Health Technology Briefing
September 2024

Dorocubicel for treating haematological malignancies in adults requiring allogeneic HSCT

Company/Developer	Cordex Biologics (ExCellThera)

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28393	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Haematological cancers also known as blood cancers, occur when abnormal cells in the blood grow out of control. They are usually categorised by site according to whether cancer is first detected in the blood (leukaemias), lymph nodes (lymphomas), or bone (myelomas). The abnormal cells can crowd out normal blood cells, which have important functions in the body. This can make it hard to fight off infections. It can also cause symptoms like breathlessness, tiredness, bruising or bleeding, fever, pain, or lumps in the glands. There is a need for new treatment options as these cancers are life-threatening and often associated with low survival outcomes and high incidence of relapse.

Dorocubicel is a cell therapy product containing stem cells derived from umbilical cord blood attached to a molecule called UM171. Dorocubicel is administered by intravenous infusion and is used in a procedure called allogeneic haematopoietic stem cell transplantation (HSCT) where the patient's bone marrow is cleared of cells and replaced by stem cells from a donor to form new bone marrow that produces healthy blood cells. Umbilical cord blood is a rich source of stem cells that can be used for transplantation and is an alternative for those who do not have a matched related or unrelated donor. However, the number of stem cells contained in a cord blood is much smaller than other sources of stem cells. UM171 enhances stem cell expansion, helping to overcome this limitation and makes the procedure more effective and lowers the risk of relapse. If licensed, dorocubicel will offer a new treatment option for adult patients with haematological cancers requiring an allogeneic HSCT who do not have access to a suitable donor.

Proposed Indication

For the treatment of adult patients with haematological malignancies requiring an allogeneic hematopoietic stem cell transplantation (HSCT) without a suitable readily available donor.[1]

Technology

Description

Dorocubicel (Zemcelpro, ECT-001-CB, UM171-expanded cord blood transplant)[a,2] is a cell therapy derived from the *ex vivo* expansion technology that combines the combination of a small molecule, UM171, and an optimised culture system for umbilical cord blood stem cells.[3,4] The technology allows the use of better HLA matched small cord blood units as starting material. UM171 enhances haematopoietic stem cell renewal by degrading histone deacetylase 1/2 and lysine-specific demethylase 1 to prevent differentiation in culture.[3,5] Non-clinical studies have shown that UM171 can expand distinct myeloid/lymphoid progenitors, enhances derivation of haematopoietic stem and progenitor cells from human pluripotent stem cells, and increases lentiviral gene transfer and recovery of hematopoietic stem cells.[6]

Dorocubicel was developed for the treatment of haematological malignancies in adults requiring an allogeneic HSCT without a suitable readily available donor.[7] In ongoing phase II clinical trials (NCT03913026, NCT04103879), adult patients with high risk leukaemia or myelodysplasia were administered dorocubicel (CD34+: 2.5-50x10E5/kg, CD3+>1x10E6/kg) by intravenous infusion.[2,8]

Key Innovation

Dorocubicel is an advanced therapy medicinal product (ATMP) within the definition of a somatic cell therapy.[4] The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[9]

There is a need for new treatment options for patients with high and very high-risk leukaemias and myelodysplasias who have low survival outcomes and high incidence of relapse.[10] Currently, patients without a suitable available donor do not have an alternative other than palliative care or experimental therapy while their illness is threatening their vital prognosis.[11-13]

Cord blood transplants are an option for adult patients lacking an HLA identical donor but are hampered by low cell dose, prolonged aplasia, and high transplant related mortality. UM171, a novel and potent agonist of hematopoietic stem cell self-renewal during *ex vivo* expansion could reduce the risk of chronic graft versus host disease (GvHD) and relapse, thereby reducing transplanted related mortality.[3,5] The number of stem cells contained in a cord blood unit is much smaller than other sources of stem cells (like peripheral blood and bone marrow). Furthermore, less than 5% of cords stored in cord banks contain a sufficient number of stem cells to transplant an adult of 70kg. Using UM171 as an ancillary reagent enables the ex vivo expansion of small cord blood units, enhancing the availability of well-matched HLA cords within cord blood banks. This process broadens transplant accessibility across all ethnic groups, reduces the risk of complications, and ensures long-term engraftment, thereby promoting positive clinical outcomes.[14] If licensed, dorocubicel may offer a potentially curative treatment option for adult patients with haematological malignancies requiring an allogeneic HSCT without a suitable readily available donor by improving access to allogeneic transplantation.

[a] Information provided by ExCellThera

Regulatory & Development Status

Dorocubicel does not currently have Marketing Authorisation in the EU/UK for any indication. A MAA for dorocubicel has been accepted for review under an Accelerated Assessment procedure by the EMA, for adult patients with hematological malignancies requiring a stem cell transplant who lack a readily available suitable donor.[1]

Dorocubicel has the following regulatory designations/awards:

- Orphan drug designation in the US in 2018 for the prevention of graft-versus-host-disease (GVHD) and in 2024 as a treatment to enhance cell engraftment and immune reconstitution in patients receiving hematopoietic stem cell transplant.[15,16]
- Orphan medicinal product designation in the EU in 2020 for treatment in haematopoietic stem cell transplantation.[17]
- PRIME designation in the EU in 2020 for blood cancers and disorders requiring stem cell transplants.[18]
- Advanced Therapy Medicinal Product (ATMP) classification in the EU in 2020.[4]
- Regenerative medicine advanced therapy (RMAT) designation in the US in 2019 for the treatment of haematological malignancies.[19]

Dorocubicel is not currently in clinical development for any other indication.[20]

Patient Group

Disease Area and Clinical Need

Haematological malignancies (blood cancers) are traditionally categorised by site according to whether cancer is first detected in the blood (leukaemias), lymph nodes (lymphomas) or bone (myelomas).[21] The signs of blood cancer vary depending on type and are different from person to person. Symptoms may include easy bruising or bleeding, excessive sweating (especially at night), fatigue or weakness, fever and chills, frequent infections, loss of appetite, pain the bones or joints and swollen lymph nodes, often in the neck, armpits or groin.[22] The risk factors vary between the different types of blood cancer. For example, myeloma only affects adults and is much more common in men and people from an African-Caribbean background, whereas Hodgkin lymphoma usually develops in people aged 15-25 or over 50, and people who already have problems with their immune system.[23]

Haematological malignancies account for approximately 8.7% of cancers diagnosed.[21] Over 40,000 people are diagnosed with a blood cancer each year in the UK, and over 250,000 people are currently living with blood cancer.[24] The categories of haematological cancers vary in prevalence, incidence and survival rates. In addition, there are subtypes of lymphoma and leukaemia, as well as rarer haematological cancers that have their own categories.[25] Most forms of leukaemia have high 5 year survival, though some subtypes have a poorer prognosis, whereas the 5 year survival for myeloma is nearly 50%. For Non-Hodgkin's lymphoma the 5 year survival is just under 70% and for Hodgkin's lymphoma the 5 year survival is 85%.[26] 5-15% of adult patients requiring an allogeneic HSCT do not have timely access to a suitable donor.[7] The likelihood of identifying HLA-matched donors correlates strongly with patient race/ethnicity and is disproportionately higher for some populations than others thus impacting survivorship. It is particularly true for patients of visible minorities who are facing important disparities in accessing potentially curative allogeneic HSCT, especially African, Asian and white Hispanic descent.[7,14] There are approximately 1,200 allogeneic HSCT procedures performed yearly in the UK for haematological malignancies in adults,

therefore it can be estimated that between 60 - 180 adult patients per year would not have access to transplantation due to the lack of a suitable donor.[b,27]

Recommended Treatment Options

The current National Institute for Health and Care Excellence (NICE) recommendations for the treatment of haematological malignancy differ based on the type and stage of haematological cancer.[25] There are currently no NICE recommended treatment options for the treatment of adult patients with haematological malignancies requiring an allogeneic hematopoietic stem cell transplantation (HSCT) without a suitable readily available donor.

Globally, the clinical management of haematological malignancies is based on autologous or allogeneic HSCT, radiation therapy, and treatments such as chemotherapies, immunotherapies, targeted therapies, and other therapies such as CAR-T cells.[28] Currently, allogeneic HSCT remains the reference treatment for high-risk haematological malignancies. Allogeneic HSCT is a treatment option for certain types of acute myeloid leukaemia, acute lymphoblastic leukaemia, myelodysplasias, lymphoma, and other diseases.[29,30]

Clinical Trial Information

Trial	NCT04103879; **EudraCT** 2022-002458-26**;** A Phase II Open-Label Study of UM171-Expanded Cord Blood Transplantation in Patients With High and Very High Risk Acute Leukemia/Myelodysplasia **Phase II –** active, not recruiting **Locations:** USA and Netherlands **Primary completion date:** February 2026
Trial Design	Open label, single-group assignment
Population	N=30 (actual); patients aged 18 to 70 years with high and very high risk leukaemia/myelodysplasia
Intervention(s)	Single UM171-Expanded CB transplant (CD34+: 2.5-50x10E5/kg, CD3+>1x10E6/kg) administered by intravenous infusion
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Adverse events of ECT-001-CB [time frame: 100 days – 2 years post-transplant]. All AEs will be graded in severity according to the modified (for HSCT) CTCAE (v. 5.0) • Relapse-free survival [time frame: At 1 – 2 years post-transplant]. RFS will be measured from time of transplant until disease relapse, death or last follow-up See trial record for full list of other outcomes.
Results (efficacy)	Pooled results from two independent studies: At 2 years, the cumulative incidence of NRM was 19% (95% CI, 8-31) while the incidence of relapse was 18% (95% CI, 6-29). The incidence of grade II-IV and III-IV acute GVHD was 69%

[b] Information provided by ExCellThera

	(95% CI, 56–82%) and 16% (95% CI, 6–27%). The rate of moderate/severe chronic GVHD was 7% (95% CI,1–15%) and translated in an incidence of a chronic-relapse-free-survival of 55% (95% CI, 42–72%).[31]
Results (safety)	-

Clinical Trial Information

Trial	NCT03913026; A Phase II Open-Label Study of UM171-Expanded Cord Blood Transplantation in Patients With High and Very High Risk Acute Leukemia/Myelodysplasia **Phase II –** active, not recruiting **Locations:** Canada **Primary completion date:** October 2024
Trial Design	Open label, single-group assignment
Population	N=30 (actual); patients aged 18 to 70 years with high and very high-risk leukaemia/myelodysplasia
Intervention(s)	Single UM171-Expanded CB transplant (CD34+: 2.5-50x10E5/kg, CD3+>1x10E6/kg) administered by intravenous infusion
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Transplant Related Mortality (TRM) [time frame: 1 year]. TRM is defined as any death of any cause other than malignant relapse, occurring after the commencement of conditioning regimen that could be related to the transplantation procedure. • Relapse Free survival (RFS) [time frame: 2 years]. RFS will be measured from time of transplant until disease relapse, death or last follow-up. • Overall survival (OS) [time frame: 2 years]. OS will be measured from time of transplant until disease relapse, death or last follow-up. See trial record for full list of other outcomes.
Results (efficacy)	Pooled results from two independent studies: At 2 years, the cumulative incidence of NRM was 19% (95% CI, 8-31) while the incidence of relapse was 18% (95% CI, 6-29). The incidence of grade II-IV and III-IV acute GVHD was 69% (95% CI, 56–82%) and 16% (95% CI, 6–27%). The rate of moderate/severe chronic GVHD was 7% (95% CI,1–15%) and translated in an incidence of a chronic-relapse-free-survival of 55% (95% CI, 42–72%).[31]
Results (safety)	-

Clinical Trial Information

Trial	NCT02668315; A Phase I-II Open-label Study of UM171 Expanded Cord Blood in a Fed-batch Culture System in Patients Who Need an Allogeneic Hematopoietic Stem Cell Transplant But Lack a Suitable Donor **Phase I/II –** completed

	Locations: Canada **Study completion date:** August 2018 (actual)
Trial Design	Open label, non-randomised, factorial assignment
Population	N=25 (actual); patients aged 18 to 65 years patients who need an allogeneic HSCT but lack a HLA matched donor
Intervention(s)	Single UM171-Expanded CB transplant (CD34+: 2.5-50x10E5/kg, CD3+>1x10E6/kg) administered by intravenous infusion
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Monitoring adverse events, toxicities and medical evolution [time frame: up to 36 months post-transplant]. To identify unexpected toxicities associated with transplantation using cord blood cells expanded with UM171/fed-batch culture system by means of history, physical examination and laboratory evaluation. All adverse events will be evaluated for duration, intensity, and causal relationship with the study medication and followed to the end of the study or until resolution. See trial record for full list of other outcomes.
Results (efficacy)	The minimal cord blood unit cell dose at thaw that achieved prompt engraftment as a single cord transplant after UM171 expansion was 0.52 × 105 CD34-positive cells. 26 (96%) of 27 cord blood units were successfully expanded with UM171. Among the 22 patients who received single UM171-expanded cord blood transplantation, median time to engraftment of 100 neutrophils per µL was 9.5 days (IQR 8–12), median time to engraftment of 500 neutrophils per µL was 18 days (12.5–20.0), and no graft failure occurred. Median time to platelet recovery was 42 days (IQR 35–47).[5]
Results (safety)	No unexpected adverse events were observed. One (5%) of 22 patients died due to treatment-related diffuse alveolar haemorrhage.[5]

Estimated Cost

The cost of dorocubicel is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages). B04/P/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- European Society of Medical Oncology. ESMO Clinical Practice Guidelines: Haematological Malignancies. 2024.[28]
- European Society of Medical Oncology. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[11]
- RM Partners, North Central and North East Cancer Alliance, and South East London Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines. 2020.[32]

Additional Information

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