best alternative allogeneic HSC source
Study ECT-001-CB.012: Prospective registry study in a real-world setting in Europe assessing the effectiveness and safety of Zemcelpro® in patients with haematological malignancies requiring an allogeneic stem cell transplantation following myeloablative conditioning for whom no other type of suitable donor cells is available.	• To evaluate the clinical outcomes of this product for the approved indication (time to neutrophil engraftment, time to platelet recovery, relapse, progression-free survival, overall survival); • To evaluate the long-term safety of patients with haematological malignancies treated with Zemcelpro in a real-world setting. • To report the dose parameters of Zemcelpro

II.C.2 Other studies in post-authorisation development plan

Not applicable.

Annexes

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Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Study 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 (Canada)

Version and date:
Version 5.0, July 02, 2021

Name and affiliation of main author:
Pierre Caudrelier, MD, Chief Medical Officer, Cordex Biologics

Aim:
To confirm low TRM of ECT-001-expanded cord blood (CB) transplant defined as ≤20% at Day 100 and 1-year post-transplant and to evaluate relapse free survival (RFS) at 1- and 2-years post-transplant in patients with high-risk acute leukemia/myelodysplasia.

Study design:
This is a multi-center open label phase II clinical trial. Patients with high risk acute leukemia/myelodysplasia will receive a single 5-7/8 HLA matched ECT-001-expanded cord blood after a myeloablative or functionally myeloablative conditioning regimen. This group of patients would be expected to have a progression free survival (PFS) or disease-free survival (DFS) ≤40% at 2 years after a conventional allogeneic transplant or would not even be eligible for transplant because of their high-risk disease's poor outcome.

Study objectives:

- **Primary:**
  - Confirm low TRM of ECT-001-expanded cord blood (CB) transplant defined as ≤20% at Day 100 and 1-year post-transplant
  - Evaluate relapse free survival (RFS) at 1- and 2-years post-transplant.
- **Secondary:**
  - Kinetics of hematologic engraftment
  - Incidence of acute and chronic GVHD by NIH criteria at 1- and 2-years post-transplant
  - Safety
  - Incidence of grade 3 or higher infectious complications
  - Hospitalization events: Duration of transplant admission and number of days in hospital in 1st 100 days, and last day of fever (≥38°C) prior to engraftment.
  - Incidence of pre-engraftment/engraftment syndrome (PES/ES) requiring therapy
  - Effect of cryopreservation of the expanded CD34+ fraction on safety and efficacy endpoints.
- **Exploratory:**
  - Immune reconstitution
  - Identification of predictors of early onset alloimmune reaction and influence on TRM and relapse
  - Influence of HLA and KIR ligand mismatch on transplant outcome
  - Relationship between mycophenolate (MMF) levels and GVHD, TRM and relapse
  - Sequencing of leukemias/myelodysplasias that relapse to identify markers suggesting escape from the immune system
  - Mucositis evaluation by measuring bacterial translocation by gene sequencing in blood, citrulline blood levels and numbers of days of parenteral feeding
  - Cost analysis
  - Relapse and survival data between 3 and 5 years post transplant by chart review.

Inclusion criteria:

1. Presence of a high-risk acute leukemia/myelodysplasia as defined by one of the following:
   a. Acute Myelogenous Leukemia (AML)
      i) Primary induction failure
      ii) Chemorefractory relapse
      iii) Relapse after autologous or allogeneic transplant
      iv) High risk AML in CR1: any adverse genetic abnormality as defined by ELN excluding FLT3 mutation, secondary or therapy related AML excluding good risk genetic abnormalities, or any

poor risk feature known to be associated with a PFS or DFS ≤40% at 2 years after a conventional transplant.
v) CR2 excluding good risk genetic abnormalities
vi) ≥CR3.

b. Acute Lymphoblastic Leukemia (ALL)
i) Primary induction failure
ii) Chemorefractory relapse
iii) Relapse after autologous or allogenic transplant
iv) High risk ALL in CR1: Philadelphia like or any poor risk feature known to be associated with a PFS or DFS ≤40% at 2 years after a conventional transplant.
v) ≥CR2
vi) MRD+ within 1 month of start of conditioning regimen.

c. Myelodysplastic Syndrome
i) Relapse after allogeneic transplant
ii) ≥10% blasts within 1 month of start of conditioning regimen
iii) Very poor risk cytogenetics (> 3 cytogenetic abnormalities)
iv) Any poor risk feature known to be associated with a PFS or DFS ≤40% at 2 years after a conventional transplant
v) TP53 mutation
vi) ≥ 40 years old and RAS or JAK-2 mutation
vii) CMML with HCT-specific CPSS score high or intermediate 2
viii) Stable disease after 6 cycles of a demethylating agent
ix) Progressive disease while on a demethylating agent

2. 18-70 years old
3. Availability of 2 CBs ≥ 4/6 HLA match when DRB1 is performed at the allele level and A, B at antigen resolution (intermediate resolution) and ≥ 4/8 HLA match when A, B, C and DRB1 are performed at the allele level. An acceptable alternative would be a 3/6 but 5/8 as long as there is no double DRB1 mismatch.
   a. Cord to be expanded:
      i) CD34+ cell count >0.5 x 10^5/kg and TNC >1.5 x 10^7/kg (pre-freeze)
      ii) Needs to be erythrodepleted by bank prior to cryopreservation
      iii) Should come from a cord bank that is FACT accredited, FDA approved or eligible for NMDP IND
   b. Back up cord: Pre-freeze TNC ≥ 2.0 x 10^7/kg with CD34+ cells ≥1.5 x 10^5/kg kg or TNC count ≥ 1.5 x 10^7 TNC/kg with CD34+ cells ≥1.7 x 10^5/kg. If a single cord does not meet these criteria any other acceptable HSC source such as 2 back up cords will be an acceptable alternative (minimum for each of 1.5 x 10^7 TNC/kg and 1.0 x 10^5 CD34+ cells/kg; an HSC back up source must be available and ready to be collected when conditioning regimen starts (for example: a haploidentical or any other acceptable donor needs to have completed medical clearance prior to start of conditioning regimen).
4. Karnofsky score ≥ 70%.
5. Bilirubin < 2 x upper limit of normal (ULN) unless felt to be related to Gilbert's disease or hemolysis; AST and ALT ≤ 2.5 x ULN; alkaline phosphatase ≤ 5 x ULN.
6. Estimated or measured creatinine clearance ≥ 60 ml/min/1.73m2.
7. HCT-CI ≤5 for patients <60 years old; HCT-CI ≤3 for patients <60 years old with acute leukemia not in CR/CRi or if 2nd allogeneic transplant; HCT-CI ≤3 for patients who are 60-65 years old; HCT-CI ≤2 for patients 60-65 years old and 2nd transplant or if acute leukemia not in CR/Cri; HCT-CI ≤1 if 66-70 years old; HCT-CI ≤1 and KPS ≥90% if 66-70 years old and 2nd transplant or if acute leukemia not in CR/CRi.
8. Left ventricular ejection fraction ≥ 40% (within 3 months unless patient has received chemotherapy or radiation therapy to the thorax since the last cardiac evaluation).
9. FVC, FEV1 and DLCOc ≥ 50% of predicted (within 3 months unless patient has received chemotherapy or radiation therapy to the thorax since last pulmonary evaluation).
10. Signed written informed consent (parents or legal guardians for minor patients)

11. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days of enrolment and must be willing to use an effective contraceptive method while enrolled in the study.

Exclusion criteria:

1. Patient never treated with cytotoxic chemotherapy and planned conditioning regimen does not include 12 Gy TBI (exceptions allowed if approved by PI).
2. Allogeneic myeloablative transplant within 6 months.
3. Autologous hematopoietic stem cell transplant within 6 months.
4. Planned use of ATG in conditioning regimen (exceptions allowed if approved by PI in which case ATG must be adjusted for weight/lymphocyte count and given more than 1 week prior to transplant; any patient who receives ATG will have immune recovery studies but will not be counted with rest of patients and will be analyzed separately).
5. Planned use of an HLA matched CB (8/8 allele matched)
6. Uncontrolled infection.
7. HLA antibodies with significant titers directed towards expanded cord blood.
8. Presence of a malignancy other than the one for which the CB transplant is being performed, with an expected survival estimated to be less than 75% at 5 years.
9. Seropositivity for HIV.
10. Hepatitis B or C infection with measurable viral load. Patients with hepatitis B or C infection regardless of viral load require clear documentation of absence of cirrhosis by either fibroscan or biopsy. If fibroscan is the method used, the test must be unequivocally negative.
11. Liver cirrhosis.
12. Active central nervous system involvement
13. Chloroma > 2 cm
14. ≥50% blasts in marrow in an evaluable marrow sample (>25% of normal cellularity for age) collected less than one month prior to start of conditioning regimen.
15. Peripheral blasts >1000/mm3
16. Pregnancy, breastfeeding or unwillingness to use appropriate contraception.
17. Participation in a trial with an investigational agent within 30 days prior to entry in the study.
18. Patient unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up, and tests.
19. Any abnormal condition or laboratory result that is considered by the PI capable of altering patient's condition or study outcome.

Accrual objective and period:
30 patients (31 were enrolled between May 2019 and October 2022)
3-year follow-up

Status:
Recruitment complete. Follow-up ongoing. Study report expected in February 2026.

Study 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 (USA/EU)

Version and date:
Version 3.5, February 06, 2024

Name and affiliation of main author:
Pierre Caudrelier, MD, Chief Medical Officer, Cordex Biologics

Aim:
To examine the safety (including assessment of rate of graft failure) and feasibility of infusing a single ECT-001-expanded cord blood and to evaluate relapse free survival at 1- and 2-years post-transplant in a group of patients with high risk acute leukemia/myelodysplasia.

Study design: Prospective, single arm, open label, multi-center, non-randomized phase II trial.

Study objectives:

- **Primary:**
  - Examine the safety (including assessment of rate of graft failure) and feasibility of infusing a single ECT-001-expanded cord blood in patients with high and very high-risk acute leukemia/myelodysplasia
  - Evaluate relapse free survival at 1- and 2-years post-transplant in a group of patients with high risk acute leukemia/myelodysplasia
- **Secondary:**
  - Determine the kinetics of hematologic engraftment (including neutrophil and platelet engraftment) following infusion of a single ECT-001-expanded cord blood.
  - Estimate the incidence of transplant related mortality at day 100 and 1-year post-transplant.
  - Determine incidence of acute and chronic GVHD by NIH criteria at 2 years post-transplant
  - Evaluate GRFS and CRFS at 1- and 2-years post-transplantation.
  - Determine incidence of grade 3 or higher infectious complications
  - Determine incidence of pre-engraftment/engraftment syndrome requiring therapy
- **Exploratory:**
  - Immune reconstitution
  - Document hospitalization events: Duration of transplant admission and number of days in hospital in 1st 100 days, last day of fever (≥38°C) prior to engraftment, number of days of parenteral feeding
  - Dendritic and mast cell analysis in patient
  - Detailed cellular and molecular analysis of graft at single cell level
  - Influence of HLA mismatch on transplant outcome
  - Sequencing of leukemias/myelodysplasias that relapse to identify markers suggesting escape from the immune system
  - QoL (EU sites)

Inclusion criteria:

1. 18-70 years old
2. Presence of a high and very high-risk hematologic malignancy defined as:
   a. Acute Myeloid Leukemia:
      i) Primary induction failure (no CR or CRi after ≥ 2 courses of intensive induction therapy or after ≥ 1 induction containing high dose Ara-C)
      ii) Chemorefractory relapse (no CR or CRi after 1 chemointensive treatment)
      iii) Relapse after allogeneic or autologous transplant.
      iv) High risk AML in CR1 as defined by European Leukemia Net (ELN)
      v) ≥ CR2
      vi) Presence of minimal residual disease at the time of transplant
   b. Acute Lymphoid leukemia
      i) Primary induction failure (≥ 2 inductions)
      ii) High risk ALL in CR1: Ph like ALL or any other poor risk feature
      iii) ≥ CR2
      iv) Chemorefractory relapse (at least 1 intensive induction chemotherapy)
      v) Relapse after allogeneic or autologous transplant
      vi) Presence of minimal residual disease at the time of transplant
   c. Myelodysplastic syndrome (MDS):
      i) Relapse after allogeneic or autologous transplant
      ii) ≥10 % blasts within 30 days of start of conditioning regimen

iii) Poor and very poor cytogenetics abnormalities
iv) CMML with HCT-specific CPSS score high or intermediate-2
v) Stable disease (absence of CR/PR/HI) after 6 cycles of azacitidine (or another demethylating agent).
vi) Progressive disease while on azacitidine (or another demethylating agent).

d. Chronic myelogenous leukemia: Patients who progressed to blast crisis.

3. Availability of 2 CBs ≥ 4/6 HLA match when DRB1 is performed at the allele level and A, B at antigen resolution (intermediate resolution) and ≥ 4/8 HLA match when A, B, C and DRB1 are performed at the allele level. An acceptable alternative would be a 3/6 or 5/8 as long as there is no double DRB1 mismatch.
   a. Selection of cord to be expanded:
      i) Pre-freeze CD34+ cell count ≥0.5 x 10^5/kg and TNC≥1.5 x 10^7/kg
      ii) Needs to be erythrodepleted by bank prior to cryopreservation
      iii) Must comply with local site regulations AND, in the USA, come from a cord bank that is FACT, or AABB accredited, or FDA approved or eligible for NMDP IND, in Europe come from a cord bank that is FACT, or AABB accredited, or complying with quality standards of the JACIE (Joint Accreditation Committee ISCT-Europe & EBMT) (unless PI approves another bank)
   b. Selection of Non-expanded CB/back-up cord (recommendation):
      i) Pre-freeze CD34+ cells ≥1.5 x 10^5/kg with TNC count ≥ 2.0 x 10^7/kg or,
      ii) Pre-freeze CD34+ cells ≥1.7 x 10^5/kg with TNC count ≥ 1.5 x 10^7 kg.
      iii) If a single cord does not meet these criteria, 2 back up cords will be an acceptable alternative with each having CD34+ cells > 1 x 10^5/kg with TNC > 1.5 x 10^7/kg
      iv) According to local regulations, must come from a cord bank that is FACT, or AABB accredited, or FDA approved or eligible for NMDP IND, or complying with quality standards of the JACIE (unless PI approves another bank)
      v) Any other HSC source would be acceptable provided it is available and ready to be collected prior to starting conditioning regimen
4. Karnofsky ≥70.
5. Left ventricular ejection fraction ≥ 40% (within 3 months unless patient has received chemotherapy or radiation therapy to the thorax since the last cardiac evaluation) or fractional shortening >22%
6. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and diffusing capacity corrected for hemoglobin (DLCOc) ≥ 50% of predicted
7. Bilirubin < 2 x upper limit of normal (ULN) unless felt to be related to Gilbert's disease or hemolysis; AST and ALT ≤ 2.5 x ULN; alkaline phosphatase ≤ 5 x ULN.
8. Adequate renal function defined as creatinine < 2.0 mg/dl (adults). All adults with a creatinine > 1.2 or a history of renal dysfunction must have estimated creatinine clearance > 50 ml/min.
9. Hematopoietic cell transplantation specific comorbidity index (HCT-CI) ≤3 if patients have ≥5% blasts in the bone marrow and HCT-CI ≤5 if 60-70 years old.

Exclusion criteria:

1. Allogeneic myeloablative transplant within 6 months.
2. Autologous hematopoietic stem cell transplant within 6 months.
3. Active or recent (prior 6 month) invasive fungal infection without ID consult and approval.
4. Presence of a malignancy other than the one for which the UCB transplant is being performed and the expected survival related to the malignancy is estimated to be less than 75% at 5 years.
5. HIV positivity.
6. Hepatitis B or C infection with measurable viral load.
7. Liver cirrhosis.
8. Pregnancy, breastfeeding or unwillingness to use appropriate contraception.
9. Participation in a trial with an investigational agent within 30 days prior to entry in the study.
10. Patient unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up, and tests.
11. Any abnormal condition or laboratory result that is considered by the principal investigator capable of altering patient condition or study outcome.
12. Active central nervous system involvement.

13. Chloroma > 2 cm.

Accrual objective and period:
30 evaluable patients (33 were enrolled between April 2020 and February 2024)
2-year follow-up

Treatment description:
The cord to be expanded is thawed about 15 days prior to transplant and undergoes CD34+ selection. The CD34- product is cryopreserved and will be thawed and infused on Day 0 (day of transplant). The CD34+ product will be placed in culture with UM171 for a 7-day expansion, cryopreserved and will be thawed and infused on Day 0. If the expanded cord or/and CD34- components do not meet release criteria, an unmanipulated cord will be infused.
There are two conditioning regimens allowed per protocol:

- Regimen A: High dose consisting of 1320 cGy TBI + Fludarabine + Cyclophosphamide (18 to < 45 years old)
- Regimen B: Intermediate dose consisting of 400 cGy TBI + Fludarabine + Cyclophosphamide + Thiotepa (18 to < 70 years old).

Patients will receive standard supportive care, growth factors and GVHD prophylaxis (tacrolimus and MMF)

Safety Management:
Stopping rules: Graft failure > 10%, TRM at Day 100 > 30%, Acute GVHD grade 3-4 > 25%
If any of the stopping rules are met, trial recruitment will be suspended pending review by the DSMB for a recommendation regarding termination or continuation of the trial. In addition, we shall carefully monitor time to engraftment, and while no formal “stopping rule” will be set for this endpoint, should the average time to engraftment among patients treated on this study appear to be longer than that in an appropriate historical control group, the study will also be suspended pending a review as described above.
Safety monitoring: An independent Data Safety Monitoring Board (DSMB), composed of transplant hematologists not directly involved with the study, will review safety data. Because of the open-label status of this phase II trial, the DSMB members will have a regular access to the key parameters of the study. They will convene at least once every year or whenever upon request of one of the Principal Investigator or one of the DSMB members. The DSMB will use their experience in reviewing the data submitted to them and decide on any necessary follow-up actions, such as review/discussion of additional data, protocol amendments, hold or discontinuation of clinical operations if they deem it justified for the safety of the patients

Status:
Recruitment complete. Follow-up ongoing. Study report expected in August 2026.

Study ECT-001-CB.010: A prospective randomized 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 (CAML study)

Version and date:

Name and affiliation of main author:

Pierre Caudrelier, MD, Chief Medical Officer, Cordex Biologics

Aim:

To evaluate the efficacy of stem cell transplant using ECT-001-CB without serotherapy compared to other stem cell sources in pediatric patients and young adult patients with high risk/refractory/relapsed AMLThis is a randomized, open-label, multi-center, phase II study to compare the efficacy of SCT using ECT-001-

CB versus other stem cell source in pediatric and young adult (age <21) patients with high-risk/refractory/relapsed AML.

Study design:

This is a randomized, open-label, multi-center, phase II study to compare the efficacy of SCT using ECT-001-CB versus other stem cell source in pediatric and young adult (age <21) patients with high-risk/refractory/relapsed AML. Donor searches will be performed by the referring centre at diagnosis of AML or relapse as part of routine standard of care. Eligible patients from throughout the UK and France with high risk (MyeChild01 criteria) or relapsed AML who have a single ≥6/8 HLA matched cord with adequate total nucleated cell (>1.5 x 10^7/kg) and CD34 (>0.5 x 10^5/kg) cell dose for ECT-001-CB to be manufactured will be enrolled at the study sites after the first course of induction chemotherapy. Following informed consent at the study site, patients will be randomised by ACT to either cord blood transplant using ECT-001-CB with no serotherapy vs best available other donor (matched sibling, unrelated donor or haploidentical) as determined by the site clinicians. Cord blood unit selection for generation of ECT-001-CB will be performed in consultation with a dedicated trial Cord Graft Selection Panel. In general, cord units which are 6-8/8 HLA matched with the patient with the highest CD34/total nucleated cell dose and CD34 viability > 70% will be selected. It is anticipated that relapsed patients will proceed to transplant after a single course of reinduction regardless of remission status and primary refractory patients/those in CR1 after 2 courses although 1 additional course is permissible if needed for logistical reasons. All patients will receive myeloablative fludarabine/busulphan based conditioning. Those on the cord blood arm will receive no serotherapy, those on the best available other donor arm will receive serotherapy with ATG if an unrelated or haploidentical donor is utilised. In all patients, immunosuppression will be withdrawn early in the absence of GVHD and donor lymphocyte infusion for mixed chimerism is permitted as per institutional standard of care.

Patients will be assessed for chimerism in the peripheral blood at 1, 3, 6, 12 and 24 months post-SCT and disease status (morphologic, flow and molecular MRD) in the bone marrow at 1, 6, 12 and 24 months post-SCT or when clinically indicated. Excess samples will be stored for future ethically approved research. All patients will be followed up at the study site for a minimum of 2 years post-SCT. Following this, patients will be followed up as per institutional guidelines.

Data on the incidence of significant and severe acute GVHD (modified Seattle criteria) and moderate/extensive chronic GVHD (NIH consensus criteria), 1 year transplant related mortality and 2-year cumulative incidence of relapse, disease-free survival, chronic GVHD-free, relapse-free survival (CRFS), GVHD-free, relapse-free survival (GRFS) and overall survival will be collected. Quality of life of patients will also be collected. Data will be analysed 2 years after the last patient is randomised.

Study objectives:

- **Primary:** 2-year chronic GVHD-free, relapse-free survival (CRFS) based on time from randomization by intention-to-treat.
- **Secondary:**
  - Neutrophil and platelet engraftment
  - Incidence of significant (≥ grade II) and severe (≥ grade III) acute GVHD and moderate/severe chronic GVHD
  - Treatment-related mortality (TRM) at 1 yr
  - 2 year cumulative incidence of relapse (CIR)
  - 2 year disease-free survival (DFS), GVHD-free, relapse-free survival (GRFS), and overall survival (OS)
  - Safety including severe infectious complications
  - Health related quality of life

Inclusion criteria:

1. Pediatric and young adult subjects (aged 0 to 21 years) with high-risk/relapsed/refractory AML:
   a. High risk patients (defined using MyeChild01 criteria) in CR1 (regardless of MRD status)
   b. Any patient refractory to 2 courses of frontline chemotherapy (defined as >5% blasts confirmed flow cytometrically)

   c. Any patient with relapsed AML regardless of remission status.
2. Presence of a single ≥6/8 HLA matched cord unit with adequate total nucleated cell (>1.5 x 10^7/kg) and CD34 (>0.5 x 10^5/kg) cell dose for generation of ECT-001-CB
3. Adequate organ function as defined by:
   a. Baseline oxygen saturation >92% on air
   b. Left ventricular shortening fraction ≥28% on echocardiogram
   c. Serum Creatinine <3 x ULN
   d. Serum bilirubin <3 x ULN
4. Lansky (age <16 years) or Karnofsky (age ≥16) score ≥60
5. Fit for myeloablative SCT
6. Written, informed consent (patient and/or parent or legal guardian)

Exclusion criteria:

1. Prior SCT
2. Therapy-related AML
3. Down's syndrome associated AML
4. Presence of donor directed HLA antibodies
5. Active hepatitis B, C or HIV infection or other uncontrolled infection
6. Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease.

Accrual objective and period:

Primary end-point (2 year CRFS): Based on historical data, we anticipate the 2 year cGRFS for patients treated in the ECT-001-CB transplant arm will be 58% compared to 32% in the best available other donor arm. With a 10% 2-sided alpha, 90 patients total would need to be randomised to show this difference with 80% power.

Data from the UK Paediatric BMT group audits from 2019-21 show that an average of 33 patients/year age <18 received a first transplant for AML in HR CR1, CR2 or with refractory disease. In addition, we would anticipate approximately 25 patients/yr would be transplanted for these indications at the French study sites, giving a potential pool of 58 patients/yr. Of these, we anticipate 20% will be excluded because of absence of a suitable cord unit or other exclusion criteria. Thus we estimate 46 patients who are currently transplanted would be potentially eligible per year. We anticipate 60% of eligible patients will agree to randomisation, giving 28 patients enrolled per year. To ensure a sufficient sample size in each paediatric subset making it possible to conduct valuable age-specific exploratory sub-analyses, a maximum of 20 children 18-21 years-old will be included, and the recruitment will aim to enroll a minimum of 20 patients in each of the 0-5, 6-11 and 12-17 year old subset. Assuming this enrollment rate, this study is projected to enroll 90 patients over a 3.2 year period. Whilst international randomised studies involving SCT have to date been challenging, the recent successful delivery of the international FORUM study in paediatric ALL and FIGARO study in adult AML has demonstrated that this is feasible and there is strong support for this study from all centres in the UK Paediatric BMT Group and amongst French Paediatric BMT colleagues.

Study ECT-001-CB.011: A Multicenter, Prospective, Randomized, 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 Leukemia/Myelodysplasia

Version and date: v5.0, 31-Mar-2025

Name and affiliation of main author:

Pierre Caudrelier, MD, Chief Medical Officer, Cordex Biologics

Study design:

Multi-center, prospective, open-label, randomized, phase III protocol to compare, in patients with high-risk and very high-risk acute leukemia/myelodysplastic syndrome, the clinical outcome post-transplantation of ECT-001-CB (ECT-001-expanded CB) transplantation versus transplantation with best alternative stem cell source (haplo, MMUD).

Once eligibility is confirmed, patients will be randomized at a ratio of 1:1 between the treatment arms with a stratification for site, disease classification (myeloid [AML/MDS] vs. lymphoid [ALL] diseases) and disease risk (high vs. very-high risk).

It is estimated that 24 months of accrual will be necessary to enroll the targeted sample size. All patients will be followed until the last patient has completed 2 years follow-up. Each individual patient will therefore be followed for a minimum of 2 years post-randomization

Study objectives:

- **Primary:** Determine whether, in patients with high-risk and very high-risk acute leukemia/MDS, ECT-001-CB (ECT-001-expanded CB) transplantation improves EFS (relapse-free, treatment failure-free survival) from the date of randomization over allogeneic transplantation with the best alternative HSC source (haplo, MMUD).
- **Secondary:**
  - Chronic GVHD-free relapse-free survival (CRFS) following HSCT
  - Incidence of malignancy relapse/progression following randomization and HSCT for transplanted patients.
  - Overall survival (OS) post-transplant following randomization and HSCT for transplanted patients.
  - Incidence of grade 3 or higher viral and bacterial infectious complications following HSCT.
  - Incidence of chronic GVHD by NIH criteria (mild, mod-severe, and that requiring systemic immunosuppression) following HSCT.
- **Exploratory:** Kinetics of hematologic recovery: cumulative incidence and median time from transplant to neutrophil (>100 and >500) and platelet (>20000) engraftment following HSCT, Incidence of graft failure following HSCT; Incidence of non-relapse mortality (NRM) following randomization and HSCT for transplanted patients; GVHD-free relapse-free survival (GRFS) following HSCT; Incidence of acute GVHD grade 2-4 and 3-4 following HSCT; Incidence of subsequent transplant for transplanted patients; Incidence of adverse events following HSCT, including AESI and AEs of donor origin; Incidence of randomized patient not achieving transplantation for any cause; Time to transplantation defined as the number of days between randomization and transplantation; CD4 counts at 30, 60 and 100 days, 6-, and 12-months; Hospitalization events: Duration of initial transplant hospitalization and total number of hospitalizations within 1st 100 days post-transplant; Patient Reported Outcome (FACT-BMT trial outcome index, EQ-5D-5L, Karnowsly); Dose parameters: Viable CD34+/kg and viable CD3+/kg dose administered at time of transplant, including pre-cryo and post-thaw doses when applicable

Inclusion criteria:

1. Age: Subjects ≥ 18 and < 70 years old at time of consent
2. Patients indicated for an alternative mismatched allogeneic HSCT (haplo, MMUD)
3. Presence of high-risk acute leukemia/myelodysplasia, as suggested by the Refined DRI for AL and IPSS-M/IPSS-R for MDS and defined as one of the following:
   a. Acute Myeloid Leukemia:
      i. Primary induction failure (no CR or CRi after ≥ 2 courses of induction therapy including Flt3 inhibitor in Flt3 mutated AML)
      ii. Chemorefractory relapse (no CR or CRi after 1 chemointensive treatment)
      iii. Relapse after allogeneic transplant (no donor-derived)
      iv. High risk AML with any adverse genetic abnormality as defined by ELN 2022
      v. ≥CR3

b. Acute Lymphoid Leukemia
   i. Primary induction failure (≥ 2 inductions)
   ii. Chemorefractory relapse (at least 1 intensive induction chemotherapy; blinatumomab, inotuzumab or CAR-T cells may be considered as an equivalent)
   iii. Relapse after allogeneic transplant (no donor-derived)
   iv. CR2 (at least 1 intensive induction chemotherapy; blinatumomab, inotuzumab or CAR-T cells may be considered as an equivalent)
   v. CR3
   vi. MRD+ at the end of induction (positive clonoSEQ® assay45 and/or ≥10-4 leukemic/normal cells by flow cytometry in bone marrow).
c. Myelodysplastic syndrome
   i. Relapse after allogeneic transplant
   ii. Multihit TP53 mutation
   iii. Very-high IPSS-M score (very-high IPSS-R score, if IPSS-M not available)
   iv. Stable disease (absence of CR/PR/HI) after 4 cycles of hypomethylating agent-based regimen.
   v. Progressive disease while on hypomethylating agent-based regimen.

4. Availability of both one CB suitable for expansion AND at least 1 alternative HSC donor readily to donate HSCs sourced from mobilized peripheral blood (donor identified and agreeable to be collected)
   a. CB to be expanded for patients assigned to the ECT-001-CB arm
      i. Availability of 1 CB ≥ 5/8 HLA match when A, B, C and DRB1 are performed at the allele level.
      ii. Minimal cell dose: CD34+ cell count >0.5 x 105/kg and TNC≥1.5 x 107/kg pre-freeze)
      iii. Needs to be erythrodepleted by bank prior to cryopreservation
      iv. Must comply with local site regulations AND, in North-America, come from a cord bank that is FACT, or AABB accredited, or FDA approved or eligible for NMDP IND, or in Europe, come from a cord bank that is FACT, or AABB accredited, or complying with quality standards of the JACIE (Joint Accreditation Committee ISCT-Europe & EBMT) (unless PI approves another bank)
      v. If conditioning regimen (chemotherapy) starts after results of expansion culture are known a backup graft is not required. Otherwise, an HSC backup source must be readily available when conditioning regimen starts (each center will follow their own institutional guidelines for the definition of an adequate graft source).
   b. Alternative HSC donor for patients assigned to the control arm:
      i. Donor must meet the selection criteria as defined by the Foundation of the Accreditation of Cell Therapy (FACT) and will be screened per the American Association of Blood Banks (AABB) guidelines.
      ii. Donor must be identified and must have agreed to donate at the time of enrolment.
      iii. For both Haplo and MMUD donors, HSCs will be harvested from mobilized peripheral blood. No collection from bone marrow source.
      iv. For mismatched (MMUD) unrelated donor. The donor must be:
         1. Mismatched for a single allele or antigen mismatching at HLA-A, B, C or DRB1 (7/8) as defined by high resolution typing.
         2. Donors are excluded when preexisting immunoreactivity is identified that would jeopardize donor hematopoietic cell engraftment. The recommended procedure for patients with 10 of 10 HLA allele level (phenotypic) match is to obtain panel reactive antibody (PRA) screens to class I and class II antigens for all patients before HCT. If the PRA shows > 10% activity, then flow cytometric or B and T cell cytotoxic cross matches should be obtained. The donor should be excluded if any of the cytotoxic cross match assays are positive. For those patients with an HLA Class I allele mismatch, flow cytometric or B and T cell cytotoxic cross matches should be obtained regardless of the PRA results. A positive anti-donor cytotoxic crossmatch is an absolute donor exclusion.
         3. Patient and donor pairs homozygous at a mismatched allele in the graft rejection vector are considered a two-allele mismatch, i.e., the patient is A*0101 and the donor is A*0102, and this type of mismatch is not allowed.
      v. For an haploidentical donor (Haplo). The donor must be:

1. A haploidentical relative of the patient. Donor-recipient compatibility will be tested through HLA typing at high resolution for the HLA loci (-A, -B, -C, - DRB1). Donor and recipient should share at least 4/8 HLA loci.- Age ≥ 12 years
2. Weight ≥ 40 Kg

5. Patient eligible for a high- or intermediate intensity conditioning regimen.
6. Patients with adequate physical function as measured by:
   a. Karnofsky score ≥ 70%.
   b. Bilirubin < 2 x upper limit of normal (ULN) unless felt to be related to Gilbert's disease or hemolysis; AST and ALT ≤ 2.5 x ULN; alkaline phosphatase ≤ 5 x ULN.
   c. Estimated or measured creatinine clearance ≥ 60 ml/min/1.73m2.
   d. Hematopoietic cell transplantation specific comorbidity index (HCT-CI):
      i. HCT-CI ≤3 for patients with active disease (≥ 5% myeloblasts at bone marrow evaluation) and/or for patients undergoing a 2nd allogeneic transplant.
      ii. Otherwise (first allogeneic transplant in CR):
         1. No exclusion for patients < 50 years old.
         2. HCT-CI ≤5 for patients 50-65 years old.
         3. HCT-CI ≤3 for patients 66-70 years old.
   e. Left ventricular ejection fraction ≥ 40% (within 3 months unless patient has received chemotherapy or radiation therapy to the thorax since the last cardiac evaluation).
   f. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and diffusing capacity corrected for hemoglobin (DLCOc) ≥ 50% of predicted (within 3 months unless patient has received chemotherapy or radiation therapy to the thorax since last pulmonary evaluation).
7. Additional inclusion criteria:
   a. Signed written informed consent.
   b. Female patients of childbearing potential must have a negative serum pregnancy test within 30 days of enrolment and within 30 days of starting of preparative regimen; patient must be willing to use an effective contraceptive method while enrolled in the study.

Exclusion criteria:

Allogeneic myeloablative transplant within 6 months.
Patients with previous allogeneic transplantation with active GVHD requiring systemic immunosuppression.
Autologous hematopoietic stem cell transplant within 6 months.
Low intensity and nonmyeloablative conditioning regimen (TCI < 2.5)
Patients with inadequate physical function as measured by:
   a. Uncontrolled bacterial, viral or fungal infection
   b. Positive anti- HLA antibodies above 2500 MFI against the selected donor, CB to be expanded or selected conventional PBMC donor
   c. Presence of a malignancy other than the one for which the HSC transplant is being performed, with an expected survival estimated to be less than 75% at 5 years.
   d. Seropositivity for HIV.
   e. Hepatitis B or C infection with measurable viral load.
   f. Liver cirrhosis.
Patients with active disease will be excluded if
   a. Active central nervous system involvement
   b. Chloroma > 2 cm
   c. ≥50% blasts in marrow in an evaluable marrow sample (>25% of normal cellularity for age) collected less than one month prior to start of conditioning regimen
   d. Peripheral blasts >1000/mm3
   e. Rapidly progressive acute leukemia
Additional exclusion criteria:
   a. Pregnancy, breastfeeding or unwillingness to use appropriate contraception.
   b. Participation in a trial with an investigational agent within 30 days prior to randomization unless documented approval is obtained from Sponsor. c) Patient unable to give informed consent or

unable to comply with the treatment protocol including appropriate supportive care, follow-up, and tests.

c. Any abnormal condition or laboratory result that is considered by the PI capable of altering patient's condition or study outcome.

Accrual objective and period:

208 patients (104 patients in each arm). The estimated accrual period is approximately 24 months.

Protocol duration:

All patients will be followed for assessment of primary (EFS) and secondary and exploratory endpoints (neutrophil and platelet engraftment, immune reconstitution, acute and chronic GVHD, NRM, GRFS, CRFS, OS, relapse/progression, infections, health-related quality of life, and cost-effectiveness) until the last patient has completed 2 years follow-up. To ensure adequate statistical power, follow-up will be extended until 123 EFS events have been observed. Each individual patient will therefore be followed for a minimum of 2 years post-randomization or until they satisfy one of the discontinuation criteria, whichever comes first.

Treatment description:

After randomization, patients will receive either a single expanded CB transplant (ECT-001-CB) or the best available alternative stem cell source transplant (haplo, MMUD) sourced from mobilized peripheral blood following an intermediate or a high intensity conditioning regimen, chosen at the treating physician's discretion that conforms with local clinical practice for their condition, age, and HSCT indication. Low intensity and nonmyeloablative regimen will not be permitted.

For the patient randomized to the ECT-001-CB arm, the CB to be expanded is thawed about 2 weeks prior to transplant and undergoes CD34+ selection. The CD34- product is formulated and cryopreserved. The CD34+ product will be placed in culture with UM171 for a 7-day expansion at the GMP manufacturing site (CETC, Montreal), formulated and cryopreserved. Both drug products are shipped frozen to the clinical site, thawed and infused according to local standards to the patient on day of transplant. For the patients randomized in the control arm, HSCT will be performed according to each local Institutional Guidelines. Use of ATG is not permitted in the ECT-001-CB arm. Use of any in vivo T-cell depletion (e.g., alemtuzumab) is not permitted in both arms.

Patients will receive standard supportive care and GVHD prophylaxis (ECT-001-CB: mycophenolate mofetil and tacrolimus; alternative haplo/MMUD: tacrolimus or cyclosporine with methotrexate or mycophenolate mofetil AND post transplant cyclophosphamide (PTCy).

Safety management:

Safety monitoring: An independent Data Safety Monitoring Board (DSMB), composed of transplant hematologists not directly involved with this protocol, will review safety data. Because of the open-label status of this phase III trial, the DSMB members will have regular access to the key parameters of the protocol data. They will convene at least yearly, or whenever upon request of the Principal Investigator or one of the DSMB members. The DSMB will use their experience in reviewing the data submitted to them, including results of the interim analysis and decide on any necessary follow up actions, such as review/discussion or additional data, protocol amendments, hold or discontinuation of clinical operations if they deem it justified for the safety of the patients.

Statistics:

Sample size and power considerations are based on the comparison of EFS after ECT-001-expanded CB transplantation and after alternative allogeneic transplantation with other HSC source (haplo, MMUD). The expected 2 years-EFS in the control arm is set at 40% based on prior experience and medical literature. Demonstrating a 20% increase of 2-years EFS in the ET-001-CB arm would represent a significant and clinically meaningful benefit for the patients. We assume that the study will last 48 months, with an accrual period of 24 months, a 24-month follow-up period, randomization of controls vs ECT-001-CB in a 1:1 ratio, a 5% drop-out rate that is exponentially distributed. We further assume that all patients will be followed until

the end of the study. Under these assumptions, the results for sample size are based on a two-sided Log-rank test with group sequential testing with 2-stages and boundary values calculated from alpha spending functions. A total of 123 EFS events are sufficient to maintain type I error of 5% with one planned interim analysis while providing 90% statistical power for a two-sided test to detect a 20% increase in the EFS probability at 2 years. This translates to an estimated sample size of 208 patients (104 per group). If 123 EFS events are not observed at the end of the follow-up period, follow-up will continue until 123 EFS events have been observed. The expected 2 year-OS in the control arm is 45% based on prior experience and medical literature. We anticipate 15% increase in OS for the intervention group, 118 deaths are expected. This study will achieve approximately 68% power to detect a 15% increase in OS with a log-rank test (2-sided alpha=0.05).

The interim analysis will be conducted once 45% of the information is available, i.e., when 56 EFS events have accumulated across both arms, approximately 24 months after accrual into randomization when 103 patients have been included in each arm. We anticipate that up to 5% of patients will be randomized but will finally not undergo transplantation, and for power calculations we assume that these patients will not receive SCT because they progress or die within 3 months following randomization. The targeted 20% increase in EFS is the effect attributable to the transplant type itself. This translates to a 19% increase in the Intent-to-Treat (ITT) populations after accounting for the 5% of randomized patients who will finally not undergo transplant.

Study ECT-001-CB.012: Prospective registry study in a real-world setting in Europe assessing the effectiveness and safety of Zemcelpro® in patients with haematological malignancies requiring an allogeneic stem cell transplantation following myeloablative conditioning for whom no other type of suitable donor cells is available

Version and date: v2.0, 15-Apr-2025

Name and affiliation of main author:

Pierre Caudrelier, MD, Chief Medical Officer, Cordex Biologics

Rationale and background:

Zemcelpro is a cryopreserved UM171 allogeneic hematopoietic stem and progenitor cell therapy derived from cord blood consisting of 2 allogeneic hematopoietic cell products: an Expanded Product of CD34+ cells (dorocubicel) and an unexpanded Product of CD34- cells that includes viable CD3+ cells (vCD3+), both derived from the same patient-specific single cord blood unit, and it is provided as a cellular suspension for intravenous infusion.

Zemcelpro is approved for the treatment of patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available.

It has been estimated that 5% to 15% of adult patients with haematologic malignancies requiring an allogeneic HSCT might not have timely access to any suitable donor cells (Sanz et al. 2020; Barker et al. 2019). This issue is particularly acute for minorities such as people of African, Hispanic or Asian descent, who have less common HLA types and are underrepresented in cell donor registries (Dumont-Lagace et al. 2022).

The assessment of outcomes in a real-world setting is of interest due to the limited data availability at the time of marketing authorization of Zemcelpro and is a post-approval commitment for the European Medicines Agency (EMA). The protocol proposes to collect real-world effectiveness and safety data of European patients treated with commercial Zemcelpro in participating countries where the product is commercially available and followed up over 2 years post-treatment.

Research question and objectives:

This prospective non-interventional study, based on secondary use of registry data, will inform on real-world effectiveness and safety of Zemcelpro. The primary objective is to evaluate the clinical outcomes of the product. The secondary objective is to evaluate the safety of patients with haematological malignancies treated with Zemcelpro in a real-world setting in the authorized indication.

Dose parameters (CD34+ and vCD3+ cell dose) will also be collected at manufacturing and reported for each Zemcelpro lot manufactured for treated patients enrolled in the study.

Study design:

This post-authorization effectiveness and safety study (PAES) with secondary use of data is a European, non-interventional study that will report on patients treated with commercial Zemcelpro in the authorized indication. Patient data will be retrieved from the established transplant registry and analysed by the EBMT which is the registry holder. All patients will be followed up until 2 years post-treatment.

Dose parameters of Zemcelpro lot manufactured for treated patients enrolled in the study will be collected at time of manufacturing.

Setting and study population:

The study population will include adult patients who received Zemcelpro infusion in the commercial setting for the authorized indication in participating countries and who consented to share their pseudonymized data with the Marketing Authorization Holder (MAH), Cordex Biologics. Participating countries are expected to include European countries once the product is licensed by the Regulatory Authorities and where it is commercialised and covered by national healthcare systems. Participation of patients will be voluntary. Participating treatment centres will enter the data into the EBMT Registry following existing EBMT Data Collection Forms (DCFs).

Data from at least 30 patients during at least 2 years of enrolment period, treated with Zemcelpro once commercially available will be collected until death, lost to follow-up, withdrawal of consent, or up to 2 years post-infusion, whichever occurs first.

Variables to be collected for demographics and baseline characteristics:

- age;
- sex;
- ethnicity (if allowed);
- country;
- treatment centre;
- primary disease diagnosis;
- disease status at time of Zemcelpro infusion;
- time from diagnosis of the primary disease to Zemcelpro infusion;
- performance score (ECOG or Karnofsky);
- comorbidity index (HCT-CI);
- prior haematopoietic stem cell transplantation and donor sources;
- immunosuppressants;
- prior GvHD;
- prior cell therapies;
- intensity of conditioning regimen administered prior to Zemcelpro infusion.

Effectiveness and safety variables used for the analysis of the primary and secondary objectives:

Primary objectives

- time to neutrophil engraftment;
- time to platelet recovery;
- relapse;
- progression-free survival;
- overall survival.

Secondary objectives

- graft failure;
- non-relapse mortality;
- acute GVHD;
- chronic GVHD;
- fungal, viral and bacterial infections of clinical importance;
- pulmonary alveolar haemorrhages;
- pneumonitis;
- post-transplant lymphoproliferative disorder;
- engraftment syndrome;
- clonal hematopoiesis;
- hypersensitivity reactions;
- infusion-related reactions.

Others

- frequency and outcome of pregnancy of female patients
- product dose parameters (CD34+ and vCD3+ cell dose) from each Zemcelpro lot manufactured for treated patients enrolled in the study

Data sources:

Clinical data for this study will be retrieved from ongoing registry holder EBMT as reported by the treating physicians from participating transplant centres to the EBMT registry. The data collection will follow the list of potential complications and outcomes identified on existing core and extended data collection forms designed, owned and implemented by the EBMT. Data collection for each patient will occur at standard timepoints defined by EBMT: Baseline / Day 0, Day 100, 6 month and 1-year assessments, then annual assessments thereafter.

EBMT will be responsible to make the participating sites accountable for the accuracy and completeness of the data entered in its database. EBMT will set up site contracts with the participating sites. 10% of the patients included in every site will be monitored by EBMT. In the context of secondary use of data, participating centres will not be monitored by the MAH.

Study size:

At least 30 patients during at least 2 years of enrolment period treated with Zemcelpro once commercially available will be enrolled. The sample size calculation for this study is not based on statistical considerations but reflective of the agreement between the MAH and the EMA.

Data analysis:

The core and extended collected complication and outcome data will be summarized in the interim reports up until the end of the study. The final Clinical Study Report (CSR) will be prepared at the end of the study to include all planned analyses on the product effectiveness and safety.

A separate report describing dose parameters (CD34+ and vCD3+ cell dose) collected at time of manufacturing for each Zemcelpro lot manufactured for treated patients enrolled in the study will be prepared at the end of the study and annexed to the CSR.

Spontaneous reporting of adverse events:

For events not collected in the DCFs, treating physicians at participating centres will be informed about the possibility to report suspected adverse reactions with Zemcelpro regardless of severity grade directly to the MAH or to the concerned Health Authorities via their respective national spontaneous reporting system. Reporting of individual adverse events and adverse reactions will follow the standard spontaneous reporting system per local regulations, agreements and timelines. As this study will make secondary use of data collected in registries, expedited reporting of individual case safety reports will not occur. Valid individual case safety reports (ICSRs) will be managed, classified and submitted by the MAH as spontaneous in line with the appropriate time frames. When made aware of them, these ICSRs will also be summarised by the MAH in PSUR in accordance with the EMA requirements and the Zemcelpro EU RMP for the duration of the study.

Planned study milestones:

- Start of data collection: 2026 (when Zemcelpro is commercially available);
- Enrolment period: at least 24 months
- End of data collection: 2030 (upon follow-up completion of at least 30 patients);
- Final report of study results: 2031.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Internal documents

Zemcelpro EU Summary of Product Characteristics (SmPC). Cordex Biologics. 2025.

ECT-001-CB Development Safety Update Report (DSUR). Cordex Biologics. 2023

ECT-001-CB Development Safety Update Report (DSUR). Cordex Biologics. 2024

References

Abbas F, El Kossi M, Shaheen IS, Sharma A, Halawa A. Post-transplantation lymphoproliferative disorders: Current concepts and future therapeutic approaches. *World J Transplant*. 2020;10(2):29-46.

Aldoss I, Song JY, Curtin PT, Forman SJ. Multiple donor-derived leukemias in a recipient of allogeneic hematopoietic cell transplantation for myeloid malignancy. *Blood Adv*. 2020 Oct 13;4(19):4798-4801.

Al Hamed R, Ngoya M, Galimard JE, et al. Unrelated or haploidentical allogeneic hematopoietic cell transplantation in second complete remission for acute myeloid leukemia-Improved outcomes over time: A European Society for Blood and Marrow Transplantation Acute Leukemia Working Party study. *Cancer*. 2023;129(17):2645-2654.

Anasetti C. What are the most important donor and recipient factors affecting the outcome of related and unrelated allogeneic transplantation? *Best Pract Res Clin Haematol*. 2008 Dec;21(4):691-7.

Appelbaum FR. Effectiveness of allogeneic hematopoietic cell transplantation for older patients with acute myeloid leukemia. *Best Pract Res Clin Haematol*. 2021;34(4):101320.

Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. 2014;123(23):3664–3671.

Atalla E, Kalligeros M, Mylona EK, et al. Impact of Influenza Infection Among Adult and Pediatric Populations With Hematologic Malignancy and Hematopoietic Stem Cell Transplant: A Systematic Review and Meta-Analysis. *Clin Ther.* 2021;43(5):e66-e85.

Auletta J, Kou J, Chen M et al. Real-world data showing trends and outcomes by race and ethnicity in allogeneic hematopoietic cell transplantation: a report from the center for international blood and marrow transplant research. *Transplant Cell Ther*. 2023;29(6):346.e1-346.e10.

Barker JN, Kempenich J, Kurtzberg J, et al. CD34+ cell content of 126 341 cord blood units in the US inventory: implications for transplantation and banking. *Blood Advances*. 2019;3(8):1267-1271.

Brissot E, Labopin M, Ehninger G, et al. Haploidentical versus unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: a report on 1578 patients from the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2019;104(3):524-532.

Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant*. 2015;21(7):1167-1187.

Challen GA, Goodell MA. Clonal hematopoiesis: mechanisms driving dominance of stem cell clones. *Blood*. 2020 Oct 1;136(14):1590-1598.

Cooling L, Sankar A, Mody R, Yanik G, Bonifant C, Choi SW. A severe umbilical cord stem cell infusion reaction due to dextran in an atopic pediatric patient. *Bone Marrow Transplantation*. 2017;52(7): 1051.

DeFilipp Z, Advani AS, Bachanova V, et al. Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2019;25:2113-2123.

DeFilipp Z, Ciurea SO, Cutler C, et al. Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. *Transplantation and Cellular Therapy*. 2023; 29(2):71-81.

Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood*. 2019;134(12), 924-934.

Dholaria B, Savani BN, Hamilton BK, et al. Hematopoietic Cell Transplantation in the Treatment of Newly Diagnosed Adult Acute Myeloid Leukemia: An Evidence-Based Review from the American Society of Transplantation and Cellular Therapy. *Transplant Cell Ther*. 2021;27(1):6-20.

Dhopeshwarkar N, Iqbal S, Wang X et al. A Retrospective Study of Comorbidities and Complications in Elderly Acute Myeloid Leukemia Patients in the United States. *Clin Lymphoma Myeloma Leuk*. 2019;19(8):e436-e456.

D'Souza A, Fretham C, Lee SJ, et al. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. *Biol Blood Marrow Transplant*. 2020; 26(8):e177-e182.

Dumont-Lagacé M, Feghaly A, Meunier MC, et al. UM171 Expansion of Cord Blood Improves Donor Availability and HLA Matching For All Patients, Including Minorities. *Transplant Cell Ther*. 2022;28(7):410.e1-410.e5.

Eapen M, Klein JP, Ruggeri A, et al. Center for International Blood and Marrow Transplant Research, Netcord, Eurocord, and the European Group for Blood and Marrow Transplantation. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. *Blood*. 2014;123(1):133-40.

Fraebel J, Engelhardt BG, Kim TK. Noninfectious Pulmonary Complications after Hematopoietic Stem Cell Transplantation. *Transplant Cell Ther*. 2023;29(2):82-93.

Fleischhauer K, Tran TH, Meisel R, Mytilineos J, Dreger P, Kröger N. Donor Selection for Allogeneic Hematopoietic Cell Transplantation. *Dtsch Arztebl Int.* 2023 Apr 14;120(15):261-268.

Gagelmann N, Kroger N. Dose intensity for conditioning in allogeneic hematopoietic cell transplantation: can we recommend “when and for whom” in 2021? *Haematologica*. 2021; 106(7):1794-1804.

Grant A, Chapman LRM, Mitchell R, O'Brien TA. Engraftment syndrome following hematopoietic stem cell transplant: A review of the literature. *Clin Transplant*. 2020;34(6):e13875.

Hagen P, Adams W, Singh S, Qin S, Campo L, Tsai S, Hossain N, Smith SE, Stiff PJ. Umbilical Cord Blood as an Alternate Donor Sources for High Risk Elderly Patients Undergoing Allogeneic Stem Cell Transplantation for Hematological Malignancies. *OBM Transplantation* 2021;5(1):136.

Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10.

Hoezler D, Bassan R, Dombret H, et al. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v69-v82.

Hwang WY, Kongtim P, Majhail NS et al. Alternate Donor Transplantation. *Bloor Cell Ther*. 2022;5(Spec Edition):S6-S14.

Ikeda K, Ohto H, Okuyama Y, et al. Adverse Events Associated With Infusion of Hematopoietic Stem Cell Products: A Prospective and Multicenter Surveillance Study. *Transfus Med Rev*. 2018;S0887-7963(18) 30023-3.

Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e1.

Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science*. 2019 Nov 1;366(6465):eaan4673.

Jiang S, Yan H, Lu X, et al. How to improve the outcomes of elderly acute myeloid leukemia patients through allogeneic hematopoietic stem cell transplantation. Front Immunol. 2023;14:1102966.

Kaleka G, Schiller G. Immunotherapy for Acute Myeloid Leukemia: Allogeneic hematopoietic cell transplantation is here to stay. *Leukemia Research*. 2022;112:106732.

Kindwall-Keller TL, Ballen KK. Umbilical cord blood: The promise and the uncertainty. *Stem Cells Transl Med*. 2020;9(10):1153-1162.

Lee S, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007;110(13): 4576-4583.

Leick M, Chen YB. A glimpse into what happens after PTCy. *Blood*. 2022;139(4):479-481.

Lennmyr E, Karlsson K, Ahlberg L, et al. Survival in adult acute lymphoblastic leukaemia (ALL): A report from the Swedish ALL Registry. Eur J Haematol. 2019 Jun 6;103(2):88–98. .Magee G, Ragon BK. Allogeneic hematopoietic cell transplantation in acute myeloid leukemia. *Best Pract Res Clin Haematol*. 2023;36(2):101466.

Maglliano G, Bacigalupo A. Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia of the Elderly: Review of Literature and New Perspectives. *Mediterr J Hematol Infect Dis*. 2020;12(1):e2020081.

Mehta RS, Ramdial J, Marin D, et al. Impact of Donor Age in Haploidentical-Post-Transplantation Cyclophosphamide versus Matched Unrelated Donor Post-Transplantation Cyclophosphamide Hematopoietic Stem Cell Transplantation in Patients with Acute Myeloid Leukemia. *Transplant Cell Ther.* 2023;29(6):377.

Mohammadi M. Comorbidity in risk and outcome of hematological malignancies. Thesis. 2016. Available online: https://openarchive.ki.se/xmlui/handle/10616/45028.

Montoro J, Piñana JL, Moscardó F, Sanz J. Infectious Complications after Umbilical Cord-Blood Transplantation from Unrelated Donors. *Mediterr J Hematol Infect Dis*. 2016;8(1):e2016051.

Mroczkowska-Bękarciak A, Wróbel T. A case report of donor cell-derived hematologic neoplasms 9 years after allogeneic hematopoietic cell transplantation. *Oncotarget*. 2025 Feb 5;16:44-50.

Nagel G, Weber D, Fromm E, et al. Epidemiological, genetic, and clinical characterization by age of newly diagnosed acute myeloid leukemia based on an academic population-based registry study (AMLSG BiO). Ann Hematol. 2017 Dec;96(12):1993-2003. Nagler A, Labopin M, Mielke S, et al. Matched related versus unrelated versus haploidentical donors for allogeneic transplantation in AML patients achieving first complete remission after two induction courses: a study from the ALWP/EBMT. *Bone Marrow Transplant*. 2023;58(7):791-800.

Negrin RS. Graft-versus-host disease versus graft-versus-leukemia. Hematology *Am Soc Hematol Educ Program*. 2015;2015:225-230.

Passweg JR, Baldomero H, Ciceri F et al. Hematopoietic cell transplantation and cellular therapies in Europe 2021. The second year of the SARS-CoV-2 pandemic. A Report from the EBMT Activity Survey. *Bone Marrow Transplant*. 2023;58(6):647-658.

Politikos I, Davis E, Nhaissi M, et al. Guidelines for cord blood unit selection. *Biology of Blood and Marrow Transplantation*. 2020;26(12), 2190-2196.

Ramanathan M, Kim S, He N, et al. The incidence and impact of clostridioides difficile infection on transplant outcomes in acute leukemia and MDS after allogeneic hematopoietic cell transplant-a CIBMTR study. *Bone Marrow Transplant*. 2023;58(4):360-366.

Roloff GW, Kosuri S, Nawas MT, DuVall AS, Patel AA, Riedell PA, Odenike O, Stock W, Larson RA, Bishop MR, Nunley E, Godley LA, Hathaway F, Del Gaudio D, Das S, Canham LE, Drazer MW. Expedited evaluation of hereditary hematopoietic malignancies in the setting of stem cell transplantation. *Haematologica*. 2024 Nov 1;109(11):3739-3744.

Rozema J, Hoogendoorn M, Kibbelaar R, van den Berg E, Veeger N, van Roon E. Comorbidities and malignancies negatively affect survival in myelodysplastic syndromes: a population-based study. *Blood Adv*. 2021;5(5):1344-1351.

Saberian C, Abdel-Wahab N, Abudayyeh A, et al. Post-transplantation cyclophosphamide reduces the incidence of acute graft-versus-host disease in patients with acute myeloid leukemia/myelodysplastic syndromes who receive immune checkpoint inhibitors after allogeneic hematopoietic stem cell transplantation. *J Immunother Cancer*. 2021;9(2):e001818.

Sanz J, Montoro J, Solano C, et al. Prospective Randomized Study Comparing Myeloablative Unrelated Umbilical Cord Blood Transplantation versus HLA-Haploidentical Related Stem Cell Transplantation for Adults with Hematologic Malignancies. *Biol Blood Marrow Transplant*. 2020; 26(2):358-366.

Servais S, Beguin Y, Baron F. Current Status and Perspectives of Allogeneic Hematopoietic Stem Cell Transplantation in Elderly Patients with Acute Myeloid Leukemia [published correction appears in *Stem Cells Transl Med*. 2022 Jul 20;11(7):790]. *Stem Cells Transl Med*. 2022;11(5):461-477.

Snowden JA, Sanchez-Ortega I, Corbacioglu S et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplantation. 2022;57:1217–1239.

Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, Thiele J. WHO classification of tumours of haematopoietic and lymphoid tissues: World Health Organisation; 4th Edition, Volume 2, 2017.

Terakura S, Nishida T, Sawa M, et al. Prospective Phase 2 Study of Umbilical Cord Blood Transplantation in Adult Acute Leukemia and Myelodysplastic Syndrome. *Biol Blood Marrow Transplant*. 2020;26(1):139-144.

Tsai SB, Liu H, Shore T, et al. Frequency and Risk Factors Associated with Cord Graft Failure after Transplant with Single-Unit Umbilical Cord Cells Supplemented by Haploidentical Cells with Reduced-Intensity Conditioning. *Biol Blood Marrow Transplant*. 2016;22(6):1065-1072.

von Bonin M, Jambor HK, Teipel R, Stölzel F, Thiede C, Damm F, Kroschinsky F, Schetelig J, Chavakis T, Bornhäuser M. Clonal hematopoiesis and its emerging effects on cellular therapies. *Leukemia*. 2021 Oct;35(10):2752-2758.

Weeks LD, Ebert BL. Causes and consequences of clonal hematopoiesis. *Blood*. 2023 Dec 28;142(26):2235-2246.

Wenger DS, Triplette M, Crothers K, et al. Incidence, Risk Factors, and Outcomes of Idiopathic Pneumonia Syndrome after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant.* 2020;26(2):413-420.

Wermann WK, Viardot A, Kayser S et al. Comorbidities Are Frequent in Older Patients with De Novo Acute Lymphoblastic Leukemia (ALL) and Correlate with Induction Mortality: Analysis of More Than 1200 Patients from GMALL Data Bases. *Blood.* 2018;132 (S1): 660.

Williams LS, Williams KM, Gillis N, Bolton K, Damm F, Deuitch NT, Farhadfar N, Gergis U, Keel SB, Michelis FV, Panch SR, Porter CC, Sucheston-Campbell L, Tamari R, Stefanski HE, Godley LA, Lai C. Donor-Derived Malignancy and Transplantation Morbidity: Risks of Patient and Donor Genetics in Allogeneic Hematopoietic Stem Cell Transplantation. *Transplant Cell Ther*. 2024 Mar;30(3):255-267.

Wu J., Fu HX., He Y. et al. Risk factors and outcomes of diffuse haemorrhage after allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2021;56:2097–2107.

Yokoyama H, Morishima Y, Fuji S, et al. HLA Working Group of the Japan Society for Hematopoietic Cell Transplantation. Impact of HLA Allele Mismatch at HLA-A, -B, -C, and -DRB1 in Single Cord Blood Transplantation. *Biol Blood Marrow Transplant*. 2020;26(3):519-528.

Zhang N., Wu J., Wang Q. et al. Global burden of hematologic malignancies and evolution patterns over the past 30 years. *Blood Cancer J*. 2023;13:82.

Zhang Y, Song Y, Ni Q, et al. Systematic review and meta-analysis: transplanted hematopoietic stem cells and killer cells on leukemia. *Ann Palliat Med*. 2021;10(7):7872-7883.

Zhu X, Tang B, Sun Z. Umbilical cord blood transplantation: Still growing and improving. *Stem Cells Transl Med*. 2021;10 (Suppl 2):S62-S74.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date/ Procedure	Change
0.1	DD-MMM-YYYY/ Centralized	Initial RMP
0.2	DD-MMM-2025/ Centralized	RMP update based on feedback received from PRAC during evaluation of the application dossier: - the list of safety concerns was changed to exclude the missing information 'Use in paediatric population' and to add the important potential risk of 'Clonal haematopoiesis'; consequently Part II section SIV, SVII and SVIII were also updated; - study ECT-001-CB.012 was added to table 9 Part III.3.1: On-going and planned additional pharmacovigilance activities as category 3 study; consequently Annex 3 was also updated; - studies ECT-001-CB.007, ECT-001-CB.010 and ECT-001-CB.011 were removed from Part III 3.2 Additional pharmacovigilance activities; consequently Part III 3.3 Summary table of additional pharmacovigilance activities and Annex 2 were also updated; - Part V1 Routine RMMs was updated to add Table 11. Description of routine risk minimisation measures by safety concern as per the guideline; - Part V2 Additional RMMs was updated to remove the Controlled distribution programme for Zemcelpro and add the Healthcare professional guide as aRMM; consequently Part V.3 Summary of risk minimisation measures by safety concern was also updated. Consequently Annex 6 was also updated. Additionally, clinical trial exposure and safety data were updated with the cut-off date of 15-Mar-2024 in line with the DLP of the new Zemcelpro SmPC 2025. Consequently Part II section SIII and section SVII were updated. Overall, all RMP sections impacted by the above changes were also updated.
0.3	DD-MMM-2025/ Centralized	RMP update based on feedback received from PRAC during evaluation of the application dossier: - Removed list of important identified risks - Added potential donor risks - Removal of educational material requirement - Updates to align with D180 answers
0.4	DD-MMM-2025/ Centralized	RMP update based on feedback received from PRAC during evaluation of the application dossier: - Removed list of important identified risks

Version	Approval date/ Procedure	Change
		- Added PAES trials
1.0	13-JUN-2025/ Centralized	RMP update based on feedback received from EMA: - Signature - Milestone changed to protocol submission for studies 010, 011 and 012 in Table 8 Part IV - Clarification of dates in Table 8 Part IV - Summary of RMP, Table II.C.1