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HEALTH TECHNOLOGY BRIEFING
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OTL-200 for Metachromatic Leukodystrophy

NIHRIO ID	23997	**NICE ID**	10171
Developer/Company	Orchard Therapeutics (Netherlands) B.V.	**UKPS ID**	650945

Licensing and market availability plans	Currently in Phase III trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

OTL-200 is in development for the treatment of metachromatic leukodystrophy (MLD). MLD is a rare hereditary disease caused by changes (mutations) in the arylsulfatase A (ARSA) gene. The disease is characterized by accumulation of fats that causes the destruction of the protective fatty layer surrounding the nerves in the brain and spinal cord. MLD is a progressive disease that is heterogeneous regarding the age of onset, disease progression and symptoms severity. Symptoms vary by subtype but can include difficulty talking, seizures, difficulty walking, personality changes, and behaviour and personality changes. There are currently no effective treatments for MLD. Drugs can be given to treat the symptoms as they occur, such as muscle spasms, infections, pain and seizures.

OTL-200 is a gene therapy that involves extraction of certain stem cells from a patient's bone marrow or blood. These stem cells are genetically modified and then returned to the patient by intravenous infusion to deliver the corrected version of the gene to the cells in charge of creating key proteins. The corrected cells then produce the protein that was missing or defective prior to treatment, aiming to halt disease progression or modify its natural course. If licensed, OTL-200 will offer a potentially curative treatment option for patients with MLD, who currently have no effective therapies available.

PROPOSED INDICATION

Metachromatic Leukodystrophy (MLD)[1]

TECHNOLOGY

DESCRIPTION

OTL-200 (previously known as GSK-2696274) is a genetically modified autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector encoding the human arylsulfatase A (ARSA) *gene*.

The mechanism of action of OTL-200 in the central nervous system (CNS) is thought to be through cross correction, in which transduced cells migrating into the brain and engrafting, synthesise and secrete arylsulfatase A (ARSA). This enzyme is in turn taken up by oligodendrocytes and neurons in the CNS, allowing the breakdown of harmful sulfatides, thereby preventing further demyelination and atrophy. A precise minimum level of ARSA activity required to deliver clinical efficacy is unknown, however a treatment delivering sustained ARSA activity levels close to or above those of healthy individuals is viewed as important in contributing to the clinical efficacy of OTL-200.[a 2]

Once the cells are collected from the patient's bone marrow or mobilised peripheral blood, the haematopoietic stem and progenitor cells ($CD34^+$ cells) are purified, modified with the ARSA LV and cryopreserved. The cells are then returned to the patient via intravenous administration after the patient has received a conditioning regimen with busulfan.

In the phase II clinical trial (NCT03392987), all subjects will receive intravenous infusion of OTL-200 gene therapy and will be followed up for 8 years post-gene therapy. Subjects will also receive conditioning regimen with busulfan. The single dose infusion is weight dependent, and in the range of 3.0 to 30.0 x 10^6 CD34+ cells/kg body weight.[a]

INNOVATION AND/OR ADVANTAGES

Currently, there are no effective treatments for metachromatic leukodystrophy (MLD). OTL-200 is a gene therapy and may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).

Data from an ongoing study has been published by Biffi et al in 2013[3] and in the Lancet in 2016 [2]. In this study, early treatment with OTL-200 has shown significant treatment effects on motor function, cognitive development and brain demyelination and atrophy when compared to disease progression in untreated natural history patients of comparable chronological ages[2]. At the time of the last data-cut for interim data analysis, all surviving subjects (n=18) had at least 3 years of post-GT follow-up, with follow-up times reaching up to 7.5 years in some patients. Treatment effects on motor function and cognition contrast with the outcomes observed in the untreated siblings and aged-matched historical controls, in whom gross motor function typically declines rapidly from the onset of symptoms leading to death in many cases by the age of 5 years. The treatment procedure was well tolerated and no serious adverse events related to the medicinal product were reported.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

[a] Information provided by Orchard Therapeutics on UK PharmaScan

OTL-200 does not currently have Marketing Authorisation in the EU/UK for any indication.

In the EU, OTL-200 was granted an orphan designation for the treatment of MLD in 2007.[5]

PATIENT GROUP

DISEASE BACKGROUND

MLD is a rare inherited autosomal recessive disorder affecting the brain, causing a progressive loss of physical and mental skills.

MLD is caused by mutation in the arylsulfatase A (ARSA) gene. The ARSA gene provides instructions for making the ARSA enzyme. This enzyme is located in cellular structures called lysosomes, which are the cell's recycling centres. Within lysosomes, the ARSA enzyme helps process substances known as sulfatides. Sulfatides are a subgroup of sphingolipids, a category of fats that are important components of cell membranes.[7] The mutation in the ARSA gene leads to a deficiency in the ARSA enzyme causing an accumulation of sulfatides which causes progressive destruction of the myelin sheath in nerve cells. As a result, patients experience a progressive deterioration in their cognitive and motor function.[8 9]

There are several forms of MLD, which are generally classified as Late-Infantile, Juvenile (sometimes subdivided into Early-Juvenile and Late-Juvenile) and adult MLD based on age at disease onset. In the late-infantile form, which is the most common form of MLD (50-60%), affected children begin having difficulty walking after the first year of life, usually at 15–24 months. Juvenile MLD has an onset between 3 and 10 years of age, usually beginning with impaired school performance. Adult -Onset MLD is the rarest form and commonly begins after age 16 years and, in the initial stages, is often mis-diagnosed as a psychiatric disorder because of personality changes.[10]

CLINICAL NEED AND BURDEN OF DISEASE

When both parents carry the same faulty gene, each pregnancy has a 25% chance of the child being affected. It is estimated that the UK incidence is approximately 1 in 40,000.[6] However, with modern diagnostic tools such as MRI Scans and genetic sequencing, it means that there are fewer incorrect diagnoses and it is possible that the incidence may prove to be higher. [10]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently, there are no effective treatments for MLD. Allogeneic haematopoietic stem cell transplantation has limited efficacy in arresting disease progression and is therefore not considered as a standard of care. [2 11 12] Drugs can be given to treat the symptoms as they occur, such as muscle spasms, infections and seizures. Pain relief and sedative drugs can be given if required, and feeding can be assisted. Physiotherapists and others can advise parents on positioning, seating and exercising the limbs to maintain comfort.[6]

CURRENT TREATMENT OPTIONS

Haematopoietic stem-cell transplant appears to mitigate disease progression in some patients with late-onset disease when treated at presymptomatic stages of the disease, who usually have not had

severe peripheral neuropathy since onset. However, it's efficacy in patients with early-onset variants is debatable.[2]

PLACE OF TECHNOLOGY

If licensed, OTL-200 will offer a potentially curative treatment option for paediatric MLD patients, who currently have no effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03392987, EudraCT2017-001730-26; **OTL-200; phase III**
Sponsor	Orchard Therapeutics (Europe) Ltd
Status	Ongoing
Source of Information	Trial registry[1] [13]
Location	Italy
Design	Single arm, open-label
Participants	pre-symptomatic early onset MLD
Schedule	Eligible subjects will receive intravenous (IV) infusion of OTL-200 gene therapy. Subjects will also receive conditioning regimen with busulfan. Patients undergo stem cell harvest and purified CD34+ cells are transduced with the lentiviral vector encoding the human ARSA gene. Patients receive busulfan conditioning before infusion of the transduced CD34+ cells. The period of hospitalization is approx. 60 days from treatment to discharge. Patients are followed up for 8 years. No further details are reported on the trial registry.
Follow-up	Follow-up 8 years
Primary Outcomes	Change in Gross Motor Function Measure (GMFM) score [Time Frame: At 24 months post gene-therapy]
Secondary Outcomes	• Time Frame: At multiple visits up to 8 years post-gene therapy: ○ Change in GMFM score ○ Change in Gross Motor Function Classification (GMFC)-MLD score ○ Change in neurological examinations ○ Change in Nerve Conduction Velocity (NCV) ○ Change in total score for brain magnetic resonance (MR) imaging ○ Change in neurocognitive function (Intelligence Quotient [IQ]) ○ Engraftment measured by percent Lentiviral (LV) positive clonogenic progenitors in bone marrow ○ Vector copy number (VCN) level in bone marrow mononuclear cells ○ VCN level in peripheral blood mononuclear cell (PBMCs) ○ Change in ARSA activity in total PBMCs ○ Change in ARSA activity in PB CD14+ cells ○ Change in ARSA activity in cerebrospinal fluid (CSF) ○ Safety and tolerability as measured by number of subjects with incidences and titers of antibodies against ARSA

	○ Safety and tolerability as measured by number of subjects with abnormal clonal proliferation (ACP) ○ Safety and tolerability as measured by number of subjects with replication competent lentivirus (RCL) • Time Frame: By Day 60 post-gene therapy: ○ Safety and tolerability as measured by number of subjects not achieving haematological recovery by Day 60 (i.e., engraftment failure)
Key Results	Pending
Adverse effects (AEs)	No treatment related AEs reported to date
Expected reporting date	Estimated primary completion date reported as August 2022. Study completion date reported as August 2022.

Trial	**NCT01560182, EudraCT2009-017349-77; OTL-200; phase I/II**
Sponsor	Orchard Therapeutics (Europe) Ltd
Status	Ongoing
Source of Information	Trial registry[13] [14]; publication[14]
Location	Italy
Design	Single arm, open label
Participants	Pre-symptomatic MLD patients with the late infantile variant , and pre or early-symptomatic MLD patients with the early juvenile variant)
Schedule	Patients undergo stem cell harvest and purified CD34+ cells are transduced with the lentiviral vector encoding the human ARSA gene. Patients receive busulfan conditioning before infusion of the transduced CD34+ cells. The period of hospitalization is approx. 60 days from treatment to discharge. Patients are followed up for 8 years. The observational long-term follow up phase of this study was extended beyond 8 years to allow additional information to be collected on study participants before they enrol into a Registry.
Follow-up	Not reported
Primary Outcomes	Efficacy: • Improvement of 10% of the total GMFM score in treated patients when compared to the GMFM scores of historical control MLD population. [Time Frame: 24 months after treatment] • Increase of residual ARSA activity compared to pre-treatment values measured in PBMC. [Time Frame: 24 months after treatment] Safety: • Conditioning regimen-related safety [Time Frame: at +60 days after transplantation; Time Frame: 3 years] • The short-term and long-term safety and tolerability of lentiviral-transduced cell infusion [Time Frame: 48 hours after transplant; Time Frame: 24 months after treatment]
Secondary Outcomes	• The absence of immune responses against the transgene [Time Frame: every three months for the first year, then once a year] • Improvement in the NCV Index for ENG and in the total score for MR [Time Frame: 24 months after treatment] • Transduced cell engraftment [Time Frame: 12 months after treatment]

	• IQ measurement above 55 [Time Frame: 24, 30 and 36 months after treatment]
Key Results	The interim analysis demonstrates that HSC-GT is a safe and well-tolerated treatment for all MLD subjects treated with a clinical follow-up ≤7.5 years. 18/20 subjects are alive after a clinical follow-up of 3-8 years. Two EJ subjects, treated after onset of symptoms, died due to rapid disease progression 8- and 15-months post-treatment. There was no treatment-related mortality, no evidence of abnormal clonal expansion, and no adverse events related to the Medicinal Product. All subjects achieved high levels of multi-linage engraftment, polyclonal hematological reconstitution and central and peripheral ARSA activity reconstitution within or above normal levels. Patients treated prior to symptom onset achieved a sustained clinical benefit in motor and cognitive function as well as on instrumental biomarkers of PNS and CNS demyelination. In addition, most patients treated showed preservation of cognitive function regardless of their symptomatic status at the time of treatment and at a chronological age when untreated patients show severe cognitive impairment These treatment effects suggest that autologous, ex-vivo HSC-GT is a highly promising therapeutic approach the treatment of MLD patients.[15]
Adverse effects (AEs)	At the time of the ad hoc analysis, the most commonly reported AEs related to the use of busulfan for conditioning and included cytopenia (reported in all patients) and mucositis of different grades of severity (in five of nine patients [grade 3 in four of five patients]). No serious AEs related to the medicinal product were reported.[2]
Expected reporting date	Interim reporting: 1H 2019

ESTIMATED COST

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 Service Specifications: Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

- No relevant guidance identified.

ADDITIONAL INFORMATION

REFERENCES

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