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 will be 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 subjects out of 35 (twins MLD-HE01 and MLD-HE02, MLD-12 and MLD-22) experienced delayed platelet engraftment which was not correlated with an increased incidence of bleeding. 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 to platelet engraftment (range 23 to 47 days). 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 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). 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 the LongTERM-MLD study (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 subjects 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 • Single-patient CUP 207394 (MLD-C02) • HE 205029 • LongTERM-MLD study 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 or AEs indicative of oncogenic transformation have been reported. There was no evidence of abnormal clonal proliferation as assessed by clinical and laboratory surveillance and BM examination. 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). 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 hematopoietic 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* • *Single-patient CUP 207394 (MLD-C02)* • *HE 205029*

	• *LongTERM-MLD study* 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	In the clinical development programme of Libmeldy including the integrated data set (N=29) and the available information from the Study 205756 (N=6) at the time of the RMP data cut, AAAs were detected transitorily, with low titres in a limited number of patients (4/35 patients, 11.4%). 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 MLDCUP05 (titre 1:800; at Year 2), who previously had positive AAA which resolved spontaneously; and secondly, patient MLDCRY09 (titre 1:400 at Day 30). There was no evidence of a negative clinical effect observed in the post-treatment ARSA activity of PB/BM (or any other relevant cellular subpopulations) nor in the ARSA activity within CSF, which was quantifiable by 3 months post treatment and reached normal range in all patients by 12 months. In addition, from a mechanistic perspective, AAAs are not anticipated to interfere with the functionality of ARSA activity in brain due to the limitations of antibodies to cross the blood-brain barrier However, as further information is needed to characterize the potential impact of the presence of AAAs on the clinical and safety profile of Libmeldy, AAAs are considered an important potential risk.
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 AAAs 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* • *Single-patient CUP 207394 (MLD-C02)* • *HE 205029*

	• *LongTERM-MLD study* 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	For successful engraftment in stem cell transplantation the body needs to accept the transplanted bone marrow or stem cells, and to produce new cells of all the normal lineages. Busulfan was used as a conditioning agent in the Libmeldy clinical development programme to enhance engraftment of the genetically modified autologous cells particularly given its capacity to cross the blood-brain barrier, get access to the brain and remove resident microglia. In Study 201222 and in the EAPs all MLD patients treated with fresh formulation achieved sustained levels of engraftment and demonstrated good haematological recovery following busulfan conditioning. Engraftment was observed from 1-month following treatment and persisted at stable levels throughout the follow-up period. There is a theoretical risk that sub-optimal engraftment may occur with cryopreserved formulation due to cell loss or damage related to the cryopreservation but to date this has not been observed in patients treated with cryopreserved (commercial) formulation in Study 205756 or in other clinical trials using cryopreserved drug products.
Risk factors and risk groups	The benefits and associated efficacy of Libmeldy are likely dependent on the stage of MLD at which it is given. In Study 201222 patients with advanced MLD symptoms were excluded because they are considered unlikely to obtain clinical benefit from Libmeldy. Additionally, patients with early-symptomatic LI MLD were excluded from participation because this population is characterised by rapid disease progression (Biffi 2008a; Keher 2011a), leaving insufficient time for transduced cells to engraft, to start producing ARSA in the nervous system, and to influence clinical parameters (a process that can take several months). The exclusion of subjects with advanced symptoms in the current study is further reinforced by clinical experience with HSCT (Martin, 2013; van Rappard, 2015; Boelens, 2010; Boucher, 2015), which has shown that disease progression is not slowed in patients with moderate to severe neurological symptoms at the time of transplantation. To date there is no evidence of engraftment failure with either fresh or cryopreserved (commercial) formulations.
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 life-long in SmPC section 5.1*

	• *Information that the doctor will collect two samples of bone marrow or blood including a stem cell backup sample in case Libmeldy does not work in PL section 3* • *Instructions to obtain a CD34$^+$ stem cell back-up 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* • *Single-patient CUP 207394 (MLD-C02)* • *HE 205029* • *LongTERM-MLD study* 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 subjects treated outside of the currently proposed label. As a result, the indication statement was restricted. OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arysulfatase 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 (see section 5.1). Clinical trials can show the treatment failure that has occurred to date as a result of use outside of the proposed label and further analyses of these cases can continue to guide recommendations for treating MLD patients in clinical practice.
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* • *Single-patient CUP 207394 (MLD-C02)* • *HE 205029* • *LongTERM-MLD study* 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*

Missing information: Long-term safety and efficacy data	
	• *Single-patient CUP 207394 (MLD-C02)* • *HE 205029* • *LongTERM-MLD study* 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

Purpose of the study: The aim of this study is to ensure that efficacy and safety of patients treated with Libmeldy in the Clinical Development Program (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 followed up for 8 years after treatment with OTL-200.

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 followed up for 8 years after treatment with OTL-200-c.

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 in up to 6 patients with late juvenile (LJ) MLD.

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 Program [CUP]) is to provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available.

Single-patient CUP 207394 (MLD-C02)

Purpose of the study: The objective of this compassionate use treatment program was to provide a mechanism to supply OTL-200 on a compassionate use basis to a patient (MLD-C02) 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.

List of References for the RMP Summary

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