EU Risk Management Plan

for

Libmeldy 2 – 10 x 10^6 cells /mL dispersion for infusion

(atidarsagene autotemcel - a $CD34^+$ 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)

RMP version to be assessed as part of this application:	
RMP Version number:	4.0
Data lock point for this RMP:	16-Dec-2024
Date of final sign off:	15-Oct-2025
Rationale for submitting an updated RMP:	First 5-year renewal of marketing authorisation
Summary of significant changes in this RMP:	Update to all data in relation to new Data Lock Point
Other RMP versions under evaluation:	
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	V3.0
Approved with procedure:	EMEA/H/C/005321/IB/023
Date of approval (opinion date):	28-Feb-2024

QPPV name: Martynas Juzenas

QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AAA	Anti-ARSA antibodies
ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ARSA	Arylsulfatase A
As2$^{-/-}$	ARSA knockout mice
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced therapy medicinal product
AUC	Area under the curve
BM	Bone marrow
cALD	Cerebral adrenoleukodystrophy
CDMO	Contract and development manufacturing organization
cDNA	Complementary deoxyribonucleic acid
CDP	Clinical development programme
CHMP	Committee for Medicinal Products for Human Use
CIS	Common insertion site
CNS	Central nervous system
CSR	Clinical study report
CUP	Compassionate Use Program
CV	Cardiovascular
CVC	Central venous catheter
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
EAP	Expanded Access Programme or Expanded Access Protocol (USA)
EEA	European Economic Area
EJ	Early juvenile
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European public assessment report

ESEJ	Early symptomatic early juvenile
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FPFV	First patient first visit
GFP LVV	LVV expressing green fluorescent protein
GLP	Good Laboratory Practice
GT	Gene therapy
GvHD	Graft vs host disease
GVP	Guideline on good pharmacovigilance practices
G-CSF	Granulocyte colony-stimulating factor
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HE	Hospital Exemption
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplant
HSPC	Haematopoietic stem and progenitor cells
INN	International nonproprietary name
IQ	Intelligence quotient
IS	Integration site
ISA	Integration site analysis
IV	Intravenous
IVF	*In vitro* fertilisation
JACIE	Joint Accreditation Committee - International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation
LI	Late infantile
Lin^-	Lineage-negative
LJ	Late juvenile
LTR	Long-terminal repeat
LVV	Lentiviral vector
MA	Marketing authorisation
MAA	Marketing authorisation application
MAC	Myeloablative conditioning

Max	Maximum
MDS	Myelodysplastic syndrome
Min	Minimum
MLD	Metachromatic leukodystrophy
mPB	Mobilised peripheral blood
MRI	Magnetic resonance imaging
NAT	Nucleic acid test
NCI CTC	National Cancer Institute Common Toxicity Criteria
N/A	Not applicable
OTL-200-c	Cryopreserved formulation of OTL-200
OTL-200-f	Fresh formulation of OTL-200
PAC	Patient alert card
PB	Peripheral blood
PBRER	Periodic benefit-risk evaluation report
PBSC	Peripheral blood stem cell
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PGK	Phosphoglycerate kinase
PK	Pharmacokinetic
PL	Package leaflet
PNS	Peripheral nervous system
PSEJ	pre-symptomatic early juvenile
PSLI	pre-symptomatic late infantile
PSUR	Periodic safety update report
PT	Preferred term
QPPV	Qualified Person responsible for Pharmacovigilance
QTC	Qualified treatment centre
RCL	Replication competent lentivirus
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SIN	Self-inactivating
SMAC	Sub-myeloablative conditioning

SmPC	Summary of product characteristics
SOC	System organ class
SR-TIGET	Istituto San Raffaele Telethon per la Terapia Genica
TA-TMA	Transplant associated thrombotic microangiopathy
USA	United States of America
USPI	United States prescribing information
VCN	Vector copy number
VSV	Vesicular stomatitis virus
VSV-G env	Vesicular stomatitis virus glycoprotein envelope
WAS	Wiskott-Aldrich syndrome
WPRE	Woodchuck hepatitis virus post-transcriptional regulatory element
WT	Wildtype
X-ALD	X-linked adrenoleukodystrophy

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	atidarsagene autotemcel
Pharmacotherapeutic group (ATC Code)	Other haematological agents A16AB21
Marketing Authorisation Applicant	Orchard Therapeutics (Netherlands) B.V.
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Libmeldy
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Not applicable
	Summary of mode of action: Libmeldy (referred to as 'OTL-200' within the body of document) is a genetically modified autologous $CD34^+$ cells enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector expressing the human arylsulfatase A (ARSA) gene. Autologous $CD34^+$ HSPCs are collected from mobilised peripheral blood (mPB) and transduced with a lentiviral vector (ARSA LVV), which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome so that genetically modified cells become capable of expressing the functional ARSA enzyme. When administered to the patient following the administration of a myeloablative conditioning regimen, the genetically modified cells engraft and are able to repopulate the haematopoietic compartment. A subpopulation of the infused HSPC and/or their myeloid progeny is able to migrate across the blood brain barrier to the brain and engraft as central nervous system (CNS) resident microglia and perivascular CNS macrophages HSPC also give rise to endoneurial macrophages in the peripheral nervous system (PNS). These genetically modified cells can produce and secrete the functional ARSA enzyme, which can be taken up by surrounding cells, a process known as cross-correction, and used to break down or prevent the intracellular accumulation of harmful sulfatides. Following successful and stable engraftment in the patient, the effects of the product are expected to be persistent.
	Important information about its composition: The finished product is composed of one or more infusion bags containing a dispersion of 2-10 x 10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains 10 to 20 mL of OTL-200. The medicinal product contains 3.5 mg sodium per mL.
Hyperlink to the Product Information	Module 1.3.1

Indication in the EEA	**Current:** Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity - in children with late infantile or early juvenile forms without clinical manifestations of the disease - in children with the early juvenile form with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline
	Proposed: (Proposed additions are underlined; text removed is in srtikethrough). Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity: - in children with the pre-symptomatic late infantile (PSLI) or pre-symptomatic early juvenile (PSEJ) forms ~~without clinical manifestations of the disease~~ - in children with the early symptomatic early juvenile (ESEJ) form ~~with early clinical manifestations of the disease~~ who still have the ability to walk independently and before the onset of cognitive decline.
Dosage in the EEA	**Current:** The minimum recommended dose of Libmeldy is 3×10^6 $CD34^+$ cells/kg. In clinical studies doses up to 30×10^6 $CD34^+$ cells/kg have been administered. Libmeldy is intended for autologous use and should only be administered once.
	Proposed: Not applicable
Pharmaceutical form and strengths	**Current:** Dispersion for infusion. A clear to slightly cloudy, colourless to yellow or pink dispersion. The medicinal product is composed of one or more infusion bags containing a dispersion of 2-10 $x10^6$ cells/mL suspended in cryopreservative solution. Each infusion bag contains 10 to 20 mL of Libmeldy. Since the total number of cells and concentration of $CD34^+$ cells vary between individual patient batches, the quantitative information regarding strength (total viable cell concentration), volume of dispersion and total number of $CD34^+$ cells per bag and supplied dose of the medicinal product are provided in the Lot Information Sheet. The Lot Information Sheet is included with the cryoshipper used to transport Libmeldy.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication:

OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity

- in children with the pre-symptomatic late infantile (PSLI) or pre-symptomatic early juvenile (PSEJ) forms
- in children with the early symptomatic early juvenile (ESEJ) form who still have the ability to walk independently and before the onset of cognitive decline.

MLD is an ultra-rare autosomal recessive lysosomal storage disorder caused by biallelic pathogenic variants (mutations) in the arylsulfatase A (*ARSA*) gene that result in deficiency of the encoded lysosomal ARSA enzyme. Arylsulfatase A is essential for the metabolism of sulfatides, a major component of oligodendrocyte and Schwann cell myelin membranes in the central nervous system (CNS) and peripheral nervous system (PNS) respectively. Arylsulfatase A deficiency results in accumulation of the undegraded substrate in the lysosomes of oligodendrocytes, microglia, certain neurons of the CNS, Schwann cells, and macrophages of the PNS leading to microglial damage, progressive demyelination, neurodegeneration, subsequent loss of motor and cognitive functions, and early death, especially in patients with early symptom onset (< 7 years of age) (van Rappard, 2015; Bergner, 2019; Gieselmann, 2010; Gomez-Ospina, 2024). Sulfatide accumulation also occurs in tissues and organs such as the gallbladder and kidneys, causing the non-neurological manifestations of gallbladder polyposis (van Rappard, 2016a; Kin, 2017; Stevens, 2021; Mutua, 2025) and renal tubular acidosis (Lorioli, 2015), respectively.

Incidence:

MLD is pan-ethnic, with affected patients described in several populations. The incidence of MLD (all subtypes) is estimated at approximately 1 per 100,000 live births (Bonkowsky, 2018; Söderholm, 2020; Heim, 1997; Poorthuis, 1999; Pinto, 2004; Lugowska, 2011; Hult, 2014; Stellitano, 2016). Studies suggest that approximately 50% to 60% of patients have the late infantile (LI) subtype, 20% to 40% have juvenile disease subtypes (early juvenile [EJ] + late juvenile [LJ]), and approximately 10% to 20% have an adult disease subtype (Heim, 1997; Poorthuis, 1999; Lugowska, 2005; Gieselmann, 2010; Gomez-Ospina, 2024; Chang, 2024).

Prevalence:

MLD occurs in all regions of the world. The birth prevalence of MLD (all subtypes) is estimated at approximately 1 per 100,000 live births (range, 1 per 40,000 to 160,000) worldwide; birth prevalence is estimated as 1 in 8,000 among Arab groups in Israel, 1 in 2,500 in the western portion of the Navajo Nation and may be even higher in the Native American population of southern Alaska. Much less is known about MLD in Africa than in other regions of the world. Data gaps on the incidence of MLD also exist in certain other countries (Chang, 2024; Amin, 2017, Gomez-Ospina, 2024).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

In patients diagnosed based on appearance of clinical symptoms, MLD is classified based on the age of symptom onset into late infantile (LI, age of onset ≤ 30 months), early juvenile (EJ, age of onset between 30 months and 7 years [i.e., had not celebrated 7th birthday]), late juvenile (LJ age of onset between 7 and 16 years), and adult (age of onset ≥ 17 years) subtypes (Figure 1). Early onset MLD includes the LI and EJ subtypes, and late-onset MLD includes the LJ and adult subtypes. Historically, the EJ and LJ subtypes of MLD have often been collectively referred to as "juvenile" MLD, but recent data describing the relationship between type of symptoms at onset and disease course strongly support the age-of-onset-based classification and the existence of distinct, clinically meaningful EJ and LJ subtypes first described many years ago (MacFaul,1982; Kehrer, 2021; Fumagalli, 2021; Schoenmakers, 2022b). Patients may also be diagnosed with MLD and classified before symptom onset based on their genotype, with or without a known family history of MLD. Within the same family, patients affected with MLD will always have the same genotype.

Approximately 300 pathogenic variants (mutations) of the ARSA gene have been described (Cesani, 2016; ClinVar, 2022), which can be functionally divided into 2 broad groups differing in predicted severity: null (0) or "severe" alleles associated with little or no enzyme activity and residual (R) alleles encoding for ARSA with higher levels of residual enzyme activity (Gomez-Ospina, 2024; Cesani, 2016; Santhanakumaran, 2022; Trinidad, 2023).

Demographic factors including age, sex, race, along with other risk factors are summarised in Table 2.

Table 2: Age, sex, racial and/or ethnic origin and risk factors in MLD

Age	MLD is classified based on the age of symptom onset into early-onset (LI [≤30 months] and EJ [between 30 months and <7 years]) and late-onset (LJ [7 to 16 years] and adult [≥17 years]) clinical subtypes. Approximately 50% to 60% of patients with MLD have the LI subtype, 20% to 40% have juvenile disease subtypes (EJ and LJ), and approximately 10% to 20% have the adult subtype.
Sex	MLD affects both males and females. There is no evidence in the literature that disease course in early-onset MLD subtypes is influenced by sex
Race or ethnic group	MLD is pan-ethnic, with affected patients described in many different populations.
Other considerations/risks	MLD is an autosomal recessive disorder caused by biallelic pathogenic variants in the ARSA gene. There are no other risk factors, although patients with MLD and other leukodystrophies may be vulnerable to disease exacerbation following febrile illness or other stress. There may be inequities in the speed of diagnosis of MLD and other leukodystrophies based on ethnicity and race. However, there is no evidence in the literature that the natural disease course in early-onset MLD subtypes is influenced by sex, ethnicity, or race.

References: Mahmood, 2010; Helman, 2015; Bonkowsky, 2018; Gomez-Ospina, 2024; Chang, 2024.

The main existing treatment options:

Standard of Care for Early-Onset MLD

Expert consensus guidelines strongly recommend treatment with OTL-200 as the standard of care for eligible patients with early-onset MLD (Laugwitz, 2024; Adang, 2024a). The best gross motor and cognitive outcomes after treatment with OTL-200 are observed in patients with MLD treated in the pre-symptomatic period (Fumagalli 2022; Libmeldy SmPC; Lenmeldy USPI). Expert opinion does not support the use of allogeneic haematopoietic stem cell transplant (HSCT) for treatment of patients with LI or EJ MLD (Wang, 2011; Tan, 2019; Kanate, 2020; MLD Scientific Workshop Summary, 2023). There are no disease-modifying therapies currently available for the treatment of patients with early-onset MLD other than OTL-200.

Standard of Care for Late-Onset MLD

Allogeneic HSCT has been used for the treatment of late-onset MLD for the past three decades. There are multiple publications on this topic (Martin, 2013; Solders, 2014; Boucher, 2015; van Rappard, 2016b; Groeschel, 2016; Beschle, 2020; Videbæk, 2021, Laugwitz, 2024), which has recently been reviewed (Armstrong, 2023). Long-term results show that individuals with LJ and adult MLD benefit from HSCT if transplanted during the pre-symptomatic or early symptomatic stages of disease, with improved survival and a stabilisation of cognitive and motor functions compared with outcomes in patients with untreated MLD. Uncertainties on the long-term outcomes of HSCT in LJ MLD still exist, and data on adult MLD are relatively sparse. Allogeneic HSCT also carries risks of mortality including graft versus host disease (GvHD) and morbidity, with increased risk if the donor match is poorer. OTL-200 is not currently approved for the treatment of patients with late-onset MLD.

Symptomatic Management of MLD

For patients with MLD who are diagnosed too late to be considered eligible for disease-modifying treatments, therapy is limited to supportive and palliative care. This multidisciplinary approach includes physical therapy and anti-spasticity medications to maintain mobility and manage complications of being bedridden, respiratory physiotherapy and management of pulmonary infections, dietary support and enteral nutrition in the advanced disease stage, anti-epileptic drugs to control seizures, pain management treatments, and family and psychological and psychiatric counselling.

Expert guidelines for the medical care of patients with symptomatic leukodystrophy have been developed and published (Bonkowsky, 2021; Keller, 2021; Adang, 2017) and considerations for the care of the common complications of symptomatic MLD have recently been summarised (Adang, 2024a; Gomez-Ospina, 2024).

The ability of supportive care to have an impact on the complex multisystem burden of MLD is limited, as patients may continue to suffer from spasticity, dysphagia, musculoskeletal and gastrointestinal complications, loss of eyesight and hearing, seizures, incontinence, and severe pain (van Rappard, 2015; Gomez-Ospina, 2024). Supportive or palliative care is not disease modifying and, consequently, motor and cognitive deterioration is unaffected and progresses regardless of the medications prescribed or interventions performed. Despite improvements in palliative care that have allowed patients with MLD to survive in a vegetative state for many years, the disease still progresses to early death in all early-onset subtypes.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

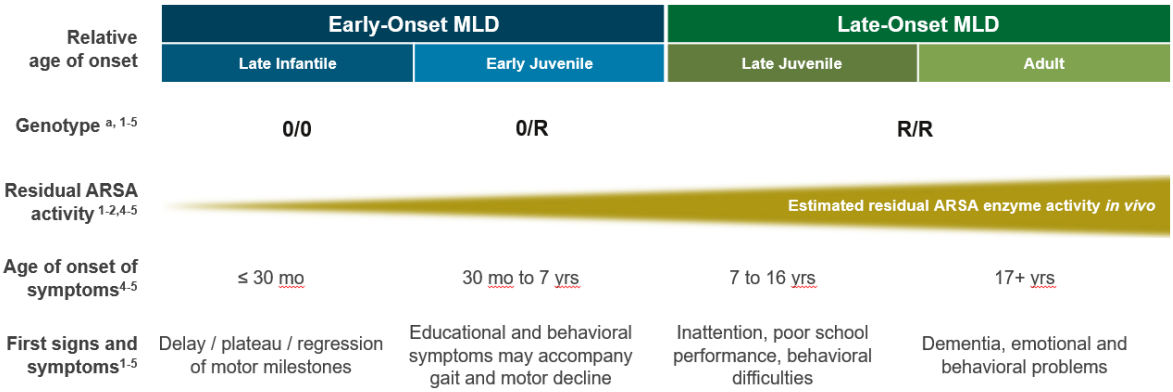
Patients who carry 2 null ARSA alleles (0/0 genotype) are invariably affected by the LI subtype, manifest first symptoms at or before 30 months of age, and suffer from predictable and homogenous rapid disease progression within months to severe disability, and eventual death typically in the first decade of life. Some patients with the LI subtype show a relative delay or stagnation in motor milestone achievement, especially at the age of independent walking (Zlotogora, 1980; MacFaul, 1982; Bindu, 2005; Harrington, 2019; Adang, 2024b). Once symptoms appear, often as an abnormal gait, there is invariably rapid psychomotor regression and loss of motor, language, and cognitive skills previously acquired (van Rappard , 2015; Gieselmann, 2010; Kehrer, 2014). Severe peripheral neuropathy is an early and characteristic feature of LI MLD (MacFaul, 1982; van Rappard, 2015; Bindu, 2005; Beerepoot, 2019). Acute strabismus and other eye movement disorders, possibly related to cranial nerve involvement, have also been recognised as an early manifestation of LI MLD (Beerepoot, 2022). As the disease progresses, patients with the LI subtype develop spasticity, seizures, and feeding problems. Almost all untreated patients with the LI subtype experience severe motor and cognitive impairment between 2 and 4 years of age (Kehrer, 2011; Kehrer, 2014). With supportive care, some patients with the LI subtype can live in a highly impaired functional state until death during late childhood (Mahmood, 2010).

Patients who are affected by the EJ subtype typically carry one null allele and one residual allele (0/R genotype), have symptom onset between the age of 30 months and 7 years, and tend to have a somewhat slower and more variable initial disease progression or plateau than patients with the LI subtype. Rarely, patients with the EJ subtype may have an R/R genotype (e.g., homozygous for the missense variant c.931G>A (p.Gly311Ser) [Cesani, 2016; Pekgül, 2020; Mahdieh, 2021]). Patients with the EJ subtype may develop behavioural and cognitive deterioration at the same time or even slightly earlier than the invariable deterioration of motor function that comprises their initial symptoms (Gordon, 1978; MacFaul, 1982; Kehrer, 2021). Once the ability to walk is lost, patients with the LI and EJ subtypes have a similarly steep decline in motor function (Kehrer, 2011; Kehrer, 2021; Fumagalli, 2021), and patients eventually experience loss of all skills. Patients affected by an intermediate clinical subtype between the LI and EJ forms have also occasionally been observed (Sessa, 2016; Schoenmakers, 2022a).

Late-onset MLD includes the LJ subtype, with symptom onset occurring between 7 and 16 years of age, and the adult subtype, where first symptoms present after 17 years of age. Patients with late-onset MLD typically have an R/R genotype. First symptoms in patients with the LJ subtype are typically behavioural or cognitive issues and patients with adult MLD frequently present with cognitive decline, behavioural and psychiatric disturbances, ataxia, polyneuropathy, and epileptic seizures (Gomez-Ospina, 2024; Kehrer, 2021). Age of symptom onset and disease progression are more variable in the late-onset subtype of MLD than in the early-onset LI and EJ subtypes (Elgün, 2019; Gomez-Ospina, 2024).

Figure 1: Spectrum of Metachromatic Leukodystrophy

- Clinically, MLD can be classified into late infantile (LI), early juvenile (EJ), late juvenile (LJ), and adult subtypes based on the age of symptom onset.



Abbreviations: ARSA= arylsulfatase A; MLD=metachromatic leukodystrophy; mo=months; yrs=years.
a.For the listed genotypes, "0" indicates a null allele and "R" indicates a moderate/mild allele in which some degree of residual enzymatic activity is typically maintained.
1. Gieselmann, 2010.
2. Wang, 2011.
3. Mahmood, 2010.
4. Biffi, 2008.
5. Kehrer, 2021.

Important co-morbidities:

As described above as part of the natural history of the disease, patients with MLD develop multiple co-morbidities that are manifestations of their CNS and PNS disease. These can include loss of motor function, loss of language and speech, cognitive decline, eye movement and other cranial nerve disorders, ataxia, spasticity, seizures, dysarthria, incontinence, dysphagia and feeding problems, and behavioural and psychiatric disturbances. Features of neurological disease in MLD, including hypotonia and spasticity, often result in progressive orthopedic abnormalities (such as equinus varus feet, kyphosis, hip subluxation or dislocation, scoliosis, and retrocurved knees) that may require adaptive equipment, physiotherapy, and orthopedic surgery (van Haren, 2015; Adang, 2017).

Additionally, patients with MLD may develop an underlying proximal (Type 2) renal tubular acidosis due to sulfatide accumulation in the renal tubules (as discussed in Module SVII.1.1.), putting them at increased risk of metabolic acidosis in various acute clinical conditions such as infections or surgical interventions (Lorioli, 2015).

Involvement of the gallbladder in MLD due to the extensive local deposition of sulfatides is common and well-characterised. Gallbladder complications in MLD include wall thickening, sludge, gallstones, and polyposis, and gallbladder polyps may undergo malignant transformation or cause severe bleeding (van Rappard, 2016a; Kim, 2017; Stevens, 2021; Mutua, 2025). Current monitoring guidelines for patients with MLD recommend regular gallbladder imaging with ultrasonography and consideration of cholecystectomy to prevent malignancy or life-threatening haemobilia.

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

A range of nonclinical studies have been conducted to support the efficacy and safety of IV administration of OTL-200 to humans. The nonclinical development programme is in line with the European Medicines Agency (EMA) guideline on human cell based medicinal products (EMA, 2008) and the EMA guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA, 2018a) as well as the FDA Guidance for Industry: Preclinical assessment of Investigational Cellular and Gene Therapy Products (FDA, 2013). Many standard non-clinical studies were considered either not feasible or not applicable to allow extrapolation of animal data to efficacy and/or safety in humans.

OTL-200 is an autologous $CD34^+$ cell enriched population that contains HSPC transduced *ex vivo* using a LVV encoding the human ARSA gene, under the control of a human phosphoglycerate kinase (PGK) gene promoter and a modified version of the woodchuck hepatitis virus post-transcriptional regulatory element (WPRE).

In vitro and *in vivo* studies support the efficacy of OTL-200 as a treatment for ARSA deficiency in humans (Module 2.4 Non-Clinical Overview). *In vitro* studies were conducted to demonstrate the transduction efficiency of ARSA LVV in $CD34^+$ cells and the reconstitution of ARSA activity in transduced cells. The *in vivo* efficacy of OTL-200 was supported by studies with murine lineage-negative (Lin^-) HSPC transduced *ex vivo* with ARSA LVV and injected into the mouse MLD disease model. *ARSA* knockout mice ($As2^{-/-}$) show a pattern of sulfatide storage and neuropathology findings which resemble those of MLD patients and, although their phenotype is milder when compared to humans, they are considered to reflect an early stage of the human disease and represent a suitable model for studying the effect of ARSA LVV based gene therapy.

The ability of OTL-200 to prevent disease manifestations or correct previously established neuropathological lesions has been assessed in two studies in which $As2^{-/-}$ mice were treated at pre-symptomatic or symptomatic phase and monitored until 12 months of age, when severe neurodegenerative changes and significant impairment in neurological functions are observed.

General toxicity and tumourigenicity following single IV injection of ARSA LVV-transduced Lin^- HSPC into wildtype (WT) and $As2^{-/-}$ mice were evaluated for up to 12 months. The pivotal toxicity and tumorigenicity study and the *in vivo* study to compare the distribution and long-term engraftment of fresh and cryopreserved formulation of OTL-200 were performed in compliance with Good Laboratory Practice (GLP). Distribution, differentiation potential and long-term repopulation of OTL-200 formulated as fresh or cryopreserved formulation were found to be comparable following transplantation to immunodeficient mice.

Biodistribution findings include:

- Murine Lin^- HSPC transduced with LVV expressing green fluorescent protein (GFP LVV) migrated into recipient nervous system and reconstituted mature resting microglia in CNS and endoneurial macrophages in the PNS. The extent of migration was higher in $As2^{-/-}$ mice.
- Myeloablative conditioning with irradiation or busulfan induced depletion of endogenous microglia and promoted macrophage/microglia replacement from donor. However, busulfan induced optimal depletion of resident microglia in brain compared with irradiation or treosulfan conditioning in $As2^{-/-}$ mice.

- Microglia derived from long-term Lin$^-$ HSPC transduced with ARSA LVV reconstituted ARSA activity in the brain and were able to cross-correct CNS and PNS neurons and glial cells.
- Transduction with ARSA LVV did not affect distribution, differentiation potential and long-term repopulation of human CD34$^+$ cells when transplanted into immunodeficient mice.
- CD34$^+$ cells transduced with ARSA LVV distributed to haematopoietic tissues and differentiated into multiple haematopoietic lineages in the chimeric mice like control mock-transduced or unmanipulated cells. Engraftment was also found in the brain confirming migration of ARSA LVV transduced cells into the target organ system for MLD.
- Integrated ARSA LVV persisted in the differentiated CD34$^+$ cell progeny in chimeric hosts and ARSA transgene expression was maintained for the duration of the observation period (up to 20 weeks).
- ARSA LVV remained stably integrated within cells of human origin and did not mobilise to mouse tissues, including testes, confirming a low risk of germline transmission.
- Distribution, differentiation potential and long-term repopulation of OTL-200 formulated as fresh or cryopreserved formulation were comparable following transplantation to immunodeficient mice.

The key safety findings from nonclinical studies and relevance to human usage are presented below:

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
Acute or repeat-dose toxicity studies General toxicity and tumourigenicity following single IV injection of ARSA LVV-transduced Lin$^-$ HSPC into WT and *As2*$^{-/-}$ mice were evaluated for up to 12 months. No increased mortality, signs of toxicity or LVV-driven abnormal or malignant growth of transplanted cells or haematopoietic tumours were observed after administration of ARSA LVV transduced Lin$^-$ HSPC, even in the presence of high and stable engraftment and ARSA overexpression. Hepatocellular tumours were found in MLD mice transplanted with ARSA LVV- transduced HSPC, mock-transduced or non transduced control cells in an initial non-GLP study. However, the finding was considered related to the conditioning regimen and genetic background of the mice. Importantly this finding was not replicated in the pivotal GLP toxicity and tumourigenicity study, in which a larger cohort of animals was treated after a less aggressive conditioning regimen and monitored for a longer period of time.	Not applicable. The hepatocellular tumours observed in the initial study were considered related to the conditioning regimen and the mouse strain rather than to OTL-200. The second study, performed to further investigate the liver findings observed in the first study and to resolve several limitations of that study, is considered as the pivotal toxicity and tumourigenicity study. Importantly no treatment-related hepatocellular tumours were found in the pivotal confirmatory study. As described below, no adverse events (AEs) related to malignancy were observed in the clinical development programme (Module SVII.3.1).

Key Safety findings (from nonclinical studies)	Relevance to human usage
Reproductive/developmental toxicity Reproductive and developmental toxicity studies were not performed. Conventional studies on fertility are not applicable and were not conducted. The potential for bystander cell transduction of germ cells (testes) upon *in vivo* infusion of ARSA LVV-transduced $CD34^+$ cells was evaluated during the main biodistribution study. ARSA LVV remained stably integrated within cells of human origin and did not mobilise to mouse tissues, including testes, confirming a low risk of germline transmission. Due to the lack of evidence for germline transmission and the limited distribution of OTL-200 (i.e., primarily to haematopoietic tissues), no specific reproductive or developmental toxicity studies were considered warranted with ARSA LVV-transduced HSPC/OTL-200.	The risk of germline transmission after direct systemic administration of gene therapy vectors is generally considered to be low (MacLachlan, 2013; Hess, 1996). As OTL-200 is an *ex vivo* gene therapy, the risk of germline transmission is exceedingly low. Transduction occurs *ex vivo* and the cell types used for *ex vivo* transduction does not contain gametes. During clinical use there is little concern for exposure of the patient germline to the vector as no vector mobilisation and bystander transduction of male gonads was found in chimera mice. Due to the nature of OTL-200 conventional studies on human fertility are not applicable. However, as the myeloablative conditioning regimen (busulfan) prior to OTL-200 administration is associated with irreversible infertility (Busilvex SmPC), to minimise the risk of impaired fertility patients and their parents/carers are advised to cryopreserve semen or ova before treatment if possible in the Libmeldy Summary of Product Characteristics (SmPC) and Package Leaflet (PL). There was no exposure of OTL-200 during pregnancy in the clinical development programme. The oldest age of a patient treated with OTL-200 was 15.5 years old (Module SIII). As a precautionary measure, a negative serum pregnancy test must be confirmed prior to the start of mobilisation and re-confirmed prior to conditioning procedures and before administration of OTL-200 in women of childbearing potential. The Libmeldy SmPC and PL state that as Libmeldy is not intended for use in adults, human data on use during pregnancy or lactation and animal reproduction studies are not available. With regards to fertility, it also recommends to consult the SmPC of the myeloablative conditioning medicinal product and that the treating physician should inform the patient's parents/carers about options for cryopreservation of spermatogonial stem cells or ovarian tissue. Pregnancy and lactation are discussed further in Module SVII.1.1.
No non-clinical studies evaluated the presence of OTL-200 in milk	There is no information regarding the presence of OTL-200 in human milk, its effects on milk production and its effects on the breastfed infants. Pregnancy and lactation are discussed further in Module SVII.1.1.
Dedicated juvenile toxicity studies were not conducted. However, neonate *As2*$^{-/-}$ mice were included in the non-GLP toxicity and	Not applicable. No effects on organ development have been observed in nonclinical studies and OTL-200 is not expected to have any effect on developing

Key Safety findings (from nonclinical studies)	Relevance to human usage
tumorigenicity study and biodistribution studies were conducted transplanting neonate immunodeficient mice. No effects on the organ development have been observed in these animals.	organs in humans. Therefore, no dedicated juvenile studies in humans were considered necessary (as confirmed by the Committee for Medicinal Products for Human Use [CHMP] during scientific advice).
Genotoxicity As part of the evaluation of the genotoxic potential of OTL-200, the integration site (IS) of ARSA LVV in human $CD34^+$ cells and murine Lin^- HSPC before and after transplantation to mice was analysed (Section 4.2, Module 2.4). As ARSA LVV and GFP LVV share the same lentiviral vector, with identical core packaging system and transfer vector backbone, data obtained with GFP LVV in an *in vitro* immortalisation assay and in a tumour prone mice model *in vivo* were considered relevant to further characterise the genotoxic potential of OTL-200. IS analysis demonstrated that ARSA LVV integrates within genes like other LVVs, without any enrichment in preferential targeted genes classes found *in vivo* comparing to *in vitro*. Polyclonal reconstitution was seen in all analysed mice, with no evidence of preferential expansion of IS near proto-oncogenes. GFP LVV, which shares the same lentiviral vector of ARSA LVV, induced replating clones in one out of eight experiments when tested in an *in vitro* immortalisation assay. However, the replating incidence was low and no sustained growth was observed. There was no increase in tumourigenesis when GFP LVV was evaluated *in vivo* in a tumour prone mouse model.	The genotoxic studies did not show preferential targeting of oncogene or tumour suppressor genes. These studies did not show any bias for vector integration into gene classes involved in cancer or cell proliferation or skewing in genomic distribution or specific gene classes, and a polyclonal reconstitution was observed. This finding, together with the lack of clonal expansion observed in the *in vitro* immortalisation assay following transduction with the same lentivirus backbone expressing GFP, suggests that OTL-200 is unlikely to be genotoxic in humans.
Carcinogenicity No standard carcinogenicity studies were conducted with OTL-200. As OTL-200 is a gene therapy intended for single administration, the tumourigenic potential and toxicological profile of a single IV administration of ARSA LVV-transduced Lin^- HSPC followed by an extended post-dose observation was evaluated in two studies (Section 4.3, Module 2.4). **Non-GLP toxicity and tumourigenicity study** The long-term toxic and tumourigenic potential of OTL-200 was initially assessed in a mouse surrogate test article Lin^- HSPC from male MLD (*As2*$^{-/-}$) mice, mock-transduced or transduced with ARSA LVV, transplanted at approximately $1x10^6$ cells/mouse (corresponding to $4\text{-}5x10^7$ cells/kg) into lethally irradiated young adult female *As2*$^{-/-}$	In the clinical development programme of OTL200, and to date, no cases of malignant clonal expansion, malignancy or AEs indicative of oncogenic transformation have been reported and there has been no evidence of aberrant clonal behaviour based on insertion site analysis (Section 2.1.5.2, Section 4.3, Module 2.7.4). Integration site analysis performed on genomic DNA from whole peripheral blood (PB) and BM samples harvested at different time points after therapy showed a highly polyclonal pattern of vector integration with no indication of abnormal clonal expansion. However, as OTL-200 consists of $CD34^+$ cells transduced *ex vivo* with a LVV which integrates permanently in the host genome, malignancy due to insertional oncogenesis is considered an important potential risk (Module SVII.3.1). The Libmeldy SmPC and PL highlight that there is a theoretical

Key Safety findings (from nonclinical studies)	Relevance to human usage
mice and neonate WT and *As2*$^{-/-}$ mice. Animals were sacrificed 8 to 11 months after transplantation and, in addition to standard toxicological evaluations, measurement of ARSA activity in peripheral blood, BM engraftment, antibody responses against ARSA and Human immunodeficiency virus (HIV)-1 gag p24 capsid protein were evaluated. No evidence of toxicity, no haematological abnormalities and no development of haematopoietic tumours were observed in neonate and adult WT or *As2*$^{-/-}$ mice transplanted with Lin^{-} HSPC transduced with ARSA LVV. Hepatocellular tumours were found in *As2*$^{-/-}$ mice transplanted either at neonatal and adult age (with Lin^{-} HSPC transduced with ARSA LVV or GFP LVV, or mock-transduced), in unmanipulated age-matched mice and irradiation controls. No hepatocellular tumours were observed in wildtype (WT) (*As2*$^{+/-}$ or *As2*$^{+/+}$) neonate and adult (C57BL/6) mice transplanted with ARSA LVV-transduced Lin^{-} HSPC although these mice shared a similar genetic background with *As2*$^{-/-}$ (*As2*$^{-/-}$ mice have a mixed C57BL/6-SV129 background). These findings suggest that the irradiation procedure and/or ARSA deficiency might influence the development of liver neoplasia in *As2*$^{-/-}$ mice. **GLP toxicity and tumourigenicity study** The toxicity and tumourigenicity study was repeated under GLP conditions. In the pivotal GLP toxicity and tumourigenicity study, lethally irradiated young adult *As2*$^{-/-}$ mice (haplotype CD45.1) were administered mock-transduced or ARSA LVV-transduced Lin^{-} HSPC obtained from CD45.2 *As2*$^{-/-}$ mice. Untreated mice were included as additional control group. Animals were dosed at $1x10^{6}$ cells/mouse, the same dose at which liver findings were observed in the previous non-GLP study and animals were observed for 12 months following transplantation. Total body irradiation at a lower dose than that used in the non-GLP toxicity and tumorigenicity study was used. No increased mortality, toxic findings or adverse neurobehavioural effects were noted in mice transplanted with Lin^{-} HSPC transduced with ARSA LVV. No abnormal expansion of myeloid or lymphoid cell lines or proliferative changes related to the transplantation of ARSA LVV-transduced Lin^{-} HSPC were observed; IS analysis showed a polyclonal	risk of leukaemia or lymphoma after treatment with OTL-200. In the event that leukaemia or lymphoma is detected in any patient who received OTL-200, blood samples should be collected for integration site analysis.

Key Safety findings (from nonclinical studies)	Relevance to human usage
reconstitution without evidence of genotoxicity. Hepatocarcinoma was found in one male mouse transplanted with ARSA LVV-transduced cells and in one male dosed with mock-transduced cells, with a frequency similar to the one reported in literature in mice with the same C57BL/6-SV129 background (Haines, 2001). This is consistent with the hypothesis that the high incidence of liver tumours observed in the previous study was influenced by the high dose of irradiation on *As2*$^{-/-}$ mice delivered in that study. It has been reported in the published literature that the development of spontaneous neoplastic lesions, including liver tumours, is accelerated and/or enhanced by irradiation (Vesselinovitch, 1971).	
Safety pharmacology	
Cardiovascular system, including potential effect on the QT interval No dedicated safety pharmacology studies have been performed with OTL-200 or murine Lin^{-} HSPC transduced with ARSA LVV. Cardiovascular (CV) and respiratory endpoints were not evaluated as OTL-200 is not expected to produce proteins or enzymes which would be active within the CV and respiratory systems.	Not applicable.
Nervous system Neurophysiological parameters, motor coordination, behavioural and/or learning endpoints were included in the primary pharmacodynamics, secondary pharmacodynamics and toxicity studies. No neurobehavioral effects were seen in transgenic mice (ARSA Tg) mice, generated to overexpress ARSA constitutively in all tissues and in MLD mice following transplantation with ARSA LVV-transduced Lin^{-} HSPC.	Not applicable.
Drug interactions	
Pharmacodynamic drug interactions Based on the biologic attributes of OTL-200 as an *ex vivo* genetically modified autologous CD34^{+} haematopoietic stem and progenitor cell gene therapy, conventional pharmacodynamic (PD) drug interaction studies were considered not applicable and, therefore, no studies were conducted.	Not applicable.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Pharmacokinetic drug interactions Based on the biologic attributes of OTL-200, conventional pharmacokinetic (PK) drug interaction studies were considered not applicable and no studies were performed to evaluate potential interactions with drugs that may be co-administered with OTL-200. There is no expectation that OTL-200 would interact with the liver cytochrome family of enzymes.	Not applicable. Patients will receive pre-treatment conditioning with IV busulfan and pre-medication with an antihistamine before administration of OTL-200. The use of these agents is well established in cell transplantation therapy (Andersson, 2002) and from the clinical data there is no evidence of any drug interactions with these agents.
Other toxicity-related information or data	
Immunotoxicity Stable, long-term expression of ARSA was observed in the peripheral blood and tissues of $As2^{-/-}$ mice reconstituted by ARSA LVV transduced Lin^- HSPC suggesting the absence of immune response against the transduced cells and the transgene product even in presence of enzyme over-expression. Furthermore, no antibodies against ARSA were detected in $As2^{-/-}$ mice following transplantation with ARSA LVV-transduced Lin^- HSPC (Section 4.5, Module 2.4). ARSA overexpression does not affect the maturation, differentiation or effector function of immune cells.	Since OTL-200 is an autologous cell-based product, transduced *ex vivo*, immune-mediated graft-versus-host or host-versus-graft reactions are not anticipated. Patients receive myeloablative conditioning prior to treatment to promote efficient engraftment of ARSA-expressing cells. Cumulatively, 12 out of 82 patients exposed to OTL-200 have developed anti-ARSA antibodies as described in Module SVII.3.1.
Generation of replication competent lentivirus (RCL) The ARSA LVV used in the production of OTL-200 is a self-inactivating (SIN), replication-defective third generation vector in which most of the U3 region of the 3' long-terminal repeat (LTR) has been deleted, and is made by a core of HIV-1 structural proteins and enzymes, the envelope of the vesicular stomatitis virus (VSV), and a genome containing HIV-1 cis-acting sequences, no viral genes, and one expression cassette for the ARSA transgene. No HIV-1 gag p24 capsid protein was detected in the plasma of immunodeficient mice transplanted with ARSA LVV-transduced $CD34^+$ cells (Section 4.5, Module 2.4), therefore excluding the occurrence of transfer of viral packaging function to transduced cells or RCL generation.	No significant risk of secondary transduction through vector mobilisation or generation of RCL was observed. Molecular monitoring for RCL has been carried out in the OTL-200 clinical development programme using the following preliminary screening tests: a) enzyme-linked immunosorbent assay (ELISA) for HIV p24 antigen, b) deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) for Vesicular Stomatitis Virus glycoprotein envelope (VSV-G env), and c) reverse transcriptase (RT) PCR for HIV-pol ribonucleic acid (RNA) (Section 4.2, Module 2.7.4). If one of the preliminary tests resulted in a positive assessment, the tests were repeated at the next planned follow up visit. If 2 of 3 of the preliminary screening tests were positive, a confirmatory culture test would have been performed. To date there has been no reported evidence of positive RCL results in either clinical lentiviral vector lots, *ex vivo* lentiviral gene therapy lots, or patients infused with these gene therapy products (Marcucci, 2018; McGarrity, 2013; Cornetta, 2018). The theoretical risk of replication competent

Key Safety findings (from nonclinical studies)	Relevance to human usage
	lentivirus generation is discussed in Module SVII.1.1. The Libmeldy SmPC specifies that molecular monitoring did not detect RCL.

Conclusions on non-clinical data

Non-clinical studies have been conducted to support the efficacy and safety of OTL-200 administration to humans. Due to the nature of OTL-200 as an autologous cell-based gene therapy product, conventional non-clinical studies were considered neither feasible nor applicable to allow extrapolation of animal data to efficacy and/or safety in humans.

Overall the non-clinical data support that treatment of MLD patients with OTL-200 is expected to be safe and to result in restoration of ARSA activity at the proposed clinical regimen.

The safety concerns from non-clinical data based on whether the findings have been confirmed by clinical data (important identified risk), have not been adequately refuted by clinical data and/or are of unknown significance (important potential risk), or require further research (missing information) are summarised below.

Important identified risks (confirmed by clinical data)

- None

Important potential risks (not refuted by clinical data or which are of unknown significance)

- Malignancy due to insertional oncogenesis
- Anti-ARSA antibodies

Missing information

- None

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The OTL-200 clinical development programme includes safety and efficacy data from patients treated in 3 clinical trials, and 3 Expanded Access Programmes (EAPs). (hereafter collectively referred to as the CDP). Data from patients who received either the fresh or cryopreserved formulation were pooled and analysed together in an integrated analysis. As requested by the EMA, the RMP reports updated information from clinical studies as well as information available from all other sources based on a common DLP with the SmPC of Libmeldy.

Brief descriptions of the clinical trials and the CDP EAPs are as follows:

- **Study 201222**: Ongoing open-label, non-randomised, single-arm, prospective, single centre clinical trial evaluating the safety and efficacy of treatment with the fresh formulation of OTL-200 in patients with early-onset MLD.
- **Study 205756**: Ongoing open-label, non-randomised, single-arm clinical trial evaluating the safety and efficacy of treatment with the cryopreserved formulation of OTL-200 in patients with pre-symptomatic early-onset MLD.
- **Study OTL-200-07**: Ongoing open label, non-randomised, single arm trial to evaluate the safety and efficacy of treatment with OTL-200 in patients with late juvenile onset MLD.
- **CUP 207394**: In 2013, one early symptomatic EJ patient was treated under an Italian compassionate use scheme (CU-IMD) sponsored by Ospedale San Raffaele (OSR). This patient did not meet the Study 201222 inclusion criterion of ≤6 months from onset of symptoms.
- **HE 205029**: Following completion of enrolment of Study 201222, pre symptomatic LI patients received treatment in 2016 with OTL-200 under the Italian Hospital Exemption (HE) scheme [Italian Decree, dated 16 January 2015, and Article 3, Nr.7 of Directive 2001/83/EC]. The objective was to provide treatment to patients affected by MLD with a gene therapy product prepared on a non-routine basis.
- **CUP 206258**: This compassionate use programme was initiated after the HE programme under the auspices of the Italian Ministerial Decree dated 07 September 2017 (superseding decree dated 08 May 2003).

Cumulatively, 45 patients with MLD have been treated with OTL-200 in the CDP. Patient exposure and follow-up duration in the CDP is based on data included in the CDP databases as of the DLP (16-Dec-2024) of Periodic Benefit Risk Evaluation Report (PBRER) #6 (Table 3).

Patients who completed their clinical trial were offered enrolment into an observational, long-term follow-up study, OTL-200-10 (for details see Part II SV.1). As of the DLP, 3 CDP patients have enrolled in Study OTL-200-10.

Table 3: OTL-200 Exposure and Follow-up Duration in Clinical Trials and CDP Expanded Access Programs

Study Identifier	Ongoing	Discontinued [a]	Completed[b]	Total	Person-time (Follow-up duration, years)
201222	16	2	2	20	211.1
205029	3	0	0	3	26.3
205756	10	0	0	10	54.6
206258	3	1	1	5	31.2
207394	1	0	0	1	11.5
OTL-200-07	6	0	0	6	11.9
Total Treated	**39**	**3**	**3**	**45**	**346.6**

[a] All the discontinuations post-OTL-200 exposure were due to death.
[b] Completed follow-up in the study under which the patient was treated. Patients continue to be followed in Study OTL-200-10.

OTL-200 exposure by age and gender in the CDP is presented in Table 4. Of these patients, 24 patients were treated when they were infants or toddlers, 19 patients were 2 to 11 years of age when treated, and 2 patients were 12 to 17 years of age when treated. The oldest age of a patient treated with OTL-200 was 15.5 years old (Calbi, 2024).

OTL-200 exposure by ethnic origin is provided in Table 5.

Table 4: OTL-200 Exposure in Clinical Trials and CDP Expanded Access Programs by Age Group and Gender

	Subjects			Person-time (Follow-up duration, years)	
Age Group	**Female (N=16)**	**Male (N=29)**	**Total (N=45)**	**Female (N=16)**	**Male (N=29)**
Infants and toddlers (28 days to 23 months)	8	16	24	79.8	134.3
Children (2 to 11 years)	8	11	19	51.6	77.6
Adolescents (12 to 17 years)	0	2	2	N/A	3.3

Abbreviations: N/A=not applicable.

Table 5: OTL-200 Exposure in Clinical Trials and CDP Expanded Access Programs by Ethnic Origin and Gender

	Subjects			Person-time (follow-up duration, years)	
Ethnic origin	**Female (N=16)**	**Male (N=29)**	**Total (N=45)**	**Female (N=16)**	**Male (N=29)**
African American/African Heritage	0	1	1	N/A	4.8
Asian – Central/South Asian Heritage	1	0	1	5.1	N/A

Table 5: OTL-200 Exposure in Clinical Trials and CDP Expanded Access Programs by Ethnic Origin and Gender (Continued)

	Subjects			Person-time (follow-up duration, years)	
Ethnic origin	**Female (N=16)**	**Male (N=29)**	**Total (N=45)**	**Female (N=16)**	**Male (N=29)**
Asian - East Asian Heritage	0	1	1	N/A	1.2
Asian - South East Asia Heritage	0	1	1	N/A	9.7
White - Arabic/North African Heritage	1	4	5	10.9	42.0
White - White/Caucasian European	14	22	36	115.5	157.5

Abbreviations: N/A=not applicable.

The duration of follow-up (observation period) for OTL-200 treated patients in the CDP is presented in Table 6.

OTL-200 is intended for autologous use and is administered once as a single treatment. The minimum recommended dose of Libmeldy to be administered is 3×10^6 $CD34^+$ cells/kg. In clinical studies doses up to 30×10^6 $CD34^+$ cells/kg have been administered. The dose to be infused should be defined by the treating physician based on the total number of $CD34^+$ cells supplied, the patient's weight at time of treatment, and the fact that any bag used should be administered in its entirety.

Table 6: Duration of Follow-up for OTL-200 Treated Subjects in Clinical Trials and CDP Expanded Access Programmes

	Late Infantile (N=20)	**Early Juvenile (N=19)**	**Late Juvenile (N=6)**	**Total (N=45)**
Duration of follow-up (years)				
Mean (SD)	9.50 (2.976)	7.62 (4.055)	1.98 (0.749)	7.70 (4.066)
Median (Min, Max)	8.83 (5.0, 14.6)	9.84 (0.6, 13.4)	2.20 (0.9, 2.7)	7.89 (0.6, 14.6)
Duration of follow-up category				
≥6 months	20 (100%)	19 (100%)	6 (100%)	45 (100%)
≥1 year	20 (100%)	18 (94.7%)	5 (83.3%)	43 (95.6%)
≥2 years	20 (100%)	16 (84.2%)	3 (50.0%)	39 (86.7%)
≥3 years	20 (100%)	16 (84.2%)	0	36 (80.0%)
≥4 years	20 (100%)	16 (84.2%)	0	36 (80.0%)
≥5 years	19 (95.0%)	13 (68.4%)	0	32 (71.1%)
≥6 years	18 (90.0%)	11 (57.9%)	0	29 (64.4%)
≥7 years	16 (80.0%)	10 (52.6%)	0	26 (57.8%)
≥8 years	12 (60.0%)	10 (52.6%)	0	22 (48.9%)

Table 6: Duration of Follow-up for OTL-200 Treated Subjects in Clinical Trials and CDP Expanded Access Programmes (Continued)

	Late Infantile (N=20)	Early Juvenile (N=19)	Late Juvenile (N=6)	Total (N=45)
≥9 years	9 (45.0%)	10 (52.6%)	0	19 (42.2%)
≥10 years	8 (40.0%)	8 (42.1%)	0	16 (35.6%)
≥11 years	6 (30.0%)	4 (21.1%)	0	10 (22.2%)
≥12 years	6 (30.0%)	1 (5.3%)	0	7 (15.6%)
≥13 years	4 (20.0%)	1 (5.3%)	0	5 (11.1%)
≥14 years	1 (5.0%)	0	0	1 (2.2%)
Duration of follow-up category				
<2 years	0	3 (15.8%)	3 (50.0%)	6 (13.3%)
≥2 years to <5 years	1 (5.0%)	3 (15.8%)	3 (50.0%)	7 (15.6%)
≥5 years to <8 years	7 (35.0%)	3 (15.8%)	0	10 (22.2%)
≥8 years	12 (60.0%)	10 (52.6%)	0	22 (48.9%)
Status				
Completed	2 (10.0%)	1 (5.3%)	0	3 (6.7%)
Discontinued	0	3 (15.8%)	0	3 (6.7%)
Ongoing	18 (90.0%)	15 (78.9%)	6 (100%)	39 (86.7%)
Primary reason for withdrawal				
Death	0	3 (15.8%)	0	3 (6.7%)

Abbreviations: CDP=clinical development programme; Max = maximum; Min = minimum; SD=standard deviation

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Human immunodeficiency virus (HIV) ribonucleic acid (RNA) and/or Hepatitis C virus (HCV) RNA and/or Hepatitis B virus (HBV) deoxyribonucleic acid (DNA)-positive subjects	This exclusion criterion, based on the list of transmissible infectious agents reported in the EU Cell and Tissue Directive, was established for safe manipulation and to minimise the HSCT-related complications associated with the presence of certain infections and to further minimise the risk of reversion of LVV to a replication-competent lentivirus.	No	The use of OTL-200 in patients with HIV, HCV or HBV in clinical practice is very unlikely as the Libmeldy SmPC advises that a negative serology test for HIV, HCV and HBV is necessary to ensure acceptance of apheresis material for OTL-200 manufacturing. Apheresis material from patients with a positive test for HIV, HCV and HBV will not be accepted for OTL-200 manufacturing.
Subjects affected by neoplastic diseases	Insertional oncogenesis is a safety concern related to integrating viral vectors for cell modification. Patients affected by neoplastic diseases were excluded so that their inclusion did not interfere with the assessment of the safety and efficacy of OTL-200 in the clinical trial, particularly with regard to the risk of malignancy due to insertional oncogenesis.	No	Use in this population is very unlikely given the rarity of MLD (Module SI). Based on what is known for other gene therapies, malignancy due to insertional oncogenesis is recognised as an important potential risk of OTL-200 (Module SVII.3.1). In the clinical development programme, no persistent expansions of clones containing lentiviral vector insertions into genes associated with leukaemia or myelodysplasia have been seen following treatment with OTL-200.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Subjects with cytogenetic alterations typical of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)	Patients with cytogenetic alterations typical of MDS/AML were excluded from the clinical trial in case their inclusion may have interfered with the safety and efficacy assessment of patients treated with OTL-200. These subjects may have developed MDS/AML necessitating chemotherapy and thus withdrawal from the study.	No	In clinical practice it is very unlikely that OTL-200 will be used in patients with cytogenetic alterations typical of MDS/AML given the rarity of MLD (Module SI).
Subjects who underwent an allogeneic HSCT in the previous 6 months & Subjects who underwent an allogeneic HSCT with evidence of residual cells of donor origin	This exclusion criterion was established to minimise potential confounding factors related to the clinical outcome of any previous allogeneic HSCT and which could have an impact on the evaluation of the efficacy profile of OTL-200 and related procedures. This exclusion criterion is also aimed at minimising the cumulative risks associated with repeated myeloablative conditioning regimen.	No	Allogeneic HSCT has been used for the treatment of late-onset MLD for the past three decades. Long-term results show that individuals with LJ and adult MLD benefit from HSCT if transplanted during the pre-symptomatic or early symptomatic stages of disease, with improved survival and a stabilisation of cognitive and motor functions compared with outcomes in patients with untreated MLD. Uncertainties on the long-term outcomes of HSCT in LJ MLD still exist, and data on adult MLD are relatively sparse. OTL-200 is not currently approved for the treatment of patients with late-onset MLD.

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 uncommon adverse reactions or adverse reactions with a long latency.

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

Table 7: Exposure of Special Populations Included or Not Included in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Pregnant and breast-feeding women were not included in the clinical development programme.
Breast-feeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with hepatic impairment were not included in the clinical development programme.
• Patients with renal impairment	Patients with renal impairment were not included in the clinical development programme.
• Patients with cardiovascular impairment	Patients with cardiac impairment were not included in the clinical development programme.
• Immunocompromised patients	Patients who were immunocompromised were not included in the clinical development programme.
• Patients with a disease severity different from inclusion criteria in clinical trials	Patients with disease severity different from the inclusion criteria were not evaluated.
Population with relevant different ethnic origin	The majority of patients included in the OTL-200 CDP were of White/Caucasian European origin (36/45 patients, 80%) with a minority of patients of White/Arabic/North African heritage (5/45 patients, 11.1%), and 1 patient (2.2%) each of African American/African heritage, Central/South Asian, East Asian, and South East Asian origin (Table 5). The efficacy of OTL-200 is not thought to be affected by ethnicity. MLD is panethnic with affected patients described in several populations including European, Japanese, Lebanese, South African, Iranian, Indian, Polynesian, Algerian, Navajo Indian, Alaskan Eskimo, Jewish, Habbanite Jew, Muslim Arab and Christian Arab, ranging from mild to severe forms of MLD (Von Figura, 2001).
Subpopulations carrying relevant genetic polymorphisms	Potential metabolic differences in subpopulations carrying genetic polymorphisms in the hepatic cytochrome P-450 family of enzymes or in drug transporters were not explored in the clinical development programme. Unlike conventional small molecule drugs, such polymorphisms are not considered relevant to OTL-200.

Table 7: Exposure of Special Populations Included or Not Included in Clinical Trial Development Programmes (Continued)

Type of special population	Exposure
Elderly patients	Elderly patients were not included in the clinical development programme.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

OTL-200 is authorised for use in EEA and in the United Kingdom (as Libmeldy) and in the United States of America (USA, as Lenmeldy).

SV.1.1 Method used to calculate exposure

Given the nature of the treatment and similar to the approach used during the OTL-200 clinical development programme, each patient treated with Libmeldy in the commercial setting is counted as one to calculate exposure.

SV.1.2 Exposure

At the Data Lock Point (DLP), 16-Dec-2024, 37 patients have been treated with OTL-200 outside the CDP (Table 8).

OTL-200-OOS-EAP is a post-authorisation expanded access protocol for patients treated with OTL-200 that does not meet the product specifications required in the USA; one patient has been treated as of the DLP.

Table 8: OTL-200 Exposure Outside the Clinical Development Programme

Treatment Setting	Total
Nominal Compassionate Use	10
OTL-200-OOS-EAP (USA)	1
Commercial	26
Total	**37**

Nominal compassionate use included patients treated with the commercial formulation of OTL-200 in the framework of SR-TIGET (CRYO-CUP) and an expanded access protocol in the USA at the University of Minnesota (CU-UMN). Details of the 10 patients who received OTL-200 under nominal compassionate use are provided in Table 9 .

Details of the 26 patients who received OTL-200 in the commercial setting are provided in Table 10.

A post-marketing, observational long-term follow-up study (Study OTL-200-10, LongTERM-MLD) has been set up to ensure that the efficacy and safety of OTL-200 in patients treated in the CDP as well as patients treated in the commercial setting are assessed for up to 15 years after treatment, in line with regulatory requirements (EMA, 2008; EMA, 2009; FDA, 2020). OTL-200-10 began enrolment in December 2022, and as of 16-Dec-2024, 14 patients have been enrolled and had data entered (Table 11). The patients were treated in clinical trials (n=3), under nominal compassionate use (n=4), or in the commercial setting (n=7). Demographic data are provided in Table 12.

Table 9: Exposure via Nominal Compassionate Use by MLD subtype age group sex and region of origin

	Number (%) of Patients (N = 10)[a]
MLD Type	
Pre-symptomatic Late Infantile (PSLI)	7 (70.0%)
Pre-symptomatic Early Juvenile (PSEJ)	1 (10.0%)
Early symptomatic Early Juvenile (ESEJ)	1 (10.0%)
Early Juvenile[b]	1 (10.0%)
Age at Treatment	
28 Days to 23 Months inclusive	7 (70.0%)
24 Months to 11 Years inclusive	3 (30.0%)
Sex	
Female	6 (60.0%)
Male	4 (44.0%)
Region of Origin	
Europe	1 (10.0%)
Middle East	2 (20.0%)
North America	6 (60.0%)
South America	1 (10.0%)

[a] 4 nominal compassionate use patients have been enrolled in Study OTL-200-10 as of 16-Dec-2024.
[b] This patient has not been categorised as either ES or PS EJ

Table 10 Post-authorisation commercial exposureby MLD subtype, age group, sex and region of origin

	Number (%) of Patients (N = 26)[a]
MLD Status	
Pre-symptomatic Late Infantile (PSLI)	10 (38.5%)
Pre-symptomatic Early Juvenile (PSEJ)	6 (26.9%)
Early symptomatic Early Juvenile (ESEJ)	10 (34.6%)
Age at Treatment	
28 Days to 23 Months inclusive	13 (50%)
24 Months to 11 Years	19 (73.1%)
Sex	
Female	7 (26.9%)
Male	19 (73.1%)
Region of Origin	
Europe	25 (96.2%)
Middle East	1 (3.8%)

[a] 7 commercial patients have been enrolled in Study OTL-200-10 as of 16-Dec-2024.

Table 11: Cumulative Patients Enrolled in the Post-Marketing Long Term Follow Up Study (OTL-200-10)

Long Term Follow-up				
Study OTL-200-10	**Ongoing**	**Discontinued**	**Completed**	**Total**
Study 201222 [a]	2	0	0	2
CUP 206258[a]	1	0	0	1
Nominal Compassionate Use[b]	4	0	0	4
Commercial[c]	7	0	0	7
Total	**14**	**0**	**0**	**14**

[a] 2 Subjects from Study 201222 and one subject from Study 206258 completed their parent study but their follow-up is continuing in OTL-200-10.
[b] 4 of 10 patients treated under nominal compassionate use have enrolled in OTL-200-10.
[c] 7 of 26 patients treated with the commercial product Libmeldy have enrolled in Study OTL-200-10 and had data entered.

Table 12: Exposure in the Post-Marketing Long Term Follow Up Study (OTL-200-10) by age group, sex, and race

	Number (%) of Patients (N = 14)
Age	
28 Days to 23 Months inclusive	8 (57.1%)
24 Months to 11 Years	6 (42.9%)
Sex	
Female	6 (42.8%)
Male	8 (57.1%)
Race	
White – Arabic/North African Heritage	2 (14.3%)
White – Caucasian/European Heritage	9 (64.3%)
Not recorded	3 (21.4%)

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

OTL-200 is an autologous treatment and should only be administered once. It is subject to restricted medical prescription as the product must be administered in a QTC with experience in HSCT. OTL-200 has no properties that would promote its use for abuse or misuse for illegal purposes. No potential for drug dependence or drug abuse has been noted for OTL-200 in the clinical development programme.

PART II: MODULE 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

- **Use in Pregnancy and lactation**

The programme focused on early onset MLD patients, which presents in the paediatric age (age range of treated patients with OTL-200-f [n=29]: 7.6-139.9 months). There was no OTL-200 exposure during pregnancy or lactation in the clinical development programme (Table 7, Module SIV.3). The oldest age of a patient treated with OTL-200 was 11.6 years old (Table 4, Module SIII).

Section 4.6 of the SmPC indicates that "

Libmeldy is not intended for use in adults, and that no human data on use during pregnancy or lactation and animal reproduction studies are not available.

the Libmeldy SmPC also states that the SmPC of the myeloablative conditioning medicinal product should be consulted with regards to fertility.

The risk of germline transmission after direct systemic administration of gene therapy vectors is generally considered to be low (MacLachlan, 2013; Hess, 1996). As OTL-200 is an *ex vivo* gene therapy, the risk of germline transmission is exceedingly low. Transduction occurs *ex vivo* and the cell types used for *ex vivo* transduction does not contain gametes. The minimal risk of inadvertent germ line transmission associated with the administration of *ex vivo* transduced human cells is supported in international guidelines (EMA, 2006; ICH, 2006).

The potential for bystander cell transduction of germ cells (testes) upon *in vivo* infusion of ARSA LVV-transduced $CD34^+$ cells was evaluated and showed that ARSA LVV remained stably integrated within cells of human origin and did not mobilise to mouse tissues, including testes, confirming a low risk of germline transmission (Module SII). Due to the lack of evidence for germline transmission and the limited distribution of OTL-200 (i.e., primarily to haematopoietic tissues), no specific reproductive or developmental toxicity studies were performed. As there is no opportunity for germline transmission of the ARSA gene after treatment with OTL-200 the likelihood that an offspring would have general somatic expression of the ARSA gene is considered negligible.

There is no information regarding the presence of OTL-200 in human milk, its effects on milk production and its effects on the breastfed infants. It is unknown whether OTL-200 is excreted in human milk.

Considering the indication for OTL-200 as well as the association of myeloablative conditioning regimen (busulfan) with irreversible infertility (Busilvex SmPC), patients treated with OTL-200 in clinical practice are not expected to become pregnant or to be lactating during treatment. Therefore, pregnancy and lactation are not considered important risks. Should pregnancy and subsequently lactation occur post-treatment naturally or through *in vitro* fertilisation (IVF), pregnancy after ovo-preservation or any other method, Orchard will consider whether additional actions are warranted and feasible to further characterise or minimise this risk.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

None

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None

Known risks that require no further characterisation as related to MLD or to the administration procedure and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- **Hepatobiliary toxicity including gallbladder polyps**

Patients with MLD are known to be at increased risk of developing gallbladder complications, including wall thickening and polyps, compared with patients with other lysosomal disorders. The deposition of accumulated sulfatide in visceral tissue has been implicated in these findings; the risk of gallbladder polyps evolving into carcinoma has been reported in MLD patients (Kim, 2017; Agarwal, 2013).

In the Integrated Safety Set, mild, non-serious gallbladder enlargement was reported in 22 subjects during the Pre-treatment phase (Section 2.1.4.3, Module 2.7.4). None of the subjects treated with OTL-200 presented with hepatic impairment prior to treatment.

In Study 205756, after treatment with OTL-200-c, 3 subjects had a total of 3 hepatobiliary events.

Including pre-treatment, all 6 subjects had at least 1 hepatobiliary AE and experienced a total of 7 hepatobiliary events. Three events (gallbladder enlargement, n=3) occurred prior to treatment with OTL-200-c, 1 event (hypertransaminasemia) occurred in the Treatment phase, and 3 events (gallbladder enlargement, hepatomegaly and acute cholecystitis, n=1 each) occurred within the 3-month post-treatment phase. None of these events were serious and all were considered to be unrelated to OTL-200-c.

During the follow-up phase, 16 subjects experienced hepatobiliary AEs that included newly reported events of gallbladder enlargement (3 subjects) and gallbladder polyps in 4 subjects with pre-existing events of gallbladder enlargement. In 2 subjects, a cholecystectomy was performed due to findings of polyps >5 mm identified by ultrasound scan. Cholecystectomies were performed in consideration of the reported risk of gallbladder polyps evolving into carcinoma. In both cases, the event was considered serious.

After excluding event terms related to the gallbladder, 11 patients in the Integrated Safety Set had events in the hepatobiliary disorders system organ class (SOC). These events included venoocclusive liver disease, drug-induced liver injury, hepatomegaly, and hypertransaminasemia. Specifically, 3 patients experienced venoocclusive liver disease. Two

patients experienced a grade 1 and grade 2 event of hypertransaminasemia respectively. Hepatic venoocclusive disease and hepatorenal failure are known complications associated with busulfan administration (Ciurea, 2009) and described in the busulfan SmPC (Busilvex SmPC).

The hepatobiliary disorders observed following OTL-200 treatment are not considered important safety concerns for OTL-200 as they were expected complications of busulfan treatment and of the background disease (Module SI). In particular, section 4.8 of the Libmeldy SmPC reports that hepatomegaly and hepatic venoocclusive disease and hypertransaminasaemia are adverse reactions attributed to myeloablative conditioning with busulfan. Section 5.1 of the Libmeldy SmPC recommends that patients receive treatment with defibrotide and/or ursodeoxycholic acid for the prophylaxis of veno-occlusive disease (VOD) and related endothelial injury complications.

- **Renal tubular acidosis**

Patients with MLD may develop an underlying proximal (Type 2) renal tubular acidosis due to sulfatide accumulation in the renal tubules (Lorioli, 2015).

In the Integrated Safety Set, renal tubular acidosis was reported in 8 subjects in the Pre-treatment phase, 4 subjects during the Treatment phase, 2 subjects in the 3-month post-gene therapy (GT) phase and 1 subject in the long-term follow-up phase. The events occurring post-GT were non-serious and considered to be related to the underlying disease and not to OTL200-f.

No renal impairments were reported in subjects treated with OTL-200.

In Study 205756 of OTL-200-c, one subject experienced Grade 1 renal tubular acidosis in the 3-month post-treatment phase. The event was non-serious and considered to be unrelated to OTL-200-c. There were no new renal tubular acidosis or metabolic acidosis events reported in Study 205756 since the MAA data cut.

Renal tubular acidosis was not considered an important risk of OTL-200 as it was related to the underlying disease as observed in the pre-treatment phase and can be managed as part of MLD symptom treatment.

- **Risks related to medical and surgical procedures (e.g. central line placement, bone marrow harvest, leukapheresis)**

Similar to other autologous gene therapies, there are multiple steps involved in OTL-200 treatment including central line placement, leukapheresis (to isolate autologous $CD34^+$ cells for the manufacturing of Libmeldy), BM harvest (used as a possible source of back-up cells for rescue treatment), that are recognised to be associated with potential complications such as infection and thrombosis. As part of the OTL-200 administration process a central venous catheter (CVC) is inserted under general anaesthesia for the administration of chemotherapy and IV medications and aseptic procedures should be adhered to.

Infections are common when a CVC is in place (WHO, 2024). Patients who are immunocompromised (e.g. undergoing myeloablative conditioning) are at increased risk of infections. Catheter occlusions and catheter-related thrombosis are common complications of catheters and catheter-related thrombosis occurs in up to 50% of children with a long-term CVC (Baskin, 2009). Central venous access is a requirement for all patients to receive conditioning regimen and to infuse OTL-200. In the Integrated Safety Set device-related infections occurred in 9/29 (31%) of subjects and are noted to be very common in patients with ports installed for central venous access (Table 14, Module 2.7.4). This included 4 AEs (4/29 subjects; 14%) up to

the 3 Month Post-GT time period and 5 AEs (5/29 subjects; 17%) in the Short Term period (Section 2.1.1, Module 2.7.4). It is important to note that of the 4 AEs (4/29 subjects; 14%) up to the 3 Month Post-GT time period, 3 AEs (3/29 subjects; 10%) occurred pre-treatment. Of the 9 device-related infections, 5 were National Cancer Institute Common Toxicity Criteria (NCI CTC) Grade 3 (5/29 subjects; 17%) including 2 AEs (2/29 subjects; 7%) up to the 3 Month Post-GT time period and 3 AEs (3/29 subjects; 10%) in the Short Term period (Table 16, Module 2.7.4).

Two subjects (7%) experienced SAEs of device-related infection in the Pre-treatment phase, and 2 subjects (7%) experienced SAEs of device-related infection in the Follow-up phase (Section 2.1.3, Module 2.7.4). All four SAEs were NCI CTC Grade 3 and resolved with antibiotic treatment. None of the device-related infections was considered related to OTL-200-f by the investigator.

In Study 205756, 2 device-related infection SAEs occurred in 2 subjects (Section 2.1.3, Module 2.7.4). Both of these SAEs occurred in the Pre-treatment phase and were considered not related to OTL200-c by the investigator.

The risks related to medical or surgical procedures (e.g. central line placement, BM harvest, leukapheresis) such as serious CVC infections and thrombosis in the device are not important risks of OTL-200 per se but risks related to the required procedure / associated therapies without which OTL-200 could not be administered. These risks are well-recognised and can be managed in clinical practice through patient monitoring and standard of care treatment as described in the guidance provided in section 4.4 of the Libmeldy SmPC and in the PL.

In order to minimise the risks related to medical and surgical procedures, OTL-200 must be administered in an QTC with experience in HSCT. The Libmeldy SmPC includes guidance on the method of administration including the precautions to be taken before handling or administering the medicinal product, and guidance on preparation for infusion, administration and after administration. Healthcare professionals are also advised that infections related to the use of CVCs have been reported in clinical trials and as there is a risk of thrombosis associated with the CVC, patients should be closely monitored for potential infections and catheter-related events.

The risks related to medical or surgical procedures (e.g. central line placement, BM harvest, leukapheresis) will continue to be monitored in clinical practice using routine pharmacovigilance.

- **Risks related to conditioning regimen**

Myeloablative conditioning is required before OTL-200 infusion to promote efficient engraftment of the genetically modified autologous $CD34^+$ cells and busulfan is the conditioning agent recommended in the Libmeldy SmPC. The use of busulfan as a standalone conditioning agent in MLD is supported by nonclinical studies showing that busulfan induces optimal depletion of resident microglia in the brain compared with irradiation or treosulfan conditioning (Module SII; Section 3.1, Module 2.4).

In conventional allogeneic HSCT, the success of the procedure relies on the use of pre-transplant conditioning therapy for eradicating the patient's marrow (myeloablation), creating space for the incoming cells to engraft, and suppressing rejection reactions. In patients with MLD, high-level engraftment in brain by a fraction of the infused genetically-modified cells and/or their myeloid progeny is likely needed for fast kinetics of microglia repopulation as well as endoneurial

macrophages in the PNS. There is a high rate of graft failure and the lack of full haematopoietic reconstitution following non-myeloablative HSCT (Boelens, 2006; Cavazzana-Calvo, 2005). Therefore in order to provide the maximal chance for gene-corrected cells to engraft, myeloablative conditioning was used in the OTL-200 clinical development programme.

In the OTL-200 development programme, busulfan was used as the conditioning agent according to 2 distinct dosing regimens; myeloablative conditioning (MAC) and sub-myeloablative conditioning (SMAC) regimens which were used depending upon the specific study protocol and clinical condition of the subject. The advantage provided by busulfan compared to other conditioning agent relies on its depleting effect of local microglia resident cells thus allowing the engraftment of a fraction of genetically modified cells crossing the blood-brain barrier and their differentiation into microglia-like cells.

In the Integrated Safety Set, 13 subjects (45%) were treated with a SMAC regimen, defined as a target cumulative area under the curve (AUC) of 67,200 µg*h/L (target range 58,800 to 78,400 µg*h/L) (Section 3.1.4.1, Module 2.7.3). Sixteen subjects (55%) were treated with the MAC regimen, defined as a target cumulative AUC of 85,000 µg*h/L (target range: 76,500 to 93,500 µg*h/L). As would be expected, subjects who received a SMAC regimen received a lower total dose (mg) and lower total dose per body weight (mg/kg) than subjects who received a MAC regimen.

As presented in Section 2.1.1.5.2, Module 2.7.4, a specific process was followed for the selection of adverse drug reactions (ADRs) potentially attributable to myeloablative conditioning using the integrated data set. After a comprehensive assessment involving a clinical evaluation, with consideration of similar preferred terms (PTs), biological plausibility, nature and timing of the events, the underlying disease, incidence of the event in the paediatric population and a comparison with the adverse drug reactions listed in the busulfan SmPC, a total of 32 PTs from 14 SOCs were determined by Orchard to be potentially attributable to myeloablative conditioning. In Study 205756, during the 3-month post-treatment phase, the following AEs were considered related to busulfan: febrile neutropenia (n=5; 6 events), neutropenia (n=3; 4 events), stomatitis (n=4; 4 events), blood IgE increased (n=2, 2 events), respiratory distress (n=1; 1 event), blister (n=1, 1 event), rash (n=1; 1 event); rash erythematous (n=1; 2 events); rash generalised (n=1, 1 event), rash maculo-papular (n=1; 1 event) and urticaria (n=1, 1 event).The adverse reactions potentially attributed to myeloablative conditioning are listed in the Libmeldy SmPC and PL and the SmPC advises that the warnings and precautions of the myeloablative conditioning agent must be considered.

The risks related to the conditioning regimen are not an important risk of OTL-200 as they are not specifically related to OTL-200 even though the conditioning regimen is a required part of the treatment process and without myeloablative conditioning OTL-200 may not be effective. The safety profile of busulfan is well established after years of use in transplant setting and the risks can be managed in clinical practice through patient monitoring and standard of care treatment as described in the busulfan SmPC (Busilvex SmPC).

Risks related to conditioning regimen will continue to be monitored in clinical practice using routine pharmacovigilance.

- **Risks related to mobilising agents**

Granulocyte-colony stimulating factor (G-CSF), with or without plerixafor, has been used for mobilising peripheral blood for cell harvesting in the OTL-200 clinical development programme.

Peripheral blood stem cell (PBSC) mobilisation, which is important as a source of haematopoietic stem cells for transplantation, is generally performed using G-CSF, a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. As G-CSF alone is not effective in all patients, the combination of G-CSF with plerixafor increases the responsiveness of individuals to mobilisation and increases the yield of HSCs from mobilisation. It further minimises the need for multiple rounds of apheresis to produce enough stem cells for OTL-200 manufacturing.

The most commonly reported adverse reactions of G-CSF are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremities, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea (Neupogen SmPC). The most serious adverse reactions that may occur during treatment include anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and Acute respiratory distress syndrome [ARDS]), capillary leak syndrome, severe splenomegaly/ splenic rupture, and GvHD in patients receiving allogeneic bone marrow transfer. These ADRs are well documented in the product information for G-CSF containing products.

Plerixafor is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma and multiple myeloma whose cells mobilise poorly (Mozobil SmPC). Plerixafor has been recently authorised in the EU for use in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours.

Toxicities associated with G-CSF and plerixafor are well established and specified within the product information of respective medicinal products. The most common adverse reactions reported in patients associated with plerixafor administration were diarrhoea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness and vomiting. Several single centre studies have reported no major AEs with plerixafor administration in children (Pham, 2012; Son, 2013; Hong, 2012; Sevilla, 2012).

Risks related to mobilising agents are not considered an important risk of OTL-200 as they are not specifically associated with OTL-200, although the use of mobilising agents is a required part of the treatment process without which OTL-200 may not be effective. All patients treated with G-CSF with or without plerixafor are expected to experience adverse reactions but these risks are well-recognised for G-CSF and plerixafor and can be managed in clinical practice through patient monitoring and standard of care treatment as described in the SmPCs (Neupogen SmPC; Mozobil SmPC).

Risks related to mobilising agents will continue to be monitored in clinical practice using routine pharmacovigilance.

Known risks that do not impact the risk-benefit profile:

- **DMSO related toxicity**

OTL-200-c contains dimethylsulfoxide (DMSO) as an excipient. DMSO is the most commonly used cryoprotectant and is associated with a risk of dose- related toxicity. Although generally mild in nature, can also include more serious events of hypersensitivity/anaphylactic reactions (Kollerup Madsen, 2018). The Libmeldy SmPC states that no hypersensitivity, anaphylactic or infusion related reactions have been reported in the clinical study with OTL-200-c. However, as

DMSO is known to possibly cause anaphylactic reactions following parenteral administration, healthcare professionals are advised that patients who have not been previously exposed to DMSO should be observed closely during the first minutes of the infusion period.

Other reasons for considering the risks not important:

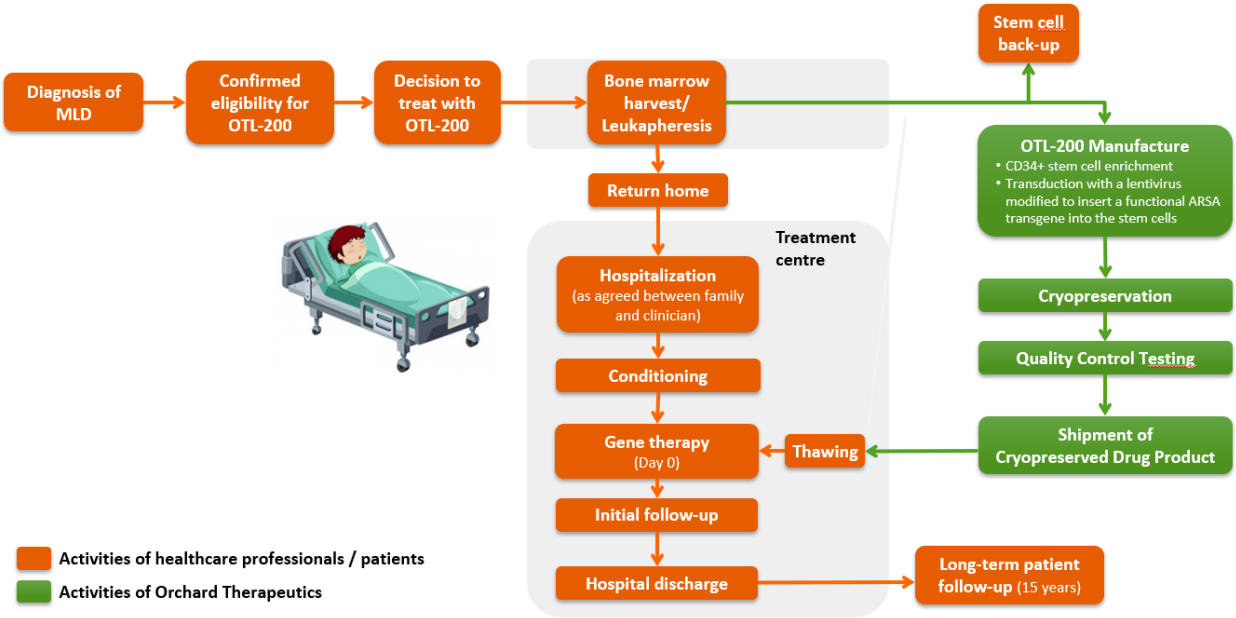
None

Advanced therapy medicinal product (ATMP) specific risks:

OTL-200 is a gene therapy and this warrants consideration of ATMP specific risks. Manufacturing and administration of OTL-200 is a multistep process (Figure 2). OTL-200 is an autologous gene therapy product, therefore, ensuring the product is linked from autologous cell procurement back to the same patient for treatment with drug product (DP) is essential. Risks associated with incorrect patient cell traceability and subsequent administration include those normally associated with allogeneic transplant, such as GvHD or transmission of infectious diseases.

The applicant is implementing a traceability system to ensure that OTL-200 DP and its starting and raw materials, including all substances contacting the cells or cellular sources, can be traced through the sourcing, manufacturing, packaging, storage, transport, and delivery, as described in Section 3.4, Module 3.2.P.3.3. The traceability system tracks collection of cellular source material, shipment to the manufacturing facility, manufacture and storage of the DP, shipment of DP back to the QTC, and receipt of DP at the QTC.

Figure 2: Flow Chart of the Logistics of Therapy



- **Risks to patients in relation to quality characteristics, storage and distribution of the product**

Libmeldy is a gene therapy consisting of an autologous $CD34^+$ cell enriched population that contains HSPC transduced *ex vivo* using a LVV encoding the human ARSA gene.

For the preparation of Libmeldy, autologous $CD34^+$ HSPC are isolated from mobilised peripheral blood (mPB). This is achieved by apheresis procedure(s) following peripheral blood mobilisation. $CD34^+$ HSPC are then transduced with an ARSA LVV, which inserts one or more copies of the human ARSA cDNA into the cell's genome so that genetically-modified cells become capable of expressing the functional ARSA enzyme. When re-administered to the patient, the engineered cells engraft and repopulate the haematopoietic compartment. A fraction of the infused cells and/or their myeloid progeny can migrate to the brain and contribute to CNS resident microglia and perivascular CNS macrophages populations after the transplant. These genetically modified cells can produce and secrete the ARSA protein, which can be taken up by surrounding cells, a process known as cross correction, and used to break down harmful sulfatides (Bergner, 2019; Sevin, 2007; Biffi, 2006; Gabande-Rodriguez, 2019).

Furthermore, microglia repopulation with genetically modified cells engrafting in the brain after treatment with OTL-200 is anticipated to address inflammatory and apoptotic components of the disease, mediated by microglial activation. The same process is also anticipated to help reconstituting the scavenging microglial function aimed at removing extracellular sulfatide, a key component involved in the pathogenesis of MLD across variants (Bergner, 2019; Sevin, 2007; Biffi, 2006; Gabande-Rodriguez, 2019).

OTL-200 DP is cryopreserved under the vapour phase of liquid nitrogen and stored at <-130 °C until the specific instructions for thaw of the product are followed prior to administration. Stability studies were performed using $CD34^+$ cells isolated from healthy donor material (BM or mPB), transduced with ARSA LVV and stored in an ethylene vinyl acetate (EVA) cryobag at the recommended storage condition <-130°C. Stability data support a 6-month shelf-life for cryopreserved OTL-200 DP when stored at <-130°C. Once thawed, the maximum shelf-life at room temperature (20°C-25°C) is 2 hours.

Incorrect storage and handling may pose a risk to the viability of the cells within the product and, therefore, could in theory pose a risk to patients or damage the product so that it may not be suitable for administration. As OTL-200 is shipped in a validated liquid nitrogen (LN2) dry vapor shipper, it will remain stable throughout shipping duration. The pack-out of OTL-200 DP is strictly controlled by the CDMO, and the receipt and handling of OTL-200 DP at the QTC is controlled by the clear instructions provided in the Product Manual. The shipment of OTL-200 is performed by trained couriers, and the process is controlled by a specialist distribution and logistics provider.

Critical characteristics of the drug product are controlled at release through testing according to the specification. Distribution of the product is qualified by a mock shipment activity to qualify the shipping route between a treatment site and CDMO for shipment of cellular source material (mPB) and cryopreserved DP.

The mock shipment for each specific treatment site confirms that patient cellular source material and cryopreserved DP can be transported between a treatment site and CDMO within an acceptable timeframe. The documentation is demonstrated to be sufficient for the shipment of patient material between the two sites. Mock shipments also confirm that the specified temperature range can be maintained during transport across the shipping route. Orchard's Distribution Team will monitor and assess all future shipping activities to ensure adherence to the acceptance criteria.

It is recommended that each bag of OTL-200 is infused within approximately 30 minutes, ideally immediately post-thaw, however, the stability of OTL-200 permits an infusion within 2 hours

post-thaw if needed. Providing the storage and administration procedures for OTL-200 are followed as per the SmPC guidance, this does not represent a safety concern.

- **Risk of transmission of an infectious agent**

Harvest of patient mPB (or bone marrow as a possible source of back-up cells) is performed at the QTC according to the standards and principles described by the Joint Accreditation Committee - International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation (JACIE) or Foundation for the Accreditation of Cellular Therapy (FACT). The mPB and BM collection facilities must also be JACIE/FACT accredited and have a Tissue Establishment License as per Directive 2004/23/EC in Europe. Additionally, the sites used conform to the Directive 2004/23/EC and sister directives for donation, procurement and testing as well as traceability requirements.

The mPB (and BM in case this material is used as source for back-up cells) are transported to the manufacturing facility via a qualified transport provider. Chain of custody begins at the collection of mPB, and continues through transport to the CDMO and the DP back to the QTC. The starting material is transported in a validated shipping container with a datalogger for tracking the temperature during transit. Quality Agreements are executed between the collection facility and Orchard, and Orchard and the transport providers.

Prior to initiation of the mPB (or BM) collection procedures, patients are tested for the presence of infectious agents as required by Directive 2004/23/EC and related directives.

All raw materials are procured from suppliers approved by CDMO under their Vendor Management Programme. Quality agreements are executed with critical raw material suppliers. Where available, material manufactured in compliance with Good Manufacturing Practice (GMP) and compliant with current compendial monographs are used for manufacture of OTL-200 drug substance (DS).

The CDMO requires a declaration of compliance with EU Directive 2006/17/EC from the clinical site as part of the documentation needed for the first step for release of the material prior to use, thereby assuring compliance to relevant standards of quality, safety testing, processing, preservation, storage and distribution of human cells and tissues.

To minimise the risk of transmission of an infectious agent, incoming cells are tested for infectious diseases and must be confirmed as acceptable prior to mPB release:

- Verification of the accompanying documentation as defined in Table 13.
- Microbiological examination of cell-based preparations, based on Ph. Eur. 2.6.27 guidelines with an acceptance criteria or culture negative for Microbiological control (or similar qualified method).

Table 13: Verification of Documentation for Mobilised Peripheral Blood (Autologous)

Description of Control	Acceptance Criteria
Chain of Identity ID (COI ID) and Donor ID (DIN) in documentation matches the same codes on primary packaging	Yes
Documentation states that donor is negative for HCV1, HBV, HIV1/2, HTLV1/2 (if applicable) and *Treponema pallidum* as per Directive 2006/17/EC	Yes
Documentation states that donor is negative for mycoplasma	Yes
Execution date of virus screening is consistent with required timing as per Directive 2006/17/EC	Yes
Confirmation that sample collection was carried out in accordance with Directive 2004/23/EC	Yes
The primary packaging of the product is intact	Yes

Note: 1. A nucleic acid test (NAT) with a limit of quantification of ≤15 international units/mL must be used to confirm the absence of ongoing HCV infection, i.e., "negative for HCV". In cases where patients have previously tested positive for HCV infection, negative NAT results are required on at least 3 sequential occasions over a period of at least 4 weeks, with the final test conducted no more than 3 days prior to cell harvest.
Abbreviations: COI ID = Chain of Identity ID; DIN = Donor ID; HCV = Hepatitis C virus; HBV = Hepatitis B virus; HIV = Human immunodeficiency virus; HTLV = Human T-cell leukaemia virus; NAT = Nucleic acid test

Although OTL-200 is tested for sterility and mycoplasma at the final release, because a small risk of transmission of infectious agents exists, this risk is communicated to healthcare professionals through the product information. As a precautionary measure the Libmeldy SmPC advises healthcare professionals administering OTL-200 to monitor patients for signs and symptoms of infections after treatment with OTL-200 and to treat appropriately, if needed.

The only other source of infectious agents would come from the vector since disposable materials for the manufacturing process are used. Lentiviral vector lots are tested for sterility adventitious agents including mycoplasma and infectious virus, RCL and viral potency prior to release for use in the OTL-200 manufacturing process.

- **Environmental risks**

There is no risk concerning the contamination of the environment with OTL-200. Genetically modified HSPC are not deliberately released in the environment and are not able to survive outside of the human body unless they are specifically cultured in humidified temperature- and gas-controlled incubators or in an adequate live model. As patient HSPC are genetically modified *ex vivo*, the probability of free viral particles being associated with the cells at administration is very low. Retroviral particles that have not entered into and transduced the HSPC are removed during the manufacturing process, and even under cultured conditions, they have a short half-life (Merten, 2004). In addition, there are no known mechanisms to enable shedding of ARSA LVV from cells transduced with OTL-200 as these cells do not contain the required viral elements to mobilise the ARSA LVV and produce infectious virions.

Although, shedding of ARSA lentiviral particles has not been assessed as part of a non-clinical programme, no shedding of the genetically-modified sequences is expected.

Even in the unlikely case that some free viral particles are present, the vector is replication-deficient and thus the expansion or survival of ARSA LVV in the environment is impossible as

such viral particles have an extremely low fitness to survive when exposed to environmental conditions.

In conclusion, it is considered that ARSA LVV particles used to modify the patients' own HSPC *ex vivo* are not shed by the patients into the environment via saliva, urine, or faeces.

- **Generation of replication competent lentivirus**

The LVV used for production of OTL-200 is a third generation, SIN HIV-based LVV with depleted LTR promoter activity and is replication-defective by design. As such, the generation of RCL is highly improbable and represent only a theoretical risk.

The ARSA LVV cell bank, plasmid design and manufacturing process were selected to ensure that the risk of RCL generation in ARSA LVV is very low. The ARSA LVV used in the production of OTL-200 is a SIN, replication-defective third generation vector in which most of the U3 region of the 3' LTR has been deleted, and is made by a core of HIV-1 structural proteins and enzymes, the envelope of the VSV, and a genome containing HIV-1 cis-acting sequences, no viral genes, and one expression cassette for the ARSA transgene. The three vector components (core, envelope and genome) are transiently expressed in vector producer cells by four different plasmid constructs: two core packaging constructs, the envelope construct and the transfer vector construct which contains the ARSA expression cassette. Only the transfer vector construct sequence is transferred and integrated into the target cells.

A RCL test is included on the release specification to monitor ARSA LVV for RCL contamination. To date, RCL has never been detected in any batch of ARSA LVV, OTL-200 or other LVV and related cell products manufactured using the common manufacturing cell bank, plasmid sequences and manufacturing process.

There was no evidence of RCL generation in the biodistribution study. A minimal to slight immune response against gag p24 was seen in 2 out of 6 mice that received ARSA LVV transduced HSPC in a toxicity and tumourigenicity study. This was likely due to the persistence of viral particles aggregated on the cell surface of the laboratory-grade product which is not purified to the same extent as clinical grade vector.

There is the possibility that free viral vector particles associated with the drug substance could be present in low levels at the end of the manufacturing process. *In vitro* shedding studies showed that any potential for viral transmission due to residual levels of viral particles in the drug product would be strongly inhibited by human serum. This is in addition to the replication defective design of the vector.

There were no positive results of RCL in any of the 35 subjects treated with either OTL-200-f (n=29) or OTL-200-c (n=6) as part of the OTL-200 clinical development programme (Section 4.2, Module 2.7.4).

In the Integrated Safety Set, 6 subjects (21%) tested positive for VSV-G env at Baseline, before exposure to OTL-200-f. During the course of post-GT follow-up, positive findings for VSV-G env were reported for several subjects. However, other RCL screening tests remained negative for all subjects, and the analysis of later time points for VSV-G env were negative for these subjects except for 1 patient. The positive results at Baseline before exposure to OTL-200-f suggest possible false positive results possibly due to contamination with a source of VSV-G DNA either (i) at the time of PBMC preparation at the clinical site or (ii) during the DNA extraction and assay process.

No patients experienced AE suggestive of RCL infection.

Other published studies have found no evidence of RCR/L including an evaluation of test results of 17 clinical vector lots, 375 manufactured T cell products, and 308 infused patients from both oncology and HIV clinical trials infusing retroviral- or lentiviral-transduced T cells from a total of 194.8 post-infusion person years of RCR/L follow-up (Marcucci, 2018).

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

Important Identified Risks: Delayed platelet engraftment

This risk is based on the safety analysis of data collected within the clinical development programme for OTL-200.

During the clinical development of OTL-200, platelet engraftment was defined as the 1st of 3 consecutive days with platelet values $\geq 20 \times 10^9$/L obtained on different days after OTL-200 infusion. This was in line with international guidelines on engraftment post-autologous haematopoietic stem cell transplantation (aHSCT) and SmPCs of other recently approved gene therapy products (Brierley, 2018; Zynteglo SmPC).

Four subjects experienced delayed platelet engraftment at day 60. No events of increased bleeding have been reported in any of the above subjects.

The median number of days until platelet engraftment in the integrated safety population treated with the fresh formulation of OTL-200 (N=29) was 41 days (range: 14-109 days). The median number of days until platelet engraftment in the population treated with the cryopreserved (commercial) formulation of OTL-200 at the time of the MAA (N=6) was 37 days (range: 23-47 days).

During the clinical development of OTL-200, all subjects received transfusion support with platelets. Most of these transfusions were considered part of the standard of care/prophylaxis for these subjects, were received during the peri-transplant period and mainly within the three months post gene therapy (≤ 100 days post-GT).

Four subjects received platelet transfusion within the context of the treatment of 3 non-serious AEs of ‘epistaxis’, one non serious AE of ‘febrile neutropenia’ (and one SAE of ‘thrombocytopenia’ (In particular, the SAE of thrombocytopaenia occurred during the 3-months post-GT phase in a complex post-transplant course, with SAEs of thrombocytopaenia, prolonged anaemia, VOD and TA-TMA captured as atypical haemolytic uremic syndrome . The patient received several platelet transfusions after gene therapy, both as standard of care and for the treatment of the SAE of prolonged thrombocytopenia which was deemed likely related to genetic predisposing factors in combination with exposure to drugs such as defibrotide (given for VOD) and busulfan. Overall, during the clinical development of OTL-200 the report of delayed platelet engraftment was not correlated with an increased incidence of bleeding. However, as this risk bears a potential for the development of serious bleeding events, this safety concern has been included as an important identified risk in the RMP Risk-benefit impact:

Delayed platelet engraftment is an important identified risk as it would have a negative impact on MLD patients in terms of associated morbidity. However, as there are no available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the potential risk of delayed platelet engraftment that has been observed in the clinical trials and that can be managed in clinical practice through patient monitoring and infusion of platelets.

Section 4.4 of the SmPC of Libmeldy reports that: "Platelet engraftment is defined as the first of 3 consecutive days with platelet values ≥ 20 x 10^9/L after Libmeldy infusion, with no platelet transfusion administered for 7 days immediately preceding and during the evaluation period (up to 60 days post gene therapy).

In clinical studies, the median number of days from treatment with Libmeldy to platelet engraftment was 35 (range 11 to 109 days). Four out of 49 subjects (8%) reported delayed platelet engraftment (median: 85.5 days, range 67-109 days) which was not correlated with an increased incidence of bleeding. As part of the standard of care/prophylaxis, all subjects in the integrated safety set (N=49) received transfusion support with platelets. Platelet counts should be monitored according to medical judgment until engraftment of these cells and recovery is achieved. Supportive transfusion of platelets should be given according to medical judgement and institutional practice."

The important identified safety concern of delayed platelet engraftment will be further characterised after the treatment of new patients in the context of clinical trials open to recruitment (Study 205756 and Study OTL-200-07), and the treatment of patients after OTL-200 marketing authorisation (MA) approval and followed up as part of LongTERM-MLD study (Part III.2).

Important Potential Risk 1: Malignancy due to insertional oncogenesis

Malignancy due to insertional oncogenesis is considered an important potential safety concern as OTL-200 consists of $CD34^+$ cells transduced *ex vivo* with a LVV which integrates permanently into the host genome. The self-inactivating design of the LVV vector used for OTL-200 abolishes viral LTR promoter and enhancer activity and ARSA transgene expression is driven by a moderately active internal human endogenous promoter, thus reducing the risk of activating neighbouring genes following insertion. The risk of insertional mutagenesis and consequent tumourigenicity following administration of OTL-200 was evaluated in several *in vitro* and *in vivo* non-clinical studies (Module SII).

Integration site analysis performed on genomic DNA from whole PB and BM samples harvested at different time points after therapy showed a highly polyclonal pattern of vector integration with no indication of abnormal clonal expansion. The hepatocellular tumours observed in *in vivo* studies were considered related to the conditioning regimen and genetic background of the mice (Section 4.3, Module 2.4). Overall there was no evidence of preferential expansion of insertion sites near proto-oncogenes in all analysed mice, with no increase in tumourigenesis found in a tumour prone mouse model.

To date, no cases of malignancy have been described with the use of lentiviral vectors. In the clinical development programme of OTL-200, no cases of malignant clonal expansion, malignancy or AEs indicative of oncogenic transformation have been reported and there has been no evidence of aberrant clonal behaviour based on insertion site analysis (Section 2.1.5.2, Module 2.7.4). These findings are similar to those reported in other LVV based HSPC gene therapy trials for X-adrenoleukodystrophy (X-ALD) and Wiskott-Aldrich syndrome (WAS) (Biffi, 2013; Aiuti, 2013).

Risk-benefit impact:

Malignancy due to insertional oncogenesis would be serious and could potentially be life-threatening.

The benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the theoretical risk of malignancy due to insertional oncogenesis that can be managed in clinical practice through patient monitoring and standard of care treatment if needed and is mitigated by the use of a self-inactivating LVV with minimal enhancer activity.

The important potential safety concern of malignancy due to insertional oncogenesis will be further characterised in multiple ongoing and planned studies including Study 201222, Study 205756, Study OTL-200-07, CUP 206258, CUP 207394, HE 205029 and LongTERM-MLD study (Part III.2).

Important Potential Risk 2: Anti-ARSA antibodies

All patients treated with OTL-200 have been monitored for potential immunogenic responses per the relevant EMA/FDA guidelines for long-term follow up of patients post-gene therapy (FDA, 2006; EMA, 2018a; FDA, 2014), with regular blood testing for immune response.

In the clinical development programme of OTL-200 including the integrated data set and the available information from the Study 205756 at the time of the RMP data cut, AAAs were detected transitorily, with low titres in a limited number of patients (4/33 patients, 12.1%). All the events resolved spontaneously or after treatment with one cycle of rituximab with no obvious impact on the clinical outcomes. In May 2020, after DLP of this RMP, data has emerged from two further AAA positive tests. One of these is the re-emergence of AAA in a patient who previously had positive AAA which resolved spontaneously.

Anti-ARSA antibodies were considered an important potential risk of OTL-200 following their identification in some of the patients and the need to confirm their impact on clinical outcomes and safety profile in the long-term.

Risk-benefit impact:

Although the analysis of the four AAA positive patients appear to show no obvious impact on the clinical outcomes, any negative impact of AAAs on the patient in terms of MLD disease progression, associated morbidity and quality of life has not been confirmed in the clinical trials.

Considering that emergence of AAAs can be managed in clinical practice through patient monitoring and the absence of available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the potential and as yet undefined risk posed by emergence of AAAs.

The important potential safety concern of anti-ARSA antibodies will be further characterised in multiple ongoing and planned studies including Study 201222, Study 205756, Study OTL-200-07, CUP 206258, CUP 207394, HE 205029 and LongTERM-MLD study (Part III.2).

Important Potential Risk 3: Engraftment failure

Engraftment failure is defined as failure to reach an absolute neutrophil count (ANC) >500 neutrophils/µL associated with no evidence of BM recovery (i.e. hypocellular marrow) by day +60. To date, none of the subjects in Study 201222 and Study 205756 met the pre-specified definition of engraftment failure (Study 201222 CSR; Study 205756 CSR). In the EAPs, one patient required unmanipulated autologous back-up bone marrow infusion to boost haematological recovery, following serious adverse events of venoocclusive liver disease, atypical haemolytic uraemic syndrome (aHUS, a form of post-transplant thrombotic

microangiopathy [TMA]), prolonged anaemia and thrombocytopenia (in the absence of active haemolytic process). The patient showed good haematopoietic and immune reconstitution at last follow-up (Calbi, 2018).

Risk-benefit impact:

Engraftment failure is an important potential risk as it would have a negative impact on the patient in terms of MLD disease progression and associated mortality. However, as there are no available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the potential risk of engraftment failure that has not been observed in the clinical trials and that can be managed in clinical practice through patient monitoring and infusion of non-transduced back-up cells, which are collected either through mPB apheresis or bone marrow harvest and kept in storage untransduced.

The important potential safety concern of engraftment failure will be further characterised after the treatment of new patients in the context of clinical trials open to recruitment (Study 205756 and Study OTL-200-07), and the treatment of patients after OTL-200 marketing authorisation (MA) approval and followed up as part of LongTERM-MLD study (Part III.2).

Important Potential Risk 4: Off label use in other MLD subgroups

OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity

- in children with the pre-symptomatic late infantile (PSLI) or pre-symptomatic early juvenile (PSEJ) forms
- in children with the early symptomatic early juvenile (ESEJ) form who still have the ability to walk independently and before the onset of cognitive decline.

While confirmation of eligibility by the treating physician at the QTC is required prior to treatment with OTL-200 to minimise the risk of off-label use, in the absence of effective treatments for MLD (Module SI), off label use in other MLD subgroups cannot be ruled out.

Risk-benefit impact:

The use of OTL-200 in MLD subgroups where disease progression is deemed unlikely to be halted or in subgroups not yet studied as part of the clinical development programme could pose serious safety risks such as treatment failure. In addition, any patient who experiences treatment failure as a result of off label use in other MLD subgroups would be burdened by the toxicities associated with mobilisation (G-CSF and plerixafor), apheresis, and the conditioning regimen (busulfan).

Off label use in other MLD subgroups is an important potential risk as it could have a negative impact on the treated patient in terms of MLD disease progression and associated morbidity, quality of life and mortality. However, as there are no available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD in the indicated population outweighs the potential risk of off label use in other MLD subgroups that can be minimised through appropriate patient selection in clinical practice.

The important potential safety concern of off label use in other MLD subgroups will be further characterised in ongoing and planned studies including Study OTL-200-07 (for late juvenile population) and LongTERM-MLD study (Part III.2).

Missing information 1: Long-term safety and efficacy data

OTL-200 is an *ex vivo* autologous $CD34^+$ haematopoietic stem cell gene therapy administered once only as a single dose for the treatment of patients with MLD. Following successful and stable engraftment, the effects of the product are expected to be persistent.

Subjects treated with OTL-200-f are followed for 8 years to assess safety and efficacy. The median duration of follow-up in the Integrated Safety Set (N=29) available at the time of this RMP was 3.160 years (range 0.64 to 7.51 years) (Table 6, Module SIII). The median duration of follow-up was similar in the LI subgroup (3.035 years) and in the EJ subgroup (3.490 years). Two LI subjects had completed more than 7 years of follow-up. To date, there is clear evidence of persistence of efficacy in the Integrated Data Set of subjects treated with OTL-200-f (n=29) (Section 5.1, Module 2.7.3), including:

- Engraftment: Durable and stable engraftment of genetically modified cells, including functional BM progenitors (CFUs), was observed in BM in both disease variants. The level of LVV^+ in BM-derived cells was maintained up to Year 6 post-GT in the LI subgroup. In the EJ subgroup, data were not available beyond Year 5; however, in the 3 EJ subjects who had data beyond Year 3, including 2 subjects with data at Year 5 the level of engraftment remained stable throughout follow-up.
- ARSA enzyme activity: Sustained increases in ARSA enzyme activity were observed in both LI and EJ subgroups, as shown by statistically significant increases from Baseline in ARSA activity in total PBMCs at 2- and 3-years post treatment.
- Motor function: In both MLD variants, subjects treated before the onset of overt symptoms showed normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction as measured by Gross Motor Function Measure (GMFM) total score and Gross Motor Function Classification in MLD (GMFC-MLD).
- Cognitive function: In both MLD variants, performance and verbal IQs remained within normal range throughout follow-up. In general, findings showed that the majority of OTL-200-f treated subjects across disease variants continued to acquire cognitive skills as expected for age.
- Overall Survival: Overall survival rate was 100% in the LI subgroup at the time of the data cut for the Integrated Efficacy Set, with a median follow-up time of 3.035 years (range 0.99 to 7.51), and 75.5% OS in the EJ subgroup at a chronological age of 11 years. The 3 deaths that occurred in the EJ subgroup and all were considered not related to OTL-200-f. Despite comparable OS rates in the treated and untreated EJ subjects with a median follow-up time of 3.49 years post-treatment (range 0.64 to 6.55), treatment with OTL-200-f resulted in a significantly longer severe motor impairment free survival. At a chronological age of 8 years, 67.7% of subjects survived and maintained locomotive and/or sitting abilities, compared with 36.0% in untreated EJ subjects.

- MRI: Prevention or stabilisation of central demyelination, as measured by MRI, was observed in most OTL-200-f treated subjects and treatment effects were consistent across variants.

In Study 205756 the median follow-up among the 6 subjects treated with OTL-200-c was 0.87 year (range: 0.0 to 1.47 years) (Module SIII).

As long-term safety and efficacy data are limited this is recognised as an area of missing information.

Risk-benefit impact:

As treatment with OTL-200 is expected to be persistent it is important to characterise the long-term safety and efficacy of OTL-200. The long-term safety and efficacy of OTL-200 will be further characterised in multiple ongoing and planned studies including Study 201222, Study 205756, Study OTL-200-07, CUP 206258, CUP 207394 , HE 205029 and LongTERM-MLD study (Part III.2).

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

Not applicable.

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

Important Identified Risks: Delayed platelet engraftment

Potential mechanisms:

During the clinical development of OTL-200, busulfan was used as a conditioning agent to promote efficient engraftment of the genetically modified autologous cells. High-dose busulfan has been used as a conditioning regimen since the late 1990s in allogeneic and autologous HSCT. For MLD and most other metabolic diseases utilising genetically modified haematopoietic stem cell therapy, a myeloablative busulfan regimen with therapeutic drug monitoring is considered standard of care to obtain optimal efficacy while minimising the risk of overexposure (Fumagalli, 2022; Oved, 2025). When used at typical myeloablative doses in both adults and children, very commonly reported adverse reactions with busulfan include neutropenia, thrombocytopenia, and pancytopenia (Busilvex SmPC).

Evidence source and strength of evidence:

This risk is based on clinical studies of OTL-200. An integrated safety analysis was completed for patients with early-onset MLD treated in the CDP (n = 39) and nominal compassionate use or commercial patients enrolled in Study OTL-200-10 (n = 10) with data cut-off dates 29 March 2024, 15 May 2023, or 31 May 2024 depending on the study. In the integrated safety analysis of patients with early-onset MLD, four patients out of 49 experienced delayed platelet engraftment (more than 60 days after OTL-200). No events of increased bleeding have been reported in any of the above patients. No other events of delayed platelet engraftment have been reported up to the DLP of 16 December 2024 for PBRER#6 from clinical study or from commercial patients.

Characterisation of the risk:

During the clinical development of OTL-200, platelet engraftment was defined as the first of 3 consecutive days with platelet values ≥ 20 x 10^9/L obtained on different days after OTL-200 infusion, with no platelet transfusion administered for 7 days immediately preceding and during the evaluation period (up to 60 days post gene therapy).

In the integrated safety population of patients with early-onset MLD (N = 49), the median number of days until platelet engraftment was 35.0 (range 11 to 109).

All patients treated with OTL-200 in the CDP received transfusion support with platelets. Most of these transfusions were considered part of the standard of care/prophylaxis for these patients, were received during the peri-transplant period and mainly within the three months post gene therapy (≤ 100 days post-GT).

Although delayed platelet engraftment was not correlated with an increased incidence of bleeding, the risk of prolonged thrombocytopenia bears a potential for development of bleeding events and consequently increased morbidity in the MLD patient population.

The important identified safety concern of delayed platelet engraftment will be further characterised with continued monitoring in study OTL-200-10 (LongTERM-MLD) (Part III.2).

Risk factors and risk groups

Delayed platelet engraftment was not correlated with an increased incidence of bleeding during the clinical development of OTL-200. AS reported at the time of the initial MAA, four patients (4/35) received platelet transfusion within the context of the treatment of unrelated adverse events. In particular 2 patients received platelet transfusion after experiencing 3 non-serious AE of ‘epistaxis’, one patient during one non serious AE of ‘febrile neutropenia’ and one patient during one SAE of ‘thrombocytopenia’. In particular, the SAE of thrombocytopaenia occurred during the 3-months post-GT phase in a complex post-transplant course, with SAEs of thrombocytopaenia, prolonged anaemia, VOD and TA-TMA captured as atypical haemolytic uremic syndrome. One patient received several platelet transfusions after gene therapy, both as standard of care and for the treatment of the SAE of prolonged thrombocytopenia which was deemed likely related to genetic predisposing factors in combination with exposure to drugs such as defibrotide (given for VOD) and busulfan. No additional reports have been received since MA approval.

Preventability

Transient thrombocytopenia is an expected outcome during treatment with OTL-200 due to the myeloablative effect of busulfan [Busilvex SmPC]. During the clinical development of OTL-200, the investigator followed internal San Raffaele Hospital processes and The European Society for Blood and Marrow Transplantation (EBMT) guidance to assess the transfusion requirements of the patients: transfusion support was mandatory for PLT count <10 × 10^9/L unless contraindicated, recommended for PLT count <20 × 10^9/L in presence of clinical signs, very young age, fever or other clinical symptoms/comorbidities. However, the threshold could sometimes be higher if there was an increased risk of bleeding, such as in case of trauma, coagulation disorder, invasive procedure, and anaesthesia. During the clinical development of OTL-200, all patients received transfusion support with platelets. This information along with recommendations for monitoring and supportive care are also provided in section 4.4 of the SmPC of Libmeldy.

Impact on the risk benefit of the product

As there are no other available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the risk of delayed platelet engraftment that has been observed in the clinical trials and that can be managed in clinical practice through patient monitoring and infusion of platelets.

Public health impact:

The potential public health impact of delayed platelet engraftment is considered to be very low given the rarity of MLD (Module SI).

Important Potential Risk 1: Malignancy due to insertional oncogenesis

Potential mechanisms:

Insertional oncogenesis is a potential safety concern with integrating viral vectors in gene-modified cell therapies (Marcucci, 2018).

Insertional oncogenesis has been seen in studies of other gene therapies but has historically been associated with the use of gammaretroviral (γRV) vectors with an intact LTR, where the mechanism of oncogenesis was directly related to the promoter-enhancer activity of the viral LTR and its ability to transactivate neighbouring growth promoting genes. Unlike γRV vectors, most self-inactivating LVVs lack strong promoter–enhancer LTR sequences and they preferentially integrate in introns, away from the transcription start sites of actively transcribed genes and are thus considered safer (Montini, 2006). The recent example of haematologic cancers associated with an LVV gene therapy product utilising a strong synthetic promoter derived from a viral LTR points to the importance of vector design and type of promoter in reducing the risk of insertional oncogenesis (Duncan, 2024; Montini, 2025).

Notably, the self-inactivating design of the LVV used for OTL-200 does not include a viral LTR promoter with enhancer activity. Instead, ARSA transgene expression is driven by the moderately active human promoter for the gene for phosphoglycerate kinase, a ubiquitous housekeeping enzyme. This design reduces the risk of transactivating neighbouring genes following vector insertion into the human genome (Kustikova, 2005; Montini, 2006, Montini, 2009; Montini, 2025).

Malignancy due to insertional oncogenesis is an important potential risk as the lentiviral vector used in the manufacturing of OTL-200 inserts one or more copies of the human ARSA cDNA into the host genome during transduction, but the potential risk that the insertion occurs close to proto-oncogenes or tumour suppressor genes leading to clonal expansion and neoplasia is considered to be low.

Evidence source and strength of evidence:

OTL-200 consists of $CD34^+$ cells transduced *ex vivo* with a LVV which integrates permanently into the host genome. The risk of insertional mutagenesis and consequent tumourigenicity has been evaluated in several *in vitro* and *in vivo* non-clinical studies.

Integration site (IS) analysis performed on genomic DNA from whole peripheral blood (PB) and BM samples harvested at different time points after therapy showed a highly polyclonal pattern of vector integration in mice with no indication of abnormal clonal expansion. Hepatocellular tumours were observed in *in vivo* studies, but they were considered related to the conditioning

regimen and genetic background of the mice. Overall, there was no evidence of preferential expansion of IS near proto-oncogenes in all analysed mice, with no increase in tumourigenesis found in a tumour prone mouse model.

Clinical trials, alongside data reported in the literature, can provide an estimate of the frequency of malignancies that are expected to occur in clinical practice.

To date, no cases of malignancy due to insertional oncogenesis have been reported. There has been no evidence of abnormal clonal proliferation as assessed by clinical and laboratory surveillance and BM examination.

Characterisation of the risk:

As OTL-200 consists of $CD34^+$ cells transduced *ex vivo* with a LVV which integrates permanently in the host genome, the risk of insertional mutagenesis and consequent tumourigenicity following administration of OTL-200 was evaluated.

The self-inactivating design of the LVV vector used for OTL-200 abolishes LTR promoter activity and transgene expression is driven by a moderately active internal human endogenous promoter, thus reducing the risk of activating neighbouring genes following insertion.

Integration site analysis, conducted in healthy donor $CD34^+$ cells transduced with ARSA LVV *in vitro* and after engraftment in immunodeficient mice, demonstrated that ARSA LVV integrates within genes like other LVVs, without any enrichment in preferential targeted genes classes found *in vivo* comparing to *in vitro* (Section 4.2, Module 2.4). ARSA LVV CISs clustered in million base pairs wide chromosomal regions of high LVV integration density and are related to the integration profile of LVVs. Similar results were obtained in ARSA LVV-transduced Lin^- HSPC transplanted in *As2*$^{-/-}$ mice. ARSA LVV showed the expected integration pattern of LVVs and polyclonal reconstitution was seen in all analysed mice, with no evidence of preferential expansion of IS near proto-oncogenes. GFP LVV, which shares the same lentiviral vector of ARSA LVV, induced replating clones in one out of eight experiments when tested in an *in vitro* immortalisation assay. However, the replating incidence was low and no sustained growth was observed. There was no increase in tumourigenesis when GFP LVV was evaluated *in vivo* in a tumour prone mouse model.

General toxicity and tumourigenicity following single IV injection of ARSA LVV-transduced Lin^- HSPC into WT and *As2*$^{-/-}$ mice were evaluated with treated animals monitored up to 12 months (Section 4.3, Module 2.4). No increased mortality, signs of toxicity or LVV-driven abnormal or malignant growth of transplanted cells or haematopoietic tumours were observed after administration of ARSA LVV transduced Lin^- HSPC, even in presence of high and stable engraftment and ARSA overexpression. Hepatocellular tumours were noted in MLD mice transplanted with ARSA transduced HSPC or non-transduced control cells (Module SII). This finding was, however, considered related to the conditioning regimen and genetic background of the mice, was not replicated in the pivotal GLP toxicity and tumourigenicity study, in which a larger cohort of animals was treated after a less aggressive conditioning regimen and monitored for a longer period of time.

To date, in the clinical development programme no cases of malignant clonal expansion or malignancy due to insertional oncogenesis have been reported after treatment with OTL-200 (Section 4.4.6, Module 2.5). Cumulatively, 82 patients have been exposed to OTL-200, and additional patients have been exposed to other GT medicinal products using similar lentiviral backbones and with use of partially reconstituted cellular promoters with no evidence to date of

insertional oncogenesis (Montini, 2025). There has been >13 years follow-up for the earliest treated patients with MLD and more than 300 patient years follow-up in patients included in the integrated analyses. In all cases, no evidence of insertional oncogenesis or clonal expansion was observed.

There was no sign of clonal dominance or clonal proliferation from insertion site analyses (Section 4.4.6 Module 2.5). The absence of clonal abnormalities and oncogenic events related to OTL-200, which utilises a human promoter, is in line with the safety profile reported in many other human stem cell gene therapy clinical trials employing lentiviral vectors (Montini, 2025). The notable exception is the gene therapy for cerebral adrenoleukodystrophy (cALD), in which haematologic cancers have been reported (Duncan, 2024). The key difference is that the cALD GT utilises a strong promoter derived from a retroviral LTR, and the transcriptional activity of that virally derived promoter appears responsible for the insertional activation of nearby oncogenes (Duncan, 2024; Montini, 2025).

Risk factors and risk groups:

Factors thought to be important in contributing to the risk of oncogenesis (EMA/CAT/190186/2012):

a) Vector design (including backbone and regulatory elements)
b) Insertion profile
c) Vector copy number (VCN)
d) Transgene product
e) Target cell population/organ
f) Risk of malignancy for the underlying disease

Preventability:

The risk of insertional oncogenesis has been minimised by the use of a human, non-viral promoter that lacks enhancer activity and has been designed and tested to minimise the potential for transactivating nearby genes. The risk can be further minimised through increasing healthcare professional and patient and parent/carer awareness and patient monitoring.

Healthcare professionals are informed that OTL-200 contains $CD34^+$ cells which have been genetically modified with a LVV. The Libmeldy SmPC advises that no cases of leukaemia or lymphoma have been reported in clinical studies and that there have been no reports of LVV-mediated insertional mutagenesis resulting in oncogenesis following treatment with OTL-200 in clinical trials. Nevertheless, there is a theoretical risk of leukaemia or lymphoma after OTL-200 treatment and in the event that leukaemia or lymphoma is detected in any patient who received OTL-200, Orchard Therapeutics should be contacted to obtain instructions on collection of blood samples for integration site analysis (ISA).

Similarly, patients and their parents/carers are advised in the Libmeldy PIL that inserting a new gene into the DNA could theoretically cause blood cancers (leukaemia and lymphoma), although no patients have developed leukaemia or lymphoma in clinical trials with OTL-200. After treatment with OTL-200 the patient will be asked to enrol in the LongTerm-MLD study (OTL-200-10) for up to 15 years after treatment to better understand the long-term effects of OTL-200 and during the long-term follow-up, the patient will be monitored for any signs of leukaemia or lymphoma (Part III.2; Annex 5).

If leukaemia/lymphoma is detected, blood samples for ISA should be collected.

Impact on the risk-benefit balance of the product:

Malignancy due to insertional oncogenesis would be serious and could potentially be life-threatening. To date, no cases of malignancy due to insertional oncogenesis have been reported with OTL-200. There was no evidence of abnormal clonal proliferation as assessed by clinical and laboratory surveillance and bone marrow examination.

The benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the potential risk of malignancy due to insertional oncogenesis that can be managed in clinical practice through patient monitoring and standard of care treatment if needed.

Public health impact:

Taking into account the rarity of MLD (Module SI), the potential public health impact is considered to be low.

Important Potential Risk 2: Anti-ARSA antibodies

Potential mechanisms:

Not yet established.

Evidence source and strength of evidence:

Cumulatively as of the DLP, 12 patients exposed to OTL-200 (N=82) have developed AAA. In 10 of 12 patients with AAA, there is no evidence of clinical significance.

Two test methods have been used to detect AAA in patients treated with OTL 200. The anti-ARSA immunoglobulin G (IgG) antibody enzyme-linked immunosorbent assay (ELISA), hereafter referred to as the ELISA assay, was used in Study 201222 and the EAP (Compassionate Use Programme 207394 [C02], Hospital Exemption 205029, and Compassionate Use Programme 206258) to screen for the presence of AAA in samples from patients before and after OTL-200 administration. After the first patient tested positive in the OTL-200 CDP in Hospital Exemption 205029, the clinical study Sponsor developed and validated a new AAA electrochemiluminescence homogeneous bridging immunoassay in accordance with their own procedures and current US FDA and EU EMA guidance (FDA, 2019; EMA, 2017a), hereafter referred to as the bridging assay. The bridging assay was used for the re-evaluation of AAA in samples from Hospital Exemption 205029 and Compassionate Use Programme 206258 and for testing samples in Study 205756 until 2019. When Orchard Therapeutics acquired the OTL-200 asset, the bridging assay developed by the previous sponsor for AAA analysis was transferred to an independent laboratory in USA. From the point of this assay validation, the Sponsor has required the CDP samples to be analysed using the bridging assay. However, the treating physician may send patient samples for testing using the ELISA assay due to convenience

Although both the ELISA and bridging assays were validated, Annex 1 of the EMA ‘Guidance on Immunogenicity assessment of therapeutic proteins’ (EMA, 2017a) points out that direct binding ELISA assays may be associated with a very high incidence of false positivity. Results obtained with the bridging assay are considered more accurate. Patients are included in the count of patients with positive AAA results if the bridging assay result was positive or if ELISA assay results were positive and bridging assay results were not available.

Characterisation of the risk:

All patients treated with OTL-200 in the CDP are monitored for potential immunogenic responses per the EMA/FDA guidelines for long-term follow up of patients post-gene therapy (FDA, 2006; EMA, 2008; FDA, 2014), with regular blood testing for immune response. This included evaluation of AAA across the MLD programme at various post-treatment timepoints.

The Libmeldy SmPC recommends monitoring for AAA in patients prior to treatment, between 1 and 2 months after gene therapy, and then at 6 months, 1 year, 3 years, 5 years, 7 years, 9 years, 12 years, 15 years post-treatment. In case of disease onset or significant disease progression, additional AAA monitoring is recommended.

Cumulatively, out of 82 patients exposed to OTL-200, 12 patients have developed AAA. Of these 12 patients, 8 patients had positive bridging assay results. The AAA were low titre in all 8 patients and resolved in 7 patients, either after treatment with rituximab or spontaneously.

Four patients had positive ELISA assay results without bridging assay results. AAA were low titre in all 4 patients and resolved spontaneously in 1 patient.

For patients with AAA in the clinical databases (n = 10), the AE database was searched using narrow standard MedDRA queries (SMQs) to evaluate any AEs related to immune response. The following SMQs were run: Anaphylactic reaction SMQ, Angioedema SMQ, Hypersensitivity SMQ, Severe cutaneous adverse reactions SMQ, and Vasculitis SMQ. There were no AEs within these SMQs causally associated with the presence of AAA in these patients. Many of the AEs captured by this SMQ output that occurred in patients with AAA also occurred in patients without AAA.

A summary of the patients who tested positive for AAA is presented in Section 4.8 of the Libmeldy SmPC. Section 4.4 of the Libmeldy SmPC specifies that regular monitoring of AAAs is recommended, and additional testing is suggested in case of disease onset or significant disease progression.

The important potential safety concern of AAA will be further characterised in multiple ongoing and planned studies including Study 201222, Study 205756, Study OTL-200-07, CUP 206258, CUP 207394 , HE 205029, and OTL-200-10 (LongTERM-MLD study) (Part III.2).

Risk factors and risk groups:

Not yet established.

Preventability:

Not yet established.

Impact on the risk-benefit balance of the product:

Considering that emergence of AAA can be managed in clinical practice through patient monitoring and the absence of available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the potential and as yet undefined risks posed by the emergence of AAA.

Public health impact:

The potential public health impact of anti-ARSA antibodies is considered to be very low given the rarity of MLD (Module SI).

Important Potential Risk 3: Engraftment failure

Potential mechanisms:

The OTL-200 procedure involves $CD34^+$ haematopoietic stem and progenitor cells enrichment from patient mPB and transduction with an ARSA LVV, which inserts 1 or more copies of the human ARSA cDNA into the cell's genome so that modified cells become capable of expressing a functional protein. When re-administered to the patient following conditioning with busulfan, the genetically-modified cells engraft and repopulate the haematopoietic compartment. A fraction of the infused cells and/or their myeloid progeny can migrate to the brain and contribute to CNS-resident microglia and perivascular CNS macrophage populations after the transplant. These modified cells can produce and secrete the ARSA protein, which can be taken up by surrounding cells (a process known as cross-correction) and used to break down harmful sulfatides. Engraftment of the transduced cells is essential for the success of treatment.

Busulfan was used as a conditioning agent in all patients treated with OTL-200 to date. For MLD and most other metabolic diseases utilising genetically modified haematopoietic stem cell therapy, a myeloablative busulfan regimen with therapeutic drug monitoring is considered standard of care to obtain optimal efficacy while minimising the risk of overexposure (Fumagalli, 2022; Oved, 2025).

Evidence source and strength of evidence:

Busulfan conditioning is recognised to cause profound myelosuppression (Busulfex US Prescribing Information, 2015; Busilvex SmPC, 2023). Although no patients treated with OTL 200 have experienced engraftment failure (defined as failure to reach an ANC >500 neutrophils/µL associated with no evidence of BM recovery [i.e., hypocellular marrow] by Day +60), neutrophil engraftment failure is a potential risk after treatment with OTL-200 based on the known effects of busulfan.

Characterisation of the risk:

In the integrated safety analysis (N = 49), no patients experienced neutrophil engraftment

failure (failure to reach an ANC >500 neutrophils/µL associated with no evidence of BM recovery [i.e. hypocellular marrow] by Day +60. There have been no reports in any patient exposed to OTL-200 (N = 82) of failure to reach an ANC > 500 neutrophils/µL associated with no evidence of BM recovery (i.e., hypocellular marrow) by Day +60.

Risk factors and risk groups:

To date, there have been no reported cases of neutrophil engraftment failure, failure to reach an ANC >500 neutrophils/µL associated with no evidence of BM recovery [i.e., hypocellular marrow] by Day +60); therefore, there are no identified risk factors or risk groups.

Preventability:

OTL-200 specifications for % $CD34^+$ and cell viability are set based upon supporting quality and non-clinical data to ensure that viable $CD34^+$ cells will meet the intended dose. In the clinical trials engraftment failure is defined as failure to reach an ANC >500 neutrophils/µL associated with no evidence of BM recovery (i.e. hypocellular marrow) by day +60.

The Libmeldy SmPC advises that OTL-200 must be administered in an Orchard QTC with experience in HSCT. Healthcare professionals are advised that in clinical trials, no patients failed to engraft bone marrow, as measured by neutrophil engraftment (N = 49). Patients should be

monitored for signs and symptoms of cytopenia for at least 6 weeks after infusion. Red blood cells should be monitored according to medical judgment until engraftment of these cells and recovery are achieved. Supportive transfusion of red cells should be given according to medical judgement and institutional practice. If cytopenia persists beyond six to seven weeks, despite the use of granulocyte mobilising agents, the non-transduced back-up cells should be infused. If cytopenia persists despite infusion of non-transduced back-up stem cells, alternative treatments should be considered.

The Libmeldy PIL informs the patient / carer that if the modified stem cells do not take hold (engraft) in the patient's body, the doctor may give them an infusion of their original stem cells that were collected and stored as a backup.

Impact on the risk-benefit balance of the product:

Engraftment failure would have a negative impact on the patient. However, as there are no available effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD outweighs the potential risk of engraftment failure that has not been observed in the OTL-200 integrated analysis (N = 49) or patients treated with OTL-200 to date (N = 82) and that can be managed in clinical practice through patient monitoring and infusion of non-transduced back-up cells.

Public health impact:

The potential public health impact of engraftment failure is considered to be very low given the rarity of MLD (Module SI).

Important Potential Risk 4: Off label use in other MLD subgroups

Potential mechanisms:

Not applicable.

Evidence source and strength of evidence:

OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity

- in children with the pre-symptomatic late infantile (PSLI) or pre-symptomatic early juvenile (PSEJ) forms, i.e. without clinical manifestations of the disease
- in children with the early symptomatic early juvenile (ESEJ) form, i.e. with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline (see section 5.1).

Off-label use of Libmeldy may occur in two different situations/types of patients: 1) either in patients with early-onset MLD who are not eligible for treatment considering the currently approved indication, possibly leading to treatment failure; or 2) in patients with late-onset MLD, i.e. Late Juvenile or Adult patients, for whom the efficacy and safety of Libmeldy has not been demonstrated.

Characterisation of the risk:

Early-onset MLD

Patients with early-onset MLD treated off label when they have entered the rapidly progressive phase of the disease may not benefit from treatment and would be burdened by the toxicities and adverse events associated with mobilisation (G-CSF and plerixafor), apheresis, and the conditioning regimen (busulfan).

At the time of the initial MAA, treatment failure was defined as MLD disease progression leading to death or disease progression in both gross motor function and cognitive development that is similar to untreated patients. A sensitivity analysis of treatment failures was performed with the objective of exploring factors (either related to critical quality attributes of the medicinal product administered, clinical characteristics at baseline or levels of engraftment and PD effects post-gene therapy among others) which could have influenced the treatment failure (Section 3.3.4, Module 2.7.3).

During the clinical development, treatment failure was seen only in four subjects who would not be eligible for treatment according to the current indication. The subgroup analyses performed for the initial MAA compared the group of patients identified as treatment failure (n=4) with non-treatment failures (n=25), all of which were part of the Integrated Efficacy Set (n=29). The analysis showed no obvious quality attributes related to the medicinal product which might have influenced the post-treatment clinical outcomes.

Levels of engraftment and PD effects post-gene therapy in the treatment failure group were within the range observed in the non-treatment failure group. No differences were observed between treatment failures and non-treatment failures with respect to percentage LVV^+ cells, VCN in BM, VCN in PBMCs, or ARSA activity in peripheral blood and cerebrospinal fluid at different timepoints post-treatment.

The patient level analyses showed low levels of engraftment in 1 treatment failure patient although only data at Month 3 post-treatment were available and similar levels of engraftment in BM have been observed in non-treatment failure patients.

All patients classified as treatment failures were treated at symptomatic stages of the disease when disease progression was entering the rapid progressive phase in two patients or entered the rapid progressive phase soon after treatment in two other patients.

Based on an analysis of the baseline characteristics of pre-symptomatic LI and EJ patients treated during the clinical development programme, the definition of pre-symptomatic status was further refined to maximise the treatment benefit, and this definition was provided in the Libmeldy SmPC:

> Taking the results of this analysis into account, treatment with Libmeldy of a pre-symptomatic patient should be considered:
>
> - For a patient with the LI form of the disease, in the absence of a delay in achievement of independent standing, or a delay in achievement of independent walking, associated with abnormal signs at neurological evaluation.
>
> - For a patient with the EJ form of the disease, in the absence of neurological signs or symptoms of the disease resulting in cognitive, motor, or behavioural functional impairment or regression (substantiated by neurological examination, gross motor function evaluation and/or age appropriate neuropsychological tests).

• Early symptomatic: at time of inclusion into the clinical studies, early symptomatic EJ patients met the following 2 criteria: intelligence quotient (IQ) ≥ 70 and the ability to walk independently for ≥ 10 steps.

Based on this analysis of baseline predictors of treatment response, the four patients in the clinical development programme classified as treatment failures would not now be considered appropriate for treatment with OTL-200 according to the indication, warning and precautions for the use of Libmeldy in the SmPC and maximises the likelihood of a positive treatment response in the target MLD population for which OTL-200 is indicated.

Late-onset MLD

A second category of patients who might potentially be treated off label are those with late onset MLD, for whom efficacy has not been demonstrated. A clinical study mandated by the paediatric investigation plan (PIP) (OTL-200-07) is being conducted by Orchard in order to generate pharmacodynamic/efficacy and safety data of Libmeldy in the LJ population. That study is fully enrolled (6 patients are included) and data collection is ongoing. No new safety signals have been detected in patients with LJ MLD treated with OTL-200.

The risk of treating patients with Adult MLD has not been characterised yet as no patients with that subtype have been exposed to treatment with OTL-200.

The important potential safety concern of off label use in other MLD subgroups will be further characterised in ongoing and planned studies including Study OTL-200-07 (for late juvenile population) and OTL-200-10 (LongTERM-MLD study that includes collection of data of any patients treated off-label with OTL-200, if any) (Part III.2).

Risk factors and risk groups:

Patients with MLD who are outside of the indication of OTL-200.

Preventability:

The risk of off label use in other MLD subgroups can be minimised through patient selection and eligibility check / confirmation that OTL-200 remains indicated prior to treatment. This will be conveyed by the training of the treating physicians at the QTC on the SmPC, clinical data and the educational materials (Module V.2).

Impact on the risk-benefit balance of the product:

Off label use in other MLD subgroups is an important potential risk that has not yet been fully established. However, as there are no other approved effective treatments for MLD (Module SI), the benefit of OTL-200 as a treatment for the progressive, life-threatening, demyelinating and neurodegenerative disease MLD in the indicated population outweighs the potential risk of treatment failure that can be minimised through patient selection in clinical practice.

Public health impact:

The potential public health impact of off label use in other MLD subgroups is considered to be very low given the rarity of MLD (Module SI), particularly for MLD subgroups that are outside of the indication of OTL-200.

SVII.3.2. Presentation of the missing information

Missing information 1: Long-term safety and efficacy data

Evidence source:

OTL-200 is an *ex vivo* autologous $CD34^+$ haematopoietic stem cell gene therapy administered once only as a single dose for the treatment of patients with MLD. Following successful and stable engraftment in the patient, the effects of the product are expected to be persistent.

Integrated efficacy and safety analyses were performed on data from 49 patients treated with OTL-200, including a median follow-up of 5.6 years (range 0.5 to 13.2 years). Results continue to demonstrate the efficacy and safety of OTL-200. Patients will continue to be followed in the OTL 200 10 (LongTERM-MLD) study for 15 years post-treatment per regulatory guidelines (EMA, 2008; EMA, 2009; FDA, 2020).

Long-term safety and efficacy data for OTL-200 remain limited and continue to be considered an area of missing information.

Population in need of further characterisation:

The long-term safety and efficacy of OTL-200 are further characterised through long-term follow-up of patients with early onset MLD (LI MLD or EJ MLD) in ongoing studies 201222 and 205756 (Part III.2). The ongoing EAPs, CUP 206258 (MLD CUP), CUP 207394 and HE 205029 (MLD-HE-GT), also provide long-term follow-up data (Part III.2). Furthermore, long-term follow-up of patients with LJ MLD is expected to provide further long-term safety and efficacy data in ongoing Study OTL-200-07 (Part III.2).

Patients will continue to be followed in the OTL-200-10 (LongTERM-MLD) study for 15 years post-treatment to monitor the long-term safety and effectiveness of OTL-200 (Part III.2, Annex 5). As of 16 December 2024, 14 patients have been enrolled and had data entered in Study OTL-200-10 (LongTERM-MLD), including 3 from CDP studies, 4 treated under nominal compassionate use, and 7 patients treated in the commercial setting.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Delayed platelet engraftment
Important potential risks	Malignancy due to insertional oncogenesis Anti-ARSA antibodies Engraftment failure Off label use in other MLD subgroups
Missing information	Long-term safety and efficacy data

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

None

Other forms of routine pharmacovigilance activities:

None

III.2 Additional pharmacovigilance activities

Follow-up phase of Study 201222 summary

Study short name and title: (Study 201222) A Phase I/II clinical trial of haematopoietic stem cell gene therapy for the treatment of Metachromatic Leukodystrophy

Rationale and study objectives: The objectives of the study are to evaluate the safety and efficacy of the fresh formulation of OTL-200 in 20 early-onset MLD patients followed up for 8 years after treatment with OTL-200.

Study design: Study 201222 is an ongoing open-label, single arm, non-randomised, prospective, comparative (non-concurrent control), single-centre study in children with late infantile (LI) or early juvenile (EJ) MLD as assessed by ARSA enzymatic activity and genetic analysis.

Following treatment patients initially undergo regular follow-up for a period of 3 years after gene therapy to assess the efficacy and safety of the treatment. A formal interim analysis was performed when a minimum of eight subjects completed at least 2 years of follow-up, to assess the efficacy and safety of the investigational product. A dedicated interim study report was generated based on all the data available at the interim. Further ad-hoc interim analyses were performed as outlined below. This part of the study relates to the follow-up phase of Study 201222.

Study population: Twenty subjects were planned for enrolment. Twenty-two subjects were screened and enrolled, two of these 22 subjects were withdrawn from the trial prior to treatment. The study treated 20 early-onset MLD patients with either pre-symptomatic LI MLD (9 subjects) or pre- or early-symptomatic EJ MLD (11 subjects) at the time of enrolment. Treated patients are followed for at least 8 years to assess safety and efficacy. The study is fully enrolled.

Milestones:

First patient first visit (FPFV; date of screening): 09-Apr-2010

Interim reports: 06-Dec-2017 (Interim Report No.1)
19-Feb-2019 (Interim Report No. 2)
28-Mar-2019 (Interim Report No. 2.1)
30-Sep-2019 (Interim Report No. 2.2)
Q1 2025 (Interim Report No. 3.0)

Final study report: Q1 2026

Study 205756 summary

Study short name and title: (Study 205756) A single arm, open label, clinical study of cryopreserved autologous $CD34^+$ cells transduced with lentiviral vector containing human ARSA cDNA OTL-200, for the treatment of early onset Metachromatic Leukodystrophy (MLD)

Rationale and study objectives: The objective of the study is to evaluate the safety and efficacy of the cryopreserved formulation of OTL-200 (OTL-200-c) in up to 10 pre-symptomatic, early-onset MLD patients.

Study design: Open-label, non-randomised, single-arm clinical trial evaluating the safety and efficacy of the cryopreserved formulation of OTL-200.

Study population: Ten paediatric subjects with pre-symptomatic, early onset MLD (i.e. either LI, EJ or an intermediate variant between LI/EJ) with a predicted age of disease onset from birth to before the age of 7 years with parental/guardian informed consent.

The study has enrolled and treated 10 patients as planned.

Milestones:

FPFV (date of screening): 25-Jan-2018

Interim reports: 14-Mar-2019 (data cut-off)

Final study report: Q4 2029

Study OTL-200-07 summary

Study short name and title: (Study OTL-200-07) An open label, single arm, non-randomised trial to evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) Metachromatic Leukodystrophy (MLD)

Rationale and study objectives: The objective of the study is to evaluate the safety and efficacy of a single infusion of OTL-200 in patients with late juvenile (LJ) MLD.

Study design: Open label, single arm, single centre Phase 3b study (with the option to open additional centres if/when identified) of a single infusion of a cryopreserved formulation of OTL-200 in subjects with pre-symptomatic and early symptomatic LJ MLD.

Study population: This study is fully enrolled and has treated 6 subjects with LJ MLD (4 pre-symptomatic LJ; 2 early symptomatic LJ). The sample size has been determined based on feasibility of enrolment. It is not based on statistical considerations.

Milestones:

FPFV: 17-Jan-2022

Interim report: 2030

Final study report: Jul 2035

CUP 206258 and HE 205029 summary

Rationale and objectives: In the absence of a suitable clinical trial that was open for enrolment, the objective of the CUP 206258 and HE 205029 was to provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available.

Protocol design: No significant differences existed between the designs of the HE and CUP protocols, and there were no significant differences in any of the programmes compared with the design of Study 201222.

Both protocols required a total of 8 years follow-up after gene therapy to evaluate safety and efficacy. After completion of the initial 3 years or at the time the product is approved for use, patients may be enrolled in a follow-up study or registry, as permitted by local regulations, and followed for at least 5 additional years.

An interim CSR presents the results of all 8 patients treated under both protocols up to the data cut-off date of 05 December 2018. At the time of data cut-off, all patients had at least 1 year of follow-up. Five patients had <2 years total follow-up and 3 patients had >2 years of follow-up.

Study population: Presymptomatic subjects with early onset MLD. The HE protocols allowed inclusion of patients with the late infantile (LI) variant of MLD only. The CUP protocol initially included patients with LI MLD only (v1.0), which was expanded to include MLD patients with LI, EJ, or an intermediate variant between LI/EJ in v2.0.

CUP 206258 summary

Programme short name and title: Compassionate use programme for haematopoietic stem cell gene therapy OTL-200 in pre-symptomatic early onset Metachromatic Leukodystrophy patients

Milestones:

FPFV: 20-Jan-2017

Interim report: 05-Dec-2018 (data cut-off)

Final study report: Q4 2026

HE 205029 summary

Study short name and title: Haematopoietic stem cell gene therapy for pre-symptomatic Late Infantile Metachromatic Leukodystrophy

Milestones:

FPFV: 29-Dec-2015

Interim report: 05-Dec-2018 (data cut-off)

Final study report: Q4 2026

CUP 207394 Summary

Study short name and title: Gene therapy protocol using autologous haematopoietic stem cells for a patient with metachromatic leukodystrophy (MLD)

Rationale and study objectives: The objective of this compassionate use treatment programme was to provide a mechanism to supply OTL-200 on a compassionate use basis to a patient with early symptomatic EJ MLD and who could not participate to Study 201222 as enrolment was closed at that time. Additionally, it was noted that this patient was symptomatic for 8 months at the time of referral, which exceeded the Study 201222 protocol inclusion requirement for EJ patients to be ≤6 months from onset of symptoms.

Protocol design: This compassionate use treatment programme enrolled a patient who had early symptomatic EJ MLD. No formal inclusion or exclusion criteria were established for this

compassionate use treatment programme; however, the patient met all the other eligibility criteria defined for Study 201222 (except for the inclusion requirement stated above).

Pre- and post-treatment assessments and methods were essentially the same as those conducted in the pivotal study (Study 201222).

Follow-up assessments occurred every 7 days after infusion up to Day 49 (i.e., Days 7, 14, 21, 28, 35, 42, and 49 post-infusion), at Day 60, in 3-month intervals up to 1 year (i.e., Months 3, 6, and 12), and then in 6-month intervals through 8 years post-gene therapy. Following completion of the programme, the patient will be contacted annually to collect information on possible AEs, treatment efficacy data, and their health status.

Study population: A patient with early symptomatic EJ MLD.

Milestones:

FPFV: 23-Apr-2013

Interim report No. 1: 05-Jan-2018 (data cut-off)

Interim Report No.2: Q1 2025

Final study report: Q1 2026

LongTERM-MLD study (OTL-200-10) summary

Study short name and title: Long-term, Efficacy and Safety follow-up of MLD patients treated with ex vivo Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced with ARSA Lentiviral Vector (Libmeldy)

Rationale and study objectives: The aim of this post-marketing long term follow up study is to ensure that efficacy and safety of patients treated with ex vivo Gene Therapy Using Autologous Haematopoietic Stem Cells Transduced with ARSA Lentiviral Vector (Libmeldy) in the Clinical Development Programme (CDP) and in post-authorisation setting are assessed for up to 15 years following treatment in line with regulatory requirements (EMA 2008; EMA, 2009; FDA 2020).

In addition, this study will aim to gather further data in Early Symptomatic Early Juvenile MLD patients. It is anticipated that data from 10 patients will adequately supplement the data previously gathered in this population during the clinical development programme.

Study design: The LongTERM-MLD Study is designed to collect long-term real-world safety and efficacy data from patients treated with OTL-200 in the CDP and in post-authorisation setting, as well as to gather further data in in Early Symptomatic Early Juvenile MLD patients.

As part of the LongTERM-MLD Study, participants will be seen at least annually by a healthcare professional (HCP) at the QTC or by their local HCP.

OTL will provide regular progress reports of the LongTERM-MLD study in the scheduled Periodic Safety Update Report (PSUR) / Periodic Benefit-Risk Evaluation Report (PBRER), as well as scheduled interim analyses

Study population:

- Group 1:

  Patients with MLD treated with OTL-200 as part of the OTL-200CPD.
- Group 2: Patients with MLD treated with OTL-200 outside of the OTL-200 CDP

MLD patients treated with Libmeldy outside of the OTL-200 CDP, i.e., patients treated with the cryopreserved formulation from 17 Jun 2020 onwards in the framework of the Ospedale San Raphael (OSR) nominal compassionate use prior to commercialization, or in the commercial setting. Group 2 patients can be offered the opportunity to enrol in the LongTERM-MLD study prior to or after receiving treatment.

Group 2 includes the cohorts below:

- Group 2a: Patients with ESEJ MLD treated in the commercial setting or under normal compassionate use
- Group 2b: Patients with early onset MLD other than ESEJ (i.e., PSLI or PSEJ treated in the commercial setting or under nominal compassionate use.
- Group 2c: Patients with MLD who received the product off-label.

Milestones:

FPFV: 23-Dec-2022

Interim study reports: #1 Dec 2025

#2 Q1 2034

#3 Q1 2039

#4 Q1 2044

Final study report: Q1 2046

In addition, safety analyses will be provided with every PSUR between the first and second interim reports (Until Q1 2034).

III.3 Summary Table of additional Pharmacovigilance activities

Table 15: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
LongTERM-MLD study (OTL-200-10): Long-term, Efficacy and Safety follow-up of MLD patients treated with ex vivo Gene Therapy Using Autologous Haematopoietic Stem Cells	To continue to monitor long-term safety and efficacy outcomes data from patients treated with Libmeldy for up to 15 years post treatment	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure	Information on the progress in the identification of a suitable registry FPFV: Interim reports: Interim report #1 Interim report #2 Interim report #3 Interim report #4	With every PSUR 23-Dec-2022 Dec 2025 Q1 2034 Q1 2039 Q1 2044

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Transduced with ARSA Lentiviral Vector (Libmeldy) Ongoing		• Off label use in other MLD subgroups • Long-term safety and efficacy data	Final study report In addition, safety analyses will be provided with every PSUR between the first and second interim reports.	Q1 2046 Until Q1 2034
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study 201222: A Phase I/II clinical trial of haematopoietic stem cell gene therapy for the treatment of Metachromatic Leukodystrophy Ongoing	To evaluate the safety and efficacy of the fresh formulation of OTL-200 in 20 early-onset MLD patients followed up for 8 years after treatment with OTL-200	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	First patient first visit (FPFV): Interim reports: No.1: No. 2: No. 2.1: No. 2.2: No. 3: Final study report:	09-Apr-2010 06-Dec-2017 19-Feb-2019 28-Mar-2019 30-Sep-2019 Q1 2025 Q1 2026
Study 205756: A Phase II, single arm, open label, clinical study of cryopreserved autologous $CD34^+$ cells transduced with lentiviral vector containing human ARSA cDNA OTL-200, for the treatment of early onset Metachromatic Leukodystrophy (MLD) Ongoing	To evaluate the safety and efficacy of the cryopreserved formulation of OTL-200 (OTL-200-c) in up to 10 pre-symptomatic, early-onset MLD patients followed up for 8 years after treatment with OTL-200-c	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final study report:	25-Jan-2018 14-Mar-2019 Q4 2029
			FPFV:	17-Jan 2022

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study OTL-200-07: An open label, non-randomised trial to evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) Metachromatic Leukodystrophy (MLD) Ongoing	To evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) Metachromatic Leukodystrophy (MLD)	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	Interim report: Final study report:	2030 Jul 2035
CUP 206258: Compassionate use programme for haematopoietic stem cell gene therapy OTL-200 in pre-symptomatic early onset Metachromatic Leukodystrophy patients Ongoing	To provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final study report:	20-Jan-2017 05-Dec-2018 (data cut-off) Q4 2026
CUP 207394 Gene therapy protocol using autologous haematopoietic stem cells for a patient with metachromatic leukodystrophy (MLD) Ongoing	To provide a mechanism to supply OTL-200 on a compassionate use basis to a patient with early symptomatic EJ MLD	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim reports: No. 1: No. 2: Final report:	23-Apr-2013 05-Jan-2018 (data cut-off) Q1 2025 Q1 2026

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
HE 205029: Haematopoietic stem cell gene therapy for pre-symptomatic Late Infantile Metachromatic Leukodystrophy Ongoing	To provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final study report:	29-Dec-2015 05-Dec-2018 (data cut-off) Q4 2026

Source: Annex 3, Annex 5
Abbreviations: ARSA = arylsulfatase A; cDNA = complementary deoxyribonucleic acid; CUP = Compassionate Use Program; EJ = early juvenile; FPFV = first patient first visit; HE = Hospital Exemption; LJ = late juvenile; MLD = metachromatic leukodystrophy; OTL200-c = cryopreserved formulation of OTL-200; OTL-200

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 16: Planned and Ongoing Post-Authorisation Efficacy Studies That Are Conditions of the Marketing Authorisation or That Are Specific Obligations

Study status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
LongTERM-MLD study (OTL-200-10): Long-term, Efficacy and Safety follow-up of MLD patients treated with ex vivo Gene Therapy Using Autologous Haematopoietic Stem Cells Transduced with ARSA Lentiviral Vector (Libmeldy) Ongoing	**For all patients:** To evaluate durability of clinical efficacy following treatment with Libmeldy **For Early Symptomatic EJ patients:** To evaluate the clinical efficacy of Libmeldy at 36 months post-treatment compared to matched natural history data	Long-term safety and efficacy data	Information on the progress in the identification of a suitable registry FPFV: Interim reports: Interim report #1 Interim report #2 Interim report #3 Interim report #4 Final study report In addition, safety analyses will be provided with every PSUR between the first and second interim reports	With every PSUR 23-Dec-2022 Dec 2025 Q1 2034 Q1 2039 Q2 2044 Q1 2046 Until Q1 2034
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 17: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Delayed platelet engraftment (Important identified risk)	Routine risk minimisation communication • *Information that there have been cases of delayed platelet engraftment in clinical studies in SmPC section 4.4* • *Information that there have been cases of delayed platelet engraftment in clinical studies in PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Information in section 4.4 of the SmPC to monitor platelets counts according to medical judgment until full engraftment* Additional risk minimisation measures • *Educational materials for healthcare professionals* • *Educational materials for patients* Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*
Malignancy due to insertional oncogenesis (Important potential risk)	Routine risk communication: • *Information that there have been no cases of leukaemia or lymphoma in clinical studies in SmPC section 4.4* • *Information that no patients have developed leukaemia or lymphoma in clinical trials with OTL-200 in PL section 2* • *Information that oncogenesis (tumorigenicity) studies performed in the mouse model of MLD found no abnormal or malignant growth of transplanted cells or haematopoietic tumours related to the integration of ARSA LVV in SmPC section 5.3* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Warning that OTL-200 may theoretically cause leukaemia or lymphoma with instructions for blood sample collection if malignancy occurs in SmPC section 4.4* • *Warning that the patient will be asked to enrol in an observational long-term follow up study for up to 15 years and will be monitored for any signs of blood cancer because of the theoretical cancer risk in PL section 2*

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*
Anti-ARSA antibodies (Important potential risk)	Routine risk communication: • *Information that there have been cases of anti-ARSA antibodies reported during the clinical development in SmPC section 4.4.* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Warning that monitoring for the presence of AAA is recommended prior to treatment and regularly during post-treatment follow-up in SmPC section 4.4.* • *Guidance on short treatment with rituximab in SmPC section 4.4.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*
Engraftment failure (Important potential risk)	Routine risk communication: • *Information that in clinical trials durable and stable peripheral engraftment of genetically modified cells was observed from 1-month in all evaluable patients and that no patients failed to engraft bone marrow, as measured by neutrophil count in peripheral blood, in SmPC sections 4.4 and 5.1* • *Information that following successful and stable engraftment in the patient, the effects of OTL-200 are expected to be persistent in SmPC section 5.1* • *Information in PL section 3 that the autologous $CD34^+$ cells are isolated from mobilised peripheral blood (mPB). This is achieved by apheresis procedure(s) following peripheral blood mobilisation. A back-up collection of HSPC may be harvested either through mPB apheresis or from bone marrow harvest. to be given to the patient as replacement stem cells if OTL-200 does not work.* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Instructions that a back-up collection of $CD34^+$ stem cells harvested either through mPB apheresis or bone marrow harvest and containing at least 2 x 10^6 $CD34^+$ cells/kg is required for use as rescue treatment should there be failure of primary engraftment, or prolonged bone marrow aplasia after treatment in SmPC section 4.2* • *Guidance that myeloablative conditioning is required before infusion of OTL-200 to promote efficient engraftment of the genetically modified autologous $CD34^+$ cells in SmPC section 4.2* • *Warning that in case of cytopenia symptoms, red blood cells and platelet counts should be monitored according to medical judgment until engraftment of these cells and recovery are achieved in SmPC section 4.4*

Safety concern	Routine risk minimisation activities
	• *Guidance to infuse the non-transduced back-up cells if cytopenia persists beyond six to seven weeks, despite the use of granulocyte mobilising agents, and then to consider alternative treatments in SmPC section 4.4.* • *Guidance that in case of engraftment failure, the non-transduced back-up cells should be infused according to local standards in SmPC section 4.4* • *Guidance that if the modified stem cells do not take hold (engraft) in the patient's body, the doctor may give an infusion of the original stem cells that were collected and stored as a backup in PL section 2* Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*
Off label use in other MLD subgroups (Important potential risk)	Routine risk communication: • *Therapeutic indication in SmPC section 4.1 and PL section 1* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Warning that eligibility to treatment should be assessed by the treating physician in SmPC section 4.4* Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*
Long-term safety and efficacy data (Missing information)	Routine risk communication: • *Information that 45 patients with PSLI, PSEJ, and ESEJ MLD were included in the integrated efficacy set. These results were generated in PSLI, PSEJ, and ESEJ patients in one registrational open-label, single-arm phase I/II study (Study 201222), one supportive open-label, single-arm phase I/II study (Study 205756), 3 expanded access programmes, and one long-term follow-up study with a median duration of post-treatment follow-up of 6.1 years in PSLI patients (range 2.0 to 13.2 years), 3.3 years in PSEJ patients (range 0.6 to 11 years),and 9.2 years in ESEJ patients (range: 0.5 to 10.9 years) in SmPC section 5.1.* • Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Guidance that the patients are expected to enrol and be followed in a long-term follow-up study in order to better understand the long-term safety and efficacy of OTL-200 in SmPC section 4.2* • *Guidance that patients will be asked to enrol in an observational, long-term follow-up study for up to 15 years to better understand the long-term effects of OTL-200 in PL section 2* Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*

V.2. Additional Risk Minimisation Measures

Educational materials

Educational materials are provided to healthcare professionals, the patients and/or their parents/carers.

Additional risk minimisation 1: Educational materials for healthcare professionals

Orchard provides educational materials (Guide for healthcare professionals; Guide for handling and method of administration) to healthcare professionals involved in OTL-200 treatment of a patient with MLD (Annex 6). Moreover, section 4.2 of the SmPC states that "Libmeldy must be administered in a qualified treatment centre with experience in Haematopoietic Stem Cell Transplantation (HSCT)". Therefore, the educational material will target professionals who are already highly specialised in the management, treatment and care of patients undergoing HSCT.

Objectives: To facilitate informed decision-making by healthcare professionals and patients, parents/carers based on the known benefits and risks of OTL-200 and to minimise the risks to patients.

To ensure that OTL-200, an autologous $CD34^+$ haematopoietic stem and progenitor cell gene therapy, is administered only to the donor patient from whom the original stem cells originated with detailed guidance on handling and the method of administration for OTL-200.

To highlight the important risks of OTL-200 to healthcare professionals with guidance on how to minimise the risks, including the identified risk of delayed platelet engraftment, the potential risk of leukaemia/lymphoma and the need for monitoring treated patients for signs and symptoms of oncogenic transformation, leukaemia or lymphoma, the potential risks of engraftment failure, and anti-ARSA antibodies and the need to monitor patients, and the important considerations to discuss with patients and/or carers about OTL-200.

To make physicians aware of the importance of monitoring and long-term follow-up, and to inform them about the LongTERM-MLD study (OTL-200-10) for further characterisation of the safety concerns including long term safety and efficacy.

Rationale for the additional risk minimisation activity: These materials supplement information in the SmPC by describing the safety concerns and actions to take to minimise the important risks associated with OTL-200 and to highlight the importance of monitoring and long term follow-up and inform them about the LongTERM-MLD study which will further characterise the important risks and long term safety.

Target audience and planned distribution path: Healthcare professionals (HCPs) involved in OTL-200 treatment of a patient with MLD working at an QTC. HCPs receive training on the HCP educational materials as part of the centre qualification process.

Plans to evaluate the effectiveness of the interventions and criteria for success: Section XVI.B.4 of Guideline on good pharmacovigilance practices (GVP) XVI revision 2 (EMA, 2017b), states that: "In rare circumstances when it is justified that the assessment of outcomes indicators is unfeasible (e.g. inadequate number of exposed patients, very rare adverse events), the effectiveness evaluation may be based exclusively on the careful interpretation of data on process indicators".

MLD is a rare/ultra-rare disease treated in highly specialised centres. The expected number of patients to be exposed to OTL-200 in post-marketing settings/clinical studies and the number of qualified centres involved in the administration of the product is expected to be very low and overall considered inadequate for the implementation of a study with sufficient statistical power to capture the effectiveness of the material itself. Moreover, as reported above, section 4.2 of the SmPC reports that OTL-200 "must be administered in a QTC with experience in Haematopoietic Stem Cell Transplantation (HSCT)". Therefore, the educational material targets professionals who are already highly specialised in the management, treatment and care of patients undergoing HSCT.

Given the above, Orchard considers that recording the physical distribution and/or the access of educational material from a digital training platform for QTCs, is a sufficient measure to ensure adequate penetration of the material itself among treating HCPs.

Criteria for success: All treating physicians at QTCs should receive educational materials.

Additional risk minimisation 2: Patient and parent/carer information pack

Orchard provides educational materials (Patient and parent/carer guide; Patient alert card) to patients and their parents/carers (Annex 6).

Objectives: To facilitate informed decision-making by patients or by their parents/carers based on the known benefits and risks of OTL-200 and to minimise the risks to patients including what actions to take and when and how to contact their specialist doctor in case of side effects.

To highlight the need for the patient or their parent/carer to carry the patient alert card to inform any treating healthcare professional that the child was treated with OTL-200.

To explain the need for regular monitoring and to report any symptoms or concerns to the specialist doctor treating the child.

To make patients aware of the importance of regular monitoring and inform them about the LongTERM-MLD study (OTL-200-10) for further characterisation of the safety concerns and to encourage patients and their parents/carers to report side effects that may occur.

Moreover, the patient alert card (PAC) reports information that the patient has received OTL-200, a gene therapy medicinal product for MLD, and should not donate blood, organs, tissues, and cells for transplantation. The card also clearly states that there is a possibility of false positive results on certain commercial HIV tests. The PAC contains the treating physician details, highlights that OTL-200 is subject to additional monitoring and how to report adverse reactions.

Rationale for the additional risk minimisation activity: These materials supplement information in the PL by describing the safety concerns and actions to take to minimise the important risks. Information about the LongTERM-MLD study is provided to encourage patient participation.

Target audience and planned distribution path: Patients with MLD eligible for OTL-200 and their parents/carers.

Plans to evaluate the effectiveness of the interventions and criteria for success: The distribution of the educational material for patients is captured as part of the enrolment process by an Orchard QTC.

Criteria for success: All patients treated with OTL-200 should receive educational materials.

Controlled Distribution

Additional risk minimisation 3: Controlled Distribution

OTL-200 is only available at QTCs with experience in HSCT to ensure that:

- this therapy is only delivered by healthcare professionals who have been adequately trained on the proper use of the product, and
- the traceability of the patients' cells and manufactured medicinal product is maintained between the QTCs and the manufacturing site.

Objectives: To ensure that OTL-200 is only available through an Orchard QTC so that only eligible patients are treated with OTL-200 and to ensure maintained traceability of OTL-200 throughout the manufacturing process to administration. Controlled distribution is an additional risk minimisation measure to be implemented for the important potential risk of 'off label use in other MLD subgroups' and for missing information on 'long-term safety and efficacy data'.

Rationale for the additional risk minimisation activity: The manufacturing process of OTL-200 is complex with multiple steps involved (Figure 2). As OTL-200 is an autologous product it is essential to ensure the product is traceable from the autologous cell procurement stage back to the same patient for treatment with medicinal product.

Target audience and planned distribution path: Treating physicians, manufacturers and QTC staff

Plans to evaluate the effectiveness of the interventions and criteria for success: The compliance with controlled distribution is an unconditional premise for OTL-200 prescription, manufacturing, and medicinal product administration to eligible MLD patients. The controlled distribution is regularly monitored (or measured) by Orchard Therapeutics.

Removal of additional risk minimisation activities

Not applicable.

V.3 Summary of risk minimisation measures

Table 18: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Delayed platelet engraftment (Important identified risk)	Routine risk minimisation communication • *Information that there have been cases of delayed platelet engraftment in clinical studies in SmPC section 4.4* • *Information that there have been cases of delayed platelet engraftment in clinical studies in PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Warning that OTL-200 may cause delayed platelet engraftment in SmPC section 4.4* Additional risk minimisation measures • *Educational materials for healthcare professionals* • *Educational materials for patients* Other routine risk minimisation measures beyond the Product Information: • *Legal status: Medicinal product subject to restricted medical prescription*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Review of aggregate safety data* Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)*
Malignancy due to insertional oncogenesis (Important potential risk)	Routine risk minimisation measures: • *Information that there have been no cases of leukaemia or lymphoma in SmPC section 4.4* • *Information that no patients have developed leukaemia or lymphoma in PL section 2* • *Information that no abnormal or malignant growth of transplanted cells or haematopoietic tumours were found in a study in mice in SmPC section 5.3* • *Warning that Libmeldy may theoretically cause leukaemia or*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	lymphoma with instructions on blood sample collection if malignancy occurs in SmPC section 4.4 • *Warning that the patient will be asked to enrol in follow up study for up to 15 years and will be monitored for any signs of blood cancer because of the theoretical cancer risk in PL section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*	
Anti-ARSA antibodies (Important potential risk)	Routine risk minimisation measures: • *Information that there have been cases of AAA reported during clinical development in SmPC section 4.4* • *Warning that monitoring for the presence of AAA is recommended prior to treatment and regularly during post-treatment follow-up in SmPC section 4.4.* • *Guidance on short treatment with rituximab in SmPC section 4.4.* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)*
Engraftment failure (Important potential risk)	Routine risk minimisation measures: • *Information that no patients failed to engraft bone marrow in SmPC sections 4.4 and 5.1* • *Information that following successful and stable engraftment the effects of Libmeldy are expected to be persistent in SmPC section 5.1*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study 201222* • *Study 205756*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• *Information in PL section 3 that the stem cells collected from the blood will be divided into a treatment sample, used to make Libmeldy and a backup sample to be given as replacement stem cells if Libmeldy cannot be given. The backup sample may also be collected from the bone marrow* • *Instructions to obtain a $CD34^+$ stem cell back-up harvested either through mPB apheresis or bone marrow harvest for use as rescue treatment in SmPC section 4.2* • *Guidance that myeloablative conditioning is required before infusion of OTL-200 to promote engraftment in SmPC section 4.2* • *Warning that in case of cytopenia symptoms, red blood cells and platelet counts should be monitored until engraftment of these cells and recovery are achieved in SmPC section 4.4* • *Guidance to infuse the non-transduced back-up cells if cytopenia persists beyond six to seven weeks in SmPC section 4.4* • *Guidance that in case of engraftment failure, the non-transduced back-up cells should be infused in SmPC section 4.4* • *Guidance that if the modified stem cells do not take hold (engraft) in the patient's body, the doctor may give an infusion of the backup original stem cells in PL section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*	• *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Off label use in other MLD subgroups (Important potential risk)	Routine risk minimisation measures: • *Therapeutic indication in SmPC section 4.1 and PL section 1* • *Warning that eligibility to treatment should be assessed by the treating physician in SmPC section 4.4* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack* • *Controlled distribution*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)*
Long-term safety and efficacy data (Missing information)	Routine risk minimisation measures: • *Information on the duration of patient follow-up in the clinical studies in SmPC section 5.1* • *Guidance that patients will be asked to enrol in a follow-up study for up to 15 years in SmPC section 4.2 and PL section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack* • *Controlled distribution*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Libmeldy (a $CD34^+$ 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).

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

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

This summary of the RMP for Libmeldy 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 are included in updates of Libmeldy 's RMP.

I. The medicine and what it is used for

Libmeldy is authorised for the treatment of patients with Metachromatic Leukodystrophy (MLD) (see SmPC for the full indication). It contains a $CD34^+$ 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 as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Libmeldy's benefits can be found in Libmeldy's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *<link to product's EPAR summary landing page on the EMA webpage>*

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

Important risks of Libmeldy, together with measures to minimise such risks and the proposed studies for learning more about Libmeldy'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 Libmeldy, 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 Libmeldy is not yet available, it is listed under 'missing information' below.

II. List of important risks and missing information

Important risks of Libmeldy 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 Libmeldy. 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 identified risks	Delayed platelet engraftment
Important potential risks	Malignancy due to insertional oncogenesis Anti-ARSA antibodies Engraftment failure Off label use in other MLD subgroups
Missing information	Long-term safety and efficacy data

II.B Summary of important risks

Important identified risk: Delayed platelet engraftment	
Evidence for linking the risk to the medicine	During the clinical development of OTL-200, busulfan was used as a conditioning agent to promote efficient engraftment of the genetically modified autologous cells. When used at typical myeloablative doses in both adults and children, very commonly reported adverse reactions with busulfan include thrombocytopenia (Busulfan SmPC). During the clinical development of OTL-200, platelet engraftment was defined as the first of 3 consecutive days with platelet values ≥ 20 x 10^9/L obtained on different days after Libmeldy infusion, with no platelet transfusion administered for 7 days immediately preceding and during the evaluation period (up to 60 days post gene therapy). Four patients out of 49 experienced delayed platelet engraftment which was not correlated with an increased incidence of bleeding. In the integrated safety population of early-onset MLD (N = 49), the median number of days until platelet engraftment was 35.0 days (range 11 to 109).

	Overall, during the clinical development of OTL-200 the report of delayed platelet engraftment was not correlated with an increased incidence of bleeding. However, all patients treated with OTL-200 in the CDP received transfusion support with platelets. Most of these transfusions were considered part of the standard of care/prophylaxis for these patients, were received during the peri-transplant period and mainly within the three months post gene therapy (≤ 100 days post-GT). The important identified safety concern of delayed platelet engraftment will be followed up as part of the LongTERM-MLD study (OTL-200-10) (Part III.2).
Risk factors and risk groups	Overall, although delayed platelet engraftment was not correlated with an increased incidence of bleeding, this risk bears a potential for development of bleeding events due to prolonged thrombocytopenia, which can be serious.
Risk minimisation measures	Routine risk minimisation measures • *SmPC section 4.4: warning that delayed platelet engraftment has been reported in 4 patients and information to monitor platelet count until engraftment.* • *PL section 2: Information to monitor platelet level and symptoms of bleeding.* • *Restricted prescription medicine* Additional risk minimisation measures • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)* See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancy due to insertional oncogenesis	
Evidence for linking the risk to the medicine	Libmeldy consists of $CD34^+$ cells transduced *ex vivo* with a LVV which integrates permanently into the host genome. The risk of insertional mutagenesis and consequent tumourigenicity has been evaluated in several *in vitro* and *in vivo* non-clinical studies. Integration site (IS) analysis performed on genomic DNA from whole peripheral blood (PB) and BM samples harvested at different time points after therapy showed a highly polyclonal pattern of vector integration in mice with no indication of abnormal clonal

	expansion. Hepatocellular tumours were observed in *in vivo* non-clinical studies but they were considered related to the conditioning regimen and genetic background of the mice. Overall there was no evidence of preferential expansion of IS near proto-oncogenes in all analysed mice, with no increase in tumourigenesis found in a tumour prone mouse model. To date, no cases of malignancy due to insertional oncogenesis have been reported after treatment with OTL-200. Cumulatively, 82 patients have been exposed to OTL-200, and additional patients have been exposed to other GT medicinal products using the same lentiviral backbone and with use of partially reconstituted cellular promoters with no evidence to date of insertional oncogenesis (Montini, 2025). There has been >13 years follow-up for the earliest treated patients with MLD and more than 300 patient-years follow-up in patients included in the integrated analyses. In all cases, no evidence of insertional oncogenesis or clonal expansion was observed. Clinical trials, alongside data reported in the literature, can provide an estimate of the frequency of malignancies that are expected to occur in clinical practice.
Risk factors and risk groups	Factors thought to be important in contributing to the risk of oncogenesis (EMA/CAT/190186/2012): a) Vector design (including backbone and regulatory elements) b) Insertion profile c) Vector copy number (VCN) d) Transgene product e) Target cell population/organ f) Risk of malignancy for the underlying disease
Risk minimisation measures	Routine risk minimisation measures: • *Information that there have been no cases of leukaemia or lymphoma in SmPC section 4.4* • *Information that no patients have developed leukaemia or lymphoma in PL section 2* • *Information that no abnormal or malignant growth of transplanted cells or haematopoietic tumours were found in a study in mice in SmPC section 5.3* • *Warning that Libmeldy may theoretically cause leukaemia or lymphoma with instructions on blood sample collection if malignancy occurs in SmPC section 4.4* • *Warning that the patient will be asked to enrol in a follow up study for up to 15 years and will be monitored for any signs of blood cancer because of the theoretical cancer risk in PL section 2* • *Restricted medical prescription* Additional risk minimisation measures:

	• *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Anti-ARSA antibodies	
Evidence for linking the risk to the medicine	Cumulatively, out of 82 patients exposed to OTL-200, 12 patients have developed AAA. Of these 12 patients, 8 patients had positive bridging assay results. The AAA were low titre in all patients and resolved in 7 patients, either after treatment with rituximab or spontaneously. Four patients had positive ELISA assay results without bridging assay results. AAA were low titre in all 4 patients and resolved spontaneously in 1 patient.
Risk factors and risk groups	Not yet established.
Risk minimisation measures	• *Information that there have been cases of anti-ARSA antibodies reported during the clinical development in SmPC section 4.4.* • *Warning that monitoring for the presence of AAA is recommended prior to treatment and regularly during post-treatment follow-up in SmPC section 4.4.* • *Guidance on short treatment with rituximab in SmPC section 4.4.* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394*

	• *HE 205029* • *LongTERM-MLD study (OTL-200-10)* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Engraftment failure	
Evidence for linking the risk to the medicine	Busulfan was used as a conditioning agent in all patients treated with OTL-200 to date. For MLD and most other metabolic diseases utilising genetically modified haematopoietic stem cell therapy, a myeloablative busulfan regimen with therapeutic drug monitoring is considered standard of care to obtain optimal efficacy while minimising the risk of overexposure (Fumagalli, 2022; Oved, 2025). Busulfan conditioning is recognised to cause profound myelosuppression (Busulfex US Prescribing Information, 2015; Busilvex SmPC, 2023). Although no patients treated with OTL 200 have experienced engraftment failure (defined as failure to reach an ANC >500 neutrophils/µL associated with no evidence of BM recovery [i.e., hypocellular marrow] by Day +60), neutrophil engraftment failure is a potential risk after treatment with OTL-200 based on the known effects of busulfan.
Risk factors and risk groups	To date, there have been no reported cases of engraftment failure (failure to reach an ANC >500 neutrophils/µL associated with no evidence of BM recovery [i.e., hypocellular marrow] by Day +60); therefore, there are no identified risk factors or risk groups.
Risk minimisation measures	Routine risk minimisation measures: • *Information that no patients failed to engraft bone marrow in SmPC sections 4.4 and 5.1* • *Information that following successful and stable engraftment the effects of Libmeldy are expected to be persistent in SmPC section 5.1* • *Information in PL section 3 that the stem cells collected from the blood will be divided into a treatment sample, used to make Libmeldy and a backup sample, to be given as replacement stem cells if Libmeldy cannot be given. The backup sample may also be collected from the bone marrow.* • *Instructions to obtain a $CD34^+$ stem cell back-up harvested either through mPB apheresis or bone marrow harvest for use as rescue treatment in SmPC section 4.2* • *Guidance that myeloablative conditioning is required before infusion of Libmeldy to promote engraftment in SmPC section 4.2*

	• *Warning that in case of cytopenia symptoms, red blood cells and platelet counts should be monitored until engraftment of these cells and recovery are achieved in SmPC section 4.4* • *Guidance to infuse the non-transduced back-up cells if cytopenia persists beyond six to seven weeks in SmPC section 4.4.* • *Guidance that in case of engraftment failure, the non-transduced back-up cells should be infused in SmPC section 4.4* • *Guidance that if the modified stem cells do not take hold (engraft) in the patient's body, the doctor may give an infusion of the backup original stem cells in PL section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Off label use in other MLD subgroups	
Evidence for linking the risk to the medicine	During the clinical development, treatment failure was seen in four patients treated outside of the currently proposed label. An analysis of treatment response was performed for the MA renewal as part of the integrated efficacy analysis. To be included in the treatment response analyses, patients must be considered PSLI, PSEJ, or ESEJ based on the current Libmeldy SmPC, and must have been followed up for at least 2 years after OTL-200 treatment. No patients classified as PSLI, PSEJ, or ESEJ according to the Libmeldy SmPC experienced a protocol-defined treatment failure. This indicates that the current Libmeldy SmPC already excludes patients unlikely to benefit from treatment with OTL 200, including symptomatic LI patients and EJ patients who have entered the rapidly progressive phase of the disease before treatment. As a result, the indication statement was restricted. OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the

	arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity - in children with the pre-symptomatic late infantile (PSLI) or pre-symptomatic early juvenile (PSEJ) forms, i.e. without clinical manifestations of the disease - in children with the early symptomatic early juvenile (ESEJ) form, i.e. with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline (see section 5.1). Clinical trials can show the treatment failure that has occurred to date as a result of use outside of the label and further analyses of these cases can continue to guide recommendations for treating MLD patients in clinical practice. The efficacy and safety of OTL-200 in patients with LJ MLD is currently being evaluated in Study OTL-200-07, which is fully enrolled. The risk of treated patients with Adult MLD has not been characterised.
Risk factors and risk groups	Patients in MLD subgroups that are outside of the indication of Libmeldy.
Risk minimisation measures	Routine risk minimisation measures: • *Therapeutic indication in SmPC section 4.1 and PL section 1* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack* • *Controlled distribution*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety and efficacy data	
Risk minimisation measures	Routine risk minimisation measures: • *Information on the duration of patient follow-up in the clinical studies in SmPC section 5.1* • *Guidance that patients will be asked to enrol in a follow-up study for up to 15 years in SmPC section 4.2 and PL section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for healthcare professionals* • *Patient and parent/carer information pack* • *Controlled distribution*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study 201222* • *Study 205756* • *Study OTL-200-07* • *CUP 206258* • *CUP 207394* • *HE 205029* • *LongTERM-MLD study (OTL-200-10)* See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

LongTERM-MLD Study (OTL-200-10)

Purpose of the study: The aim of this study is to ensure that efficacy and safety of patients treated with Libmeldy in the CDP and in post-authorisation setting are assessed for up to 15 years following treatment in line with regulatory requirements.

In addition, this study will also aim to gather further data in early Symptomatic Early Juvenile MLD patients. It is anticipated that data from 10 patients will adequately supplement the data previously gathered in this population during the clinical development programme.

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

Study 201222

Purpose of the study: The objectives of the study are to evaluate the safety and efficacy of the fresh formulation of OTL-200 in 20 early-onset MLD patients.

Study 205756

Purpose of the study: The objective of the study is to evaluate the safety and efficacy of the cryopreserved formulation of OTL-200 (OTL-200-c) in up to 10 pre-symptomatic, early-onset MLD patients.

Study OTL-200-07

Purpose of the study: The objective of the study is to evaluate the safety and efficacy of a single infusion of OTL-200. Six patients have been enrolled and the study now closed.

CUP 206258

Purpose of the study: In the absence of a suitable clinical trial that was open for enrolment, the objective of the Expanded Access Programs (EAPs) (Hospital Exemption [HE] and Compassionate Use Programme [CUP]) is to provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available.

CUP 207394

Purpose of the study: The objective of this compassionate use treatment programme was to provide a mechanism to supply OTL-200 on a compassionate use basis to a single patient with early symptomatic EJ MLD.

HE 205029

Purpose of the study: In the absence of a suitable clinical trial that was open for enrolment, the objective of the EAPs (HE and CUP) is to provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available.

PART VII: ANNEXES

Table of contents

Annex 4 Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 Details of proposed additional risk minimisation activities

Prior to launch of Libmeldy in each Member State the Applicant will agree the content and format of the educational materials and controlled distribution programme with the National Competent Authority. The educational and controlled distribution programme is aimed at providing information on the safe use of Libmeldy.

The MAH shall ensure that in each Member State where Libmeldy is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense and/or use Libmeldy have access to/are provided with the following educational package

– Physician educational material

– Patient information pack.

The physician educational material should contain:

The Summary of Product Characteristics

Guide for healthcare professionals

Guide for handling and method of administration for Libmeldy

The Guide for healthcare professionals shall contain the following key elements:

- Warning that there is a theoretical possibility that the treatment with Libmeldy may be associated with the risk of insertional mutagenesis, potentially leading to development of malignancy. All patients should receive monitoring for signs and symptoms of oncogenic transformation, leukaemia or lymphoma; and must be advised on the symptoms and signs of leukaemia or lymphoma and to seek immediate medical attention if they develop any of the symptoms.
- Warning about delayed platelet engraftment and guidance on its management
- Warning about emergence of anti-ARSA antibodies and guidance on its management
- Warning about the potential risk of engraftment failure and the need to monitor patients
- Information that treatment with Libmeldy should be performed before the disease enters its rapidly progressive phase
- Information on LongTERM-MLD (OTL-200-10) study and what it will involve
- Recommendation of the important considerations to discuss with patients and/or carers about Libmeldy:
  - Potential risks of a treatment with Libmeldy
  - Signs of any malignancy such as leukaemia/lymphoma and what action to take
  - Content of the patient and parent/carer guide
  - The need to carry the patient alert card and to show it to every healthcare professional

  - The importance of regular monitoring and long term follow-up.
- Provision of contact details for reporting all suspected adverse reactions and to include the individual medicinal product lot number which can be found within the patient alert card.

The Guide for handling and method of administration for Libmeldy for healthcare professionals with the following key elements:

- Guidance that Libmeldy must be administered in a QTC with experience in haematopoietic stem cell transplantation (HSCT)
- Instructions on the precautions to be taken before handling or administering Libmeldy
- Instructions for receiving and storing Libmeldy
- Instructions to check Libmeldy prior to administration
- Instructions for the thawing of Libmeldy
- Provision of contact details for reporting all suspected adverse reactions and to include the individual medicinal product lot number which can be found within the patient alert card.

1. The patient information pack shall contain:

- The Package leaflet
- The Patient and parent/carer guide
- The Patient alert card

Patient and parent/carer guide with the following key messages:

- Warning to monitor the patient for symptoms of leukaemia or lymphoma and to contact the specialist doctor immediately in case of any symptoms as there is a small risk that a patient may develop leukaemia or lymphoma. The specialist doctor will check the patient's blood for any signs of leukaemia or lymphoma during the routine yearly check-ups, which will continue after treatment.
- Guidance about the need for the patient or their parent/carer to carry the patient alert card to inform any treating healthcare professional that the child was treated with Libmeldy.
- Guidance on the importance of regular monitoring and to report any symptoms or concerns to the specialist doctor treating the child.
- Information about the LongTERM-MLD study and the purpose of the study.
- Provision of contact details for reporting any side effects or symptoms of the patient and what a medicine subject to additional monitoring (▼) means.

Patient alert card with the following key messages:

- Statement that the patient was treated with Libmeldy, with the medicinal product lot number and treatment date to ensure traceability as per the Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008).
- Contact details of the treating physician.
- Information on the possibility of false positivity of certain commercial HIV tests because of Libmeldy.
- Statement that the patient was treated with gene therapy and should not donate blood, organs, tissues, or cells.
- Details on reporting of adverse reactions and that Libmeldy is subject to additional monitoring▼.
- Contact details where a healthcare professional can receive further information.

Controlled Distribution

The Applicant shall ensure that in each Member State where Libmeldy is marketed, a system aimed to control distribution to Libmeldy beyond the level of control is ensured by routine risk minimisation measures. The following requirements need to be fulfilled before the product is prescribed, manufactured, dispensed and used:

- Libmeldy shall only be available through QTCs to ensure traceability of the patient's cells and manufactured medicinal product between the treating hospital and manufacturing site. The selection of the QTCs shall be conducted in collaboration with national health authorities as appropriate. The HCPs will receive training on the HCP educational materials as part of the centre qualification process.