ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Libmeldy (atidarsagene autotemcel) 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.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Libmeldy contains atidarsagene autotemcel at a batch-dependent concentration of genetically modified autologous $CD34^+$ cells enriched population.
The medicinal product is packaged in one or more infusion bags overall containing a dispersion of 2-10 x 10^6 cells/mL of viable $CD34^+$ cells enriched population suspended in a cryopreservative solution.

Each infusion bag contains 10 to 20 mL of Libmeldy.

The quantitative information of medicinal product, including the number of infusion bags (see section 6) to be administered, is presented in the Lot information sheet (LIS) located inside the lid of the cryoshipper used for transport.

Excipients with known effect

This medicinal product contains 3.5 mg sodium per mL and 55 mg dimethylsulfoxide (DMSO) per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to slightly cloudy, colourless to yellow or pink dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized 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 (see section 5.1).

4.2 Posology and method of administration

Libmeldy must be administered in a qualified treatment centre by a physician with experience in Haematopoietic Stem Cell Transplantation (HSCT) and trained for administration and management of patients treated with the medicinal product.

Posology

Libmeldy is intended for autologous use (see section 4.4) and should only be administered once.

The dose of Libmeldy must be determined based on the patient's body weight at the time of infusion.

Treatment consists of a single dose for infusion containing a dispersion of viable $CD34^+$ cells in one or more infusion bags.

The minimum recommended dose of Libmeldy is 3×10^6 $CD34^+$ cells/kg of body weight. In clinical studies, doses up to 30×10^6 $CD34^+$ cells/kg have been administered.
See the accompanying Lot information sheet (LIS) for additional information pertaining to dose.

Peripheral blood mobilisation and apheresis
The autologous $CD34^+$ cells are isolated from mobilised peripheral blood (mPB). This is achieved by apheresis procedure(s) following peripheral blood mobilisation.

For manufacture of Libmeldy, the patient must be able to donate a minimum of 8×10^6 $CD34^+$ cells/kg, considering that the optimal range is between 20-30 $\times 10^6$ $CD34^+$ cells/kg.
The minimum $CD34^+$ cell quantity may be achieved using one or more days of apheresis.

If, after medicinal product manufacturing, the minimum dose of Libmeldy of 3×10^6 $CD34^+$ cells/kg is not achieved, the patient may undergo a further mobilisation protocol with one or more cycles of apheresis, in order to obtain more cells for additional manufacture (see *Mobilisation and apheresis* in section 5.1).

A back-up collection of HSPC containing at least 2 x 10^6 $CD34^+$ cells/kg is also required for use as rescue treatment should the quality of Libmeldy be compromised after initiation of myeloablative conditioning and before Libmeldy infusion, failure of primary engraftment, or prolonged bone marrow aplasia after treatment with Libmeldy (see section 4.4).
These cells must be collected from the patient and be cryopreserved according to institutional procedures prior to myeloablative conditioning. The back-up cells may be harvested either through mPB apheresis or bone marrow harvest.

Peripheral blood mobilisation
Patients are required to undergo HSPC mobilisation with Granulocyte colony-stimulating factor (G-CSF) with or without plerixafor followed by apheresis to obtain $CD34^+$ stem cells for medicinal product manufacturing (see section 5.1 for a description of the mobilisation regimen used in clinical studies).

Pre-treatment (conditioning)

The treating physician should confirm that autologous HSPC gene therapy administration is clinically appropriate for the patient before myeloablative conditioning is initiated (see section 4.4).

A myeloablative conditioning is required before infusion of Libmeldy to promote efficient engraftment of the genetically modified autologous $CD34^+$ cells (see section 5.1 for a description of the myeloablative regimen used in clinical studies).
Busulfan is the recommended conditioning medicinal product.

Myeloablative conditioning should not begin until the complete set of infusion bag(s) constituting the dose of Libmeldy has been received and stored at the qualified treatment centre, and the availability of the back-up collection is confirmed.

Concurrently with the conditioning regimen, and prior to treatment with Libmeldy, it is recommended that patients receive prophylaxis for veno-occlusive disease (VOD) and related endothelial injury complications i.e. transplant-associated thrombotic microangiopathy (TA-TMA) or atypical haemolytic uremic syndrome (aHUS), in line with local guidelines.

Depending on the myeloablative conditioning regimen administered, prophylaxis for seizures should also be considered. Phenytoin is not recommended as it may increase busulfan clearance.

Prophylactic and empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections especially during the neutropenic period following conditioning. Routine monitoring of most common viruses subject to re-activation is recommended as per local guidelines. Infection control measures and isolation procedures should be employed during the hospitalization according to local standards.

Pre-medication

It is recommended that pre-medication with intravenous chlorpheniramine (0.25 mg/kg, max. dose 10 mg), or equivalent medicinal products, be administered 15-30 minutes before the infusion of Libmeldy to reduce the possibility of an infusion reaction.

Special populations

Elderly
Libmeldy has not been studied in patients over 65 years of age.

Renal impairment
Libmeldy has not been studied in patients with renal impairment. Patients should be assessed for renal impairment to ensure autologous HSPC gene therapy administration is appropriate. No dose adjustment is required.

Hepatic impairment
Libmeldy has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure autologous HSPC gene therapy administration is appropriate. No dose adjustment is required.

Paediatric population
The safety and efficacy of Libmeldy have not yet been established in patients with the late juvenile form of the disease (i.e. with a typical onset after 7 years of age). No data are available.

Method of administration

Libmeldy is for intravenous infusion only.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human cells. Healthcare professionals should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases when handling the product.

Preparation for infusion
Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Libmeldy infusion bag(s) and accompanying documentation. The total number of infusion bags to be administered must also be confirmed with the patient specific information on the Lot information sheet (LIS) (see section 4.4).

The timing of thaw and infusion of Libmeldy should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that Libmeldy is available for infusion when the patient is ready. To maintain product viability, as soon as thawing is complete, it is recommended that Libmeldy be administered immediately. Administration must be completed within 2 hours from the time of thawing.

Administration
The product should be administered as an intravenous infusion via a central venous catheter. When more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour. Each bag should be infused at an infusion rate which does not exceed 5 mL/kg/h, within approximately 30 minutes. The recommended administration set consists of a blood transfusion set equipped with a 200 µm filter (see section 6.6).

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Libmeldy, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Previous treatment with haematopoietic stem cell gene therapy.

Contraindications to the mobilisation and the myeloablative medicinal products must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the product.

Autologous use

Libmeldy is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Libmeldy must not be administered if the information on the product labels and Lot Information Sheet (LIS) do not match the patient's identity.

Rapidly progressive phase of the disease

Treatment with Libmeldy should be performed before the disease enters its rapidly progressive phase. Eligibility for treatment with Libmeldy should initially be assessed by the treating physician via full neurological examination, motor function assessment and neurocognitive assessment, as appropriate for the patient's age.
Prior to the commencement of cellular harvest, and prior to the commencement of conditioning, the treating physician should ensure that autologous HSPC gene therapy administration remains clinically appropriate for the patient, and that treatment with Libmeldy is still indicated.

Mobilisation and myeloablative conditioning medicinal products

Warnings and precautions of the mobilisation and myeloablative conditioning medicinal products must be considered.

Central venous catheter (CVC) complications including infections and thromboses

Infections related to the use of CVCs have been reported in clinical studies and there is a risk of thrombosis associated with the CVC. Patients should be closely monitored for potential infections and catheter-related events.

Transmission of an infectious agent

Although Libmeldy is tested for sterility and mycoplasma, a risk of transmission of infectious agents exists. Healthcare professionals administering Libmeldy must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Interference with virological testing

Due to limited and short spans of identical genetic information between the lentiviral vector used to manufacture Libmeldy, and HIV, some HIV nucleic acid tests (NAT) may give a false positive result. Patients who have received Libmeldy should not be screened for HIV infection using a PCR-based assay.

Blood, organ, tissue and cell donation

Patients treated with Libmeldy must not donate blood, organs, tissues and cells for transplantation. This information is provided in the Patient Alert Card which must be given to the patient after treatment.

Hypersensitivity and infusion-related reactions

Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethylsulfoxide (DMSO) in Libmeldy. Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored prior to the start of the infusion, during the infusion and after the infusion of each Libmeldy bag as per institution guidelines.
When more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour, and the absence of any immediate hypersensitivity reaction should be confirmed before starting the infusion of the subsequent bag.

Engraftment failure

In clinical studies, no patients failed to engraft bone marrow, as measured by neutrophil count in peripheral blood. Failure of neutrophil engraftment is a short-term but potentially important risk, defined as failure to reach an absolute neutrophil count (ANC) > 500 cells/μL associated with no evidence of bone marrow recovery (i.e. hypocellular marrow) by day 60 after Libmeldy infusion. In case of engraftment failure, the non-transduced back-up stem cells should be infused according to local standards (see section 4.2).

Prolonged cytopenia

Patients may exhibit severe cytopenias, including severe neutropenia [defined as Absolute Neutrophil Count (ANC) < 500 cells/μL] and prolonged thrombocytopenia, for several weeks following myeloablative conditioning and Libmeldy infusion. In clinical studies, the median number of days with absolute aplasia was 6 (range 2 to 29 days, i.e. up to 4 weeks) and the median number of days from treatment with Libmeldy to neutrophil engraftment was 38 (range 18 to 50 days, i.e. up to

7 weeks). Patients should, therefore, be monitored for signs and symptoms of cytopenia for at least 7 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 and platelets should be given according to medical judgement and institutional practice. Blood cell count determination and other appropriate testing should be promptly considered whenever clinical symptoms suggestive of anaemia arise.
If cytopenia persists beyond seven to eight weeks, despite the use of granulocyte mobilising medicinal products, the non-transduced back up stem cells should be infused. If cytopenia persists despite infusion of non-transduced back-up stem cells, alternative treatments should be considered.

Delayed platelet engraftment

Platelet engraftment is defined as the first of 3 consecutive days with platelet values $\geq 20 \times 10^9$/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 patients (8%) reported delayed platelet engraftment (median: 85.5 days, range 67 to 109 days), which was not correlated with an increased incidence of bleeding. As part of the standard of care/prophylaxis, all patients (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.

Metabolic acidosis

Prior to treatment with Libmeldy, the presence of renal tubular acidosis should be evaluated alongside risks of the conditioning medicinal product and risks of the gene therapy procedure, which may contribute to the development of metabolic acidosis. Acid-base status should be monitored throughout conditioning and until the patient is no longer under metabolic stress. The treating physician should consider sodium bicarbonate replacement alongside any other required treatment and should aim to correct any concurrent adverse reaction(s) that might contribute to metabolic acidosis.

Thyroid monitoring

Transient increases in thyroid stimulating hormone (TSH), free T4 (FT4; thyroxine) and free T3 (FT3; tri-iodothyronine) were observed in some patients during clinical studies. Considering that thyroid disorders could potentially be masked by critical illness or induced by concomitant medication, patients should be assessed for thyroid function and structure prior to treatment with Libmeldy. Thyroid function and structure should also be monitored in the short term after treatment, and as necessary thereafter.

Risk of insertional oncogenesis

There is a theoretical risk of leukaemia or lymphoma after treatment with Libmeldy. In the event that leukaemia or lymphoma is detected in any patient who received Libmeldy, blood samples should be collected for integration site analysis.

Anti-ARSA antibodies

All patients (N=39) in the clinical studies were tested for anti-ARSA antibodies (AAA) and 15% had a positive result. A similar percentage of patients treated either in the context of nominal compassionate use or in the commercial setting had positive AAA results reported. Titers were generally low and the majority of cases resolved spontaneously or after treatment with rituximab (see section 4.8).
Monitoring of AAA is recommended 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 and 15 years post treatment. In case of disease onset or significant disease progression, additional AAA monitoring is recommended.

Serological testing

Libmeldy has not been studied in patients with HIV-1, HIV-2, HTLV-1, HTLV-2, HBV, HCV or mycoplasma infection.
All patients should be tested for HIV-1/2, HTLV-1/2, HBV, HCV and mycoplasma prior to mobilisation to ensure acceptance of the cellular source material for Libmeldy manufacturing.

Anti-retroviral use

Patients should not take anti-retroviral medicinal products from at least one month prior to mobilisation until at least 7 days after Libmeldy infusion (see section 4.5). If a patient requires anti-retrovirals following exposure to HIV/HTLV, initiation of Libmeldy treatment should be delayed until an HIV/HTLV western blot and viral load assay have been performed at 6 months post-exposure.

After Libmeldy administration

After the infusion, standard procedures for patient management after HSPC transplantation should be followed.
Immunoglobulin G should be maintained above 5 g/L to prevent potential late infections (occurring later than 100 days post therapy) associated with severe hypogammaglobinaemia, resulting from apheresis and conditioning.
Any blood products required within the first 3 months after Libmeldy infusion should be irradiated.

Long-term follow-up

Patients are expected to be enrolled in a long-term follow-up scheme in order to better understand the long-term safety and efficacy of Libmeldy.

Sodium content

This medicinal product contains 35–560 mg sodium per dose, which is equivalent to 2 to 28% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The nature of Libmeldy is such that no pharmacokinetic interactions are expected with other medicinal products.

Anti-retrovirals

Patients should not take anti-retroviral medicinal products from at least one month prior to mobilisation until at least 7 days after Libmeldy infusion (see section 4.4).

Live vaccines

The safety of immunisation with live viral vaccines during or following treatment with Libmeldy has not been studied. As a precautionary measure, vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of conditioning regimens, during Libmeldy treatment, and until haematological recovery following treatment.

4.6 Fertility, pregnancy and lactation

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 regard to fertility, the SmPC of the myeloablative conditioning medicinal product should be consulted. It should be noted that the treating physician should inform the patient's parents/carers about options for cryopreservation of spermatogonial stem cells or ovarian tissue.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The safety of Libmeldy was evaluated in 49 patients with MLD. The median duration of follow-up was 5.6 years (range: 0.5 to 13.2 years). Three patients died and a total of 46 patients remained in the follow-up phase.
Given the small patient population, adverse reactions in the table below do not provide a complete perspective on the nature and frequency of these events.

Treatment with Libmeldy is preceded by medical interventions, namely haematopoietic stem cell collection through peripheral blood mobilisation with G-CSF with or without plerixafor followed by apheresis, and myeloablative conditioning (preferably using busulfan), which carry their own risks. When assessing the safety of a treatment with Libmeldy, the safety profile and product information of the medicinal products used for peripheral blood mobilisation and myeloablative conditioning should be considered, in addition to the risks linked to the gene therapy.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA body system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), and common (≥ 1/100 and < 1/10).

Table 1 Adverse reactions attributed to Libmeldy

System Organ Class	Very Common	Common
Immune system disorders	Antibody Test Positive (Anti-ARSA Antibody)	

Table 2 Adverse reactions potentially attributed to myeloablative conditioning**

System Organ Class	Very Common	Common
Infections and infestations		Cytomegalovirus infection, Pneumonia, Rhinitis, Sepsis, Staphylococcal infection, Urinary tract infection, Viral infection
Blood and lymphatic system disorders	Febrile neutropenia, Neutropenia	Anaemia, Leukopenia, Thrombocytopenia
Metabolism and nutrition disorders		Metabolic acidosis, Hypervolaemia
Psychiatric disorders		Insomnia
Nervous system disorders		Headache
Respiratory, thoracic and mediastinal disorders		Epistaxis, Oropharyngeal pain
Gastrointestinal disorders	Stomatitis, Vomiting	Ascites, Constipation, Diarrhoea, Dyspepsia, Gastrointestinal haemorrhage, Nausea

System Organ Class	Very Common	Common
Hepatobiliary disorders	Hepatomegaly	Hypertransaminasaemia, Hypoalbuminaemia, Veno-occlusive liver disease
Skin and subcutaneous tissue disorders		Skin exfoliation, Dermatitis diaper, Pruritus, Rash
Musculoskeletal and connective tissue disorders		Arthralgia, Back pain, Bone pain
Renal and urinary disorders		Oliguria
Reproductive system and breast disorders	Ovarian failure	
General disorders and administration site conditions		Pyrexia, Mucosal inflammation
Investigations		Alanine aminotransferase increased, Aspartate aminotransferase increased, Aspergillus test positive, Hepatic enzyme increased, Transaminases increased

** Based on 49 patients who have undergone myeloablative conditioning by busulfan in the integrated safety set.*

Description of selected adverse reactions

Presence of Anti-ARSA Antibodies
All patients (N=39) in the clinical studies were tested for anti-ARSA antibodies (AAA) and 15% had a positive result. A similar percentage of patients treated either in the context of nominal compassionate use or commercial setting had positive AAA results reported (see section 4.4).
Antibody titres were generally low and the majority of cases resolved either spontaneously or after treatment with rituximab.
Patients treated with Libmeldy should be regularly monitored for AAA (see section 4.4).

Peripheral blood mobilisation and apheresis
During the clinical studies, haematopoietic stem cell collection was performed either through bone marrow harvest or peripheral blood mobilisation. The safety profile of the bone marrow harvest and mobilisation/apheresis were consistent with the known safety and tolerability of both procedures and the SmPC of mobilisation agents (G-CSF and plerixafor).
No serious adverse events were reported as potentially attributable to mobilisation and apheresis and none of the patients who underwent mobilisation experienced any adverse events in the pre-treatment phase which could have been attributed to the mobilising agents.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of Libmeldy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, ATC code: A16AB21.

Mechanism of action

Libmeldy is an *ex vivo* genetically modified autologous $CD34^+$ haematopoietic stem and progenitor cell (HSPC) gene therapy. 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 HSPCs 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 build-up, of harmful sulfatides.
Following successful and stable engraftment in the patient, the effects of the product are expected to be persistent.

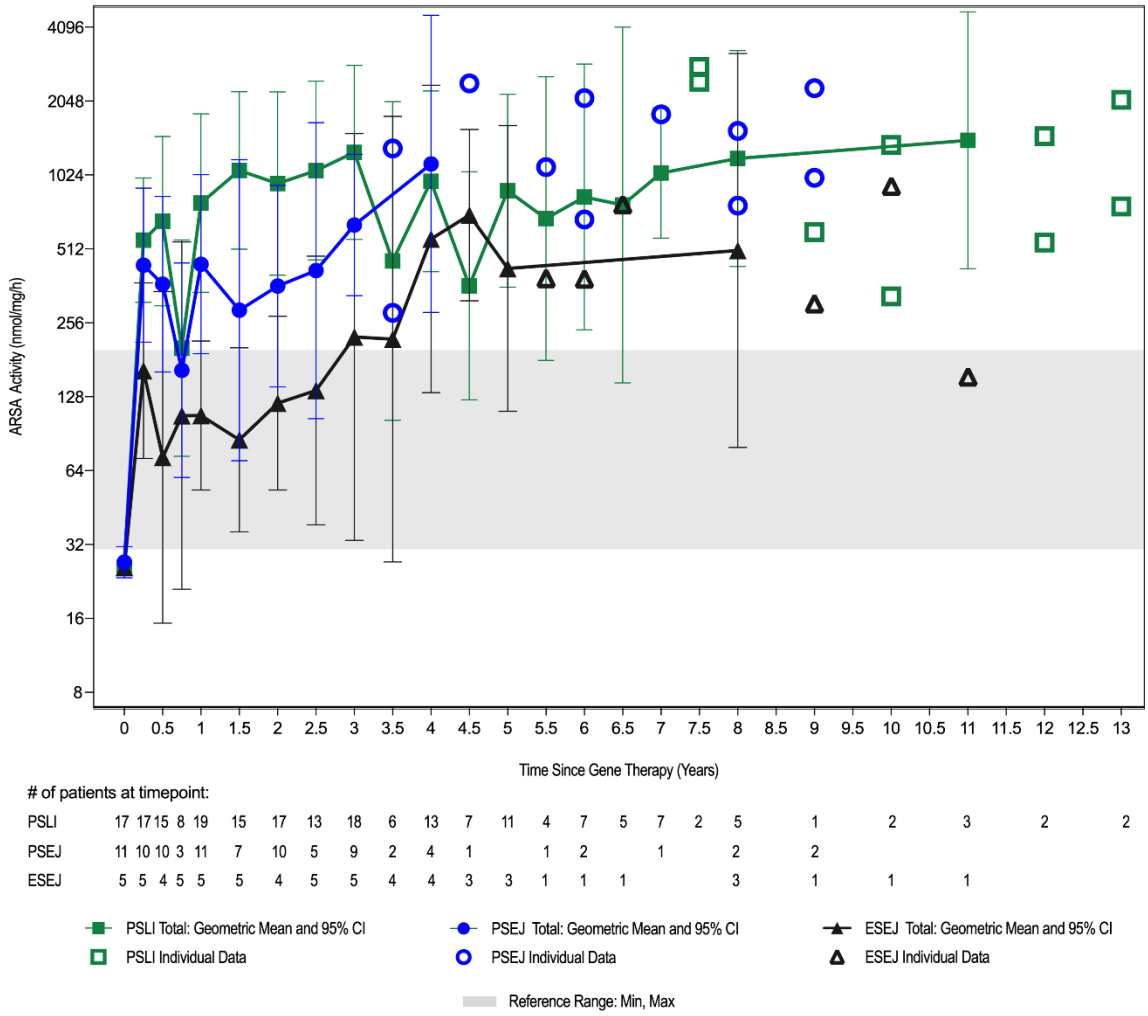
Pharmacodynamic effects

Durable and stable peripheral engraftment of genetically modified cells, i.e. vector copy number (VCN) in total peripheral blood mononuclear cells (PBMCs), was observed from 1-month post Libmeldy administration and continued throughout the follow-up period. A persistent VCN was also observed in $CD34^+$ cells isolated from the bone marrow throughout the follow-up period. Biological findings demonstrate a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting the long-term production of ARSA and resulting in long-term clinical benefit.

At Year 1 post-treatment, the geometric mean proportion of BM-derived colonies harbouring the LVV genome ($\%LV^+$) in PSLI, PSEJ and ESEJ patients treated in the clinical studies was 56.9% (95% CI: 47.6 to 68.0%, [n=33]). The geometric mean proportion of BM-derived colonies harbouring the LVV genome ($\%LV^+$) at Year 5 was 59.8% (95% CI: 45.6% to 78.5%, [n=15]), indicative of stable engraftment over time in the treated population.

Reconstitution of ARSA activity in the haematopoietic system was observed in all PSLI, PSEJ and ESEJ MLD patients treated in the clinical studies, with a progressive reconstitution of ARSA levels in PBMCs which reached geometric mean values within the normal reference range by 3 months post-treatment and remained stable within or above the normal range throughout the duration of the follow-up (see Figure 1).

Figure 1 ARSA activity in PBMCs over time (geometric mean and 95% CIs) in PSLI, PSEJ and ESEJ patients (N=35)



Note: Values < LLQ are imputed at LLQ. LLQ is 25.79 nmol/mg/h. Geometric means and 95% CIs are presented where there are at least 3 patients with non-missing data.
ARSA: arylsulfatase A; CI: confidence interval; LLQ: lower limit of quantification; PBMCs: peripheral blood mononuclear cells; PSLI: pre-symptomatic late infantile; PSEJ: pre-symptomatic early juvenile; ESEJ: early symptomatic early juvenile.

ARSA activity was also measured in cerebrospinal fluid (CSF) as a surrogate compartment of metabolic correction in the brain. The geometric mean value for ARSA activity in CSF increased from undetectable at Baseline to within the reference range by 6 months post-treatment and was maintained near or within the reference range throughout follow up.

Clinical efficacy

Clinical efficacy was evaluated in the integrated efficacy set (N=45), including PSLI, PSEJ, ESEJ MLD patients treated with Libmeldy. This included patients treated in the Registrational Study (Study 201222), patients treated in a study with the commercial (cryopreserved) formulation (Study 205756), patients treated in the context of 3 expanded access programs, and patients enrolled in an observational long-term follow up study and treated either in the nominal compassionate use or the commercial setting.
The median duration of post-treatment follow-up was 6.1 years in PSLI patients (range: 2.0 to 13.2 years), 3.3 years in PSEJ patients (range: 0.6 to 11.0 years) and 9.2 years in ESEJ patients (range: 0.5 to 10.9 years).

The MLD disease spectrum can present in a variety of clinical forms, primarily based on the age of onset of the first symptoms of the disease. PSLI, PSEJ and ESEJ MLD patients, with biallelic

mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity were included in the clinical studies of Libmeldy. 'Biallelic mutations leading to a reduction of the ARSA enzymatic activity' refers to mutations leading to partial or total disruption of the ARSA enzymatic activity and resulting in accumulation of sulfatides. These biallelic mutations exclude common neutral mutations described in association with ARSA pseudo-deficiency alleles.

Patients and disease characteristics

The MLD subtypes were defined by the presence of the following criteria during the clinical development:

- Late infantile (LI): age at onset of symptoms in the older sibling(s) ≤ 30 months and/or 2 null (0) mutant ARSA alleles and/or peripheral neuropathy at electroneurography (ENG) study.
- Early juvenile (EJ): age at onset of symptoms (in the patient or in the older sibling) between 30 months and before 7 years, and/or 1 null (0) and 1 residual (R) mutant ARSA allele(s) and/or peripheral neuropathy at ENG study.

In the above definition, null (0) or residual (R) alleles refer to either known or novel mutations.

The symptomatic status of the patients was defined as follows:

- Pre-symptomatic: at time of inclusion into the clinical studies, LI or EJ patients were without neurological impairment (disease-related symptoms), with or without signs of the disease revealed by instrumental evaluations i.e. electroneurographic study (ENG) and brain magnetic resonance imaging (MRI).

  Based on an analysis of the baseline characteristics of pre-symptomatic LI and EJ patients treated during the clinical development program, the definition of pre-symptomatic status was further refined to maximise the treatment benefit.
  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 the analysis of clinically relevant benefits on the motor and cognitive functions, efficacy was only demonstrated in patients treated before the onset of cognitive deterioration at a time when they were still able to walk independently.
  Taking these results into consideration, treatment with Libmeldy of a patient with an early-symptomatic EJ form of the disease should be considered:
  - If this patient is able to walk independently, which means that the patient's GMFC-MLD (Gross Motor Function Classification for Metachromatic Leukodystrophy) score is ≤ 1, and
  - If the patient's cognitive function is not rapidly declining, and the patient's IQ is ≥ 85.

Of the 45 MLD patients in the integrated efficacy set, 24 were PSLI, 14 were PSEJ and 7 were ESEJ (see Table 3). All presymptomatic patients were identified after an older sibling had developed symptoms and received an MLD diagnosis, prompting testing in other family members.

Table 3 Summary of demographic characteristics of the PSLI, PSEJ and ESEJ patients at time of gene therapy (Integrated efficacy set [N=45])

	PSLI (n=24)	PSEJ (n =14)	ESEJ (n=7)
Sex, n (%)			
Female	9 (38)	3 (21)	3 (43)
Male	15 (63)	11 (79)	4 (57)
Age at GT, in years			
Median	0.9	3.1	7.8
Min	0.6	0.8	3.2
Max	1.5	6.3	11.6

Mobilisation and apheresis

During the clinical studies, 17 patients with data available for whom the decision was made to use mPB as the source material – and not to conduct a bone marrow harvest - were administered G-CSF (range 7.9-13.6 mcg/kg/day) to mobilise $CD34^+$ cells prior to the apheresis procedure. Starting from day 3 of G-CSF administration, an additional mobilising agent, plerixafor, was given once daily (range 0.22–0.37 mg/kg, subcutaneous), if clinically indicated, depending on the white blood cells and $CD34^+$ cell counts in the patient's peripheral blood. Apheresis was performed as soon as the $CD34^+$ cell count reached an adequate level, according to standard procedures.

If the target number of collected $CD34^+$ cells to manufacture Libmeldy and to provide the back-up transplant were not reached with a single apheresis, a second procedure was performed. For all patients, the minimum number of $CD34^+$ cells to manufacture Libmeldy (8×10^6 $CD34^+$ cells/kg) was collected with 1 cycle of mobilisation and 1 or 2 days of apheresis.

Pre-treatment conditioning

Pre-treatment conditioning exposure was evaluated in the integrated safety set (n=49).

All 49 patients received systemic conditioning with busulfan prior to treatment with Libmeldy. The median cumulative area under the curve (AUC) was 79 964 mcg*h/L in the integrated safety set (range 63 420 to 88 310 mcg*h/L [N= 49]). The median cumulative AUC was 79 948 mcg*h/L in the PSLI patients (range 63 420 to 87 741 mcg*h/L [n=24]), 79 995 in the PSEJ patients (range 72 000 to 84 995 mcg*h/L [n=14]), and 79 299 mcg*h/L in the ESEJ patients (range 70 843 to 85 000 mcg*h/L [n=7]).

In the patients from the integrated safety set who were treated in clinical development studies or the EAP (n=39), thirteen patients (33.3%) were treated with a sub-myeloablative conditioning (SMAC) regimen, defined as a target cumulative AUC of 67 200 mcg*h/L. Twenty-six patients (66.7%) were treated with a myeloablative (MAC) conditioning regimen, defined as a target cumulative AUC of 85 000 mcg*h/L.

For the SMAC conditioning regimen, patients received a total of 14 doses of busulfan (according to patient's weight), as a 2-hour intravenous infusion administered every 6 hours from Day -4 to Day -1. Busulfan plasma levels were monitored by serial pharmacokinetic sampling and adjusted using a target dose AUC of 4 800 mcg*h/L (range: 4 200 to 5 600 mcg*h/L), which corresponds to an expected cumulative AUC of 67 200 mcg*h/L (range 58 800 to 78 400 mcg*h/L). The average, cumulative AUC in patients who received a SMAC regimen was higher than expected but remained within the target range (median 70 843 mcg*h/L; range 63 420 to 84 305 mcg*h/L).

For the MAC conditioning regimen, patients received body-surface area-based dosing of busulfan according to the patients age (80 mg/m^2/dose if ≤ 1 year; 120 mg/m^2/dose if > 1 year) for a total of 4 doses, administered as a 3-hour intravenous infusion every 20 to 24 hours from Day -4 to Day -1. Busulfan plasma levels were monitored by serial pharmacokinetic sampling and adjusted using a target cumulative AUC of 85 000 mcg*h/L (range: 76 500 to 93 500 mcg*h/L). The average, cumulative AUC in patients who received a MAC regimen remained within the target range (median 80 036 mcg*h/L; range 78 000 to 88 310 mcg*h/L).

Subgroup analyses by conditioning regimen i.e. comparison of the subgroups of patients who received the MAC vs. the SMAC regimen, didn't show noticeable differences in the level of transduced cell engraftment nor in ARSA enzyme activity (in total PBMCs and BM-derived mononuclear cells). Moreover, the safety profiles of both regimens were shown to be comparable.

The decision to use the MAC or SMAC regimen for pre-treatment conditioning is at the discretion of the treating physician, taking into consideration the patient's clinical characteristics such as, but not limited to, age, hepatic function, prematurity and thrombophilia. A fully myeloablative busulfan regimen is recommended (see section 4.2).

During clinical development, prophylaxis for veno-occlusive disease (VOD) and related endothelial injury complications was required per institutional practice with ursodeoxycholic acid or defibrotide.

Libmeldy administration

All patients (N=49) were administered the medicinal product with a median (min, max) cell dose of 14.3 x 10^6 (4.2, 37.2) $CD34^+$ cells/kg as an intravenous infusion.

Integrated efficacy results in PSLI, PSEJ and ESEJ MLD patients (N=45)

GMFM and ARSA activity in PBMCs

In the registrational study of Libmeldy (Study 201222), the co-primary efficacy endpoints were:

- Gross Motor Function Measure (GMFM): An improvement of > 10% of the total GMFM score in treated patients, when compared to the GMFM scores in the age-matched, untreated historical control MLD population (i.e. TIGET natural history [NHx] Study), evaluated at Year 2 after treatment (see Table 4), and

- ARSA activity: A significant (≥ 2 SD) increase in residual ARSA activity as compared to pre-treatment values, measured in peripheral blood mononuclear cells (PBMC) at Year 2 after treatment (see Pharmacodynamic Effects, Figure 1 and Table 5).

Data are presented for these endpoints at 2-, 3- and 5-years post treatment for the integrated efficacy population (n=45) for PSLI, PSEJ and ESEJ patients. Early-onset MLD patients treated before the onset of overt symptoms showed normal motor development, stabilisation, or slowing in the rate of progression of motor dysfunction as measured by GMFM total score (%) (see Table 4).

Using an ANCOVA model adjusted for age at GMFM assessment and treatment, the mean difference between treated PSLI patients and age-matched untreated LI patients from the NHx study was 70.5% at Year 2, 82.5% at Year 3 and 81.7% at Year 5. The mean difference between treated PSEJ patients and age matched untreated EJ patients was 45.4% at Year 2 and 49.9% at Year 3. Limited data was available at Year 5 in PSEJ patients. The mean difference between treated ESEJ patients and age matched untreated EJ patients was 41.3% at Year 2 and 43.8% at Year 3. These treatment differences were all statistically significant in favour of Libmeldy.
Although not statistically significant, a clear difference in GMFM total score was also noted between treated ESEJ patients and age matched untreated EJ patients at Year 5 (31.4%; p=0.176).

Table 4 **GMFM total score (%) at Year 2, Year 3 and Year 5 after treatment in PSLI, PSEJ and ESEJ patients with comparison to age-and disease subtype-matched natural history data (integrated efficacy set).**

Years after treatment	Adjusted mean GMFM total score		Mean treatment difference in GMFM total score between treated patients and age-matched untreated natural history patients
	Treated patients	Untreated NHx patients	
PSLI			
Year 2[a]	80.1% (n=17)	9.6% (n=12)	70.5% (95% CI: 62.7 – 78.2); p<0.001
Year 3	86.4% (n=19)	4.0% (n=9)	82.5% (95% CI: 75.1 – 89.8); p<0.001
Year 5	83.3% (n=10)	1.6% (n=9)	81.7% (95% CI: 62.9 – 100.0); p<0.001
PSEJ			
Year 2[a]	95.2% (n=10)	49.9% (n=10)	45.4% (95% CI: 21.9 – 68.8); p=0.002
Year 3	95.4% (n=10)	45.5% (n=11)	49.9% (95% CI: 26.9 – 72.8); p<0.001
Year 5	NC (n=1)	NC (n=1)	NC
ESEJ			
Year 2[a]	75.9% (n=5)	34.6% (n=11)	41.3% (95% CI: 2.0– 80.6); p=0.041
Year 3	69.6% (n=5)	25.8% (n=10)	43.8% (95% CI: 4.1 – 83.5); p=0.034
Year 5	44.9% (n=3)	13.6% (n=7)	31.4% (95% CI: -23.6 – 86.3); p=0.176

[a] The Gross Motor Function Measure at two years after treatment was a co-primary endpoint of the registrational clinical study. Note: Analysis of covariance adjusting for treatment and age. P-values are from a two-sided 5% hypothesis test with null hypothesis of 10% difference.
CI: confidence interval; GMFM: gross motor function measurement; NC: not calculated; NHx: natural history.

A statistically significant increase in ARSA activity in PBMCs was observed post-treatment compared to pre-treatment baseline levels at Year 2 (46.2 fold increase; p<0.001), Year 3 (54.7 fold increase; p<0.001) and Year 5 (43.1 fold increase; p<0.001) in PSLI patients. In PSEJ patients, a statistically significant increase in ARSA activity in PBMCs was observed at Year 2 (13.4 fold increase; p<0.001) and Year 3 (26.5 fold increase; p<0.001). Limited data were available at Year 5 in PSEJ patients. In ESEJ patients, statistically significant increase in ARSA activity in PBMCs was observed at Year 2 (4.7 fold increase; p=0.033), Year 3 (8.7 fold increase; p=0.004) and Year 5 (16.6 fold increase; p=0.002) (see Table 5).

Table 5 ARSA activity measured in PBMCs (nmol/mg/h) at Baseline, Year 2, Year 3 and Year 5 after treatment in PSLI, PSEJ and ESEJ patients (integrated efficacy set).

	Adjusted Mean ARSA Activity in PBMCs				Fold Increase from Baseline to Year 2[a]	Fold Increase from Baseline to Year 3	Fold Increase from Baseline to Year 5
	Baseline	**Year 2**	**Year 3**	**Year 5**			
PSLI	25.9 (95% CI: 15.1, 44.3) (n=21)	1 195.7 (95% CI: 652.9, 2 189.7) (n=15)	1 416.9 (95% CI: 782.8, 2 564.3) (n=17)	1 116.5 (95% CI: 543.8, 2 292.5) (n=9)	46.2 (95% CI: 18.0, 118.5) p<0.001	54.7 (95% CI: 26.9, 111.1) p<0.001	43.1 (95% CI: 21.4, 86.7) p<0.001
PSEJ	27.5 (95% CI: 15.5, 48.9) (n=11)	368.0 (95% CI: 200.7, 675.0) (n=10)	730.6 (95% CI: 400.4, 1 333.4) (n=9)	NC (n=0)	13.4 (95% CI: 5.8, 30.8) p<0.001	26.5 (95% CI: 15.3, 46.1) p<0.001	NC
ESEJ	26.2 (95% CI: 10.9, 63.3) (n=5)	122.1 (95% CI: 44.1, 338.0) (n= 4)	227.6 (95% CI: 94.3, 549.5) (n=5)	435.1 (95% CI: 129.4, 1 463.3) (n=3)	4.7 (95% CI: 1.2, 18.6) p=0.033	8.7 (95% CI: 2.4, 31.6) p=0.004	16.6 (95% CI: 3.6, 76.6) p=0.002

[a] Ratio in adjusted means from a mixed model repeated measures of data on the log scale, adjusting for visit, baseline, baseline by visit interaction, disease subtype and disease subtype by visit interaction. CI: confidence interval; NC: not calculated.

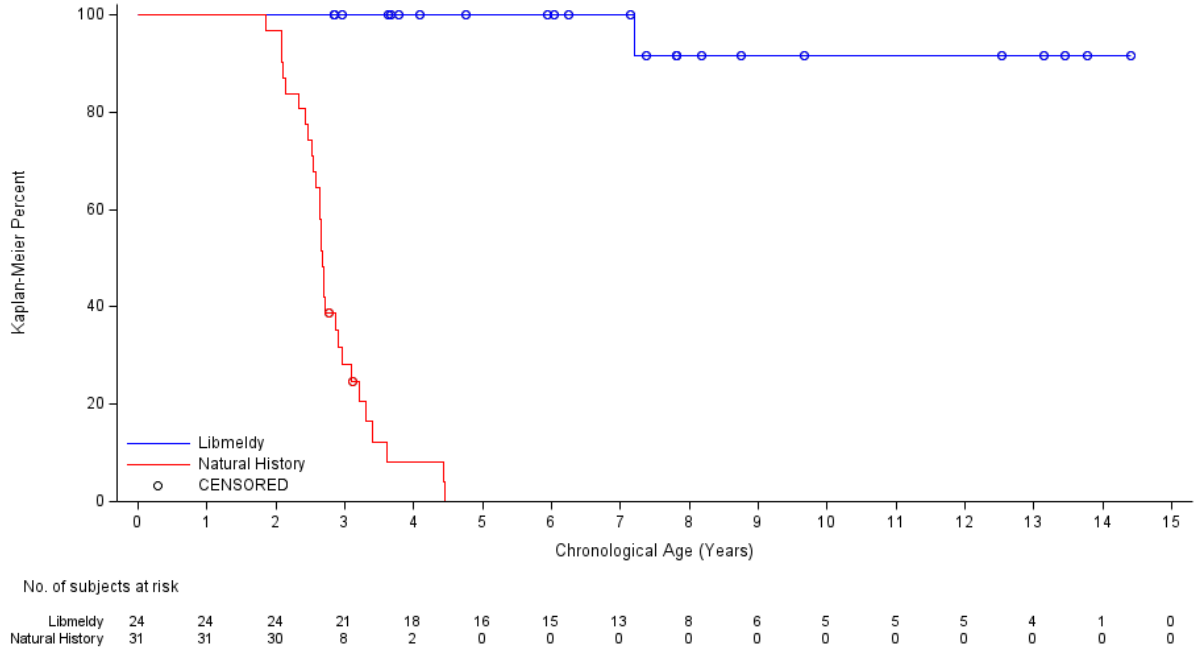
Severe motor impairment free survival

Deterioration of gross motor function was also assessed using the endpoint severe motor impairment-free survival (interval from birth to the earlier of the first occurrence of GMFC-MLD level 5 or higher or death) in the PSLI, PSEJ and ESEJ patients in the integrated efficacy set (N=45).

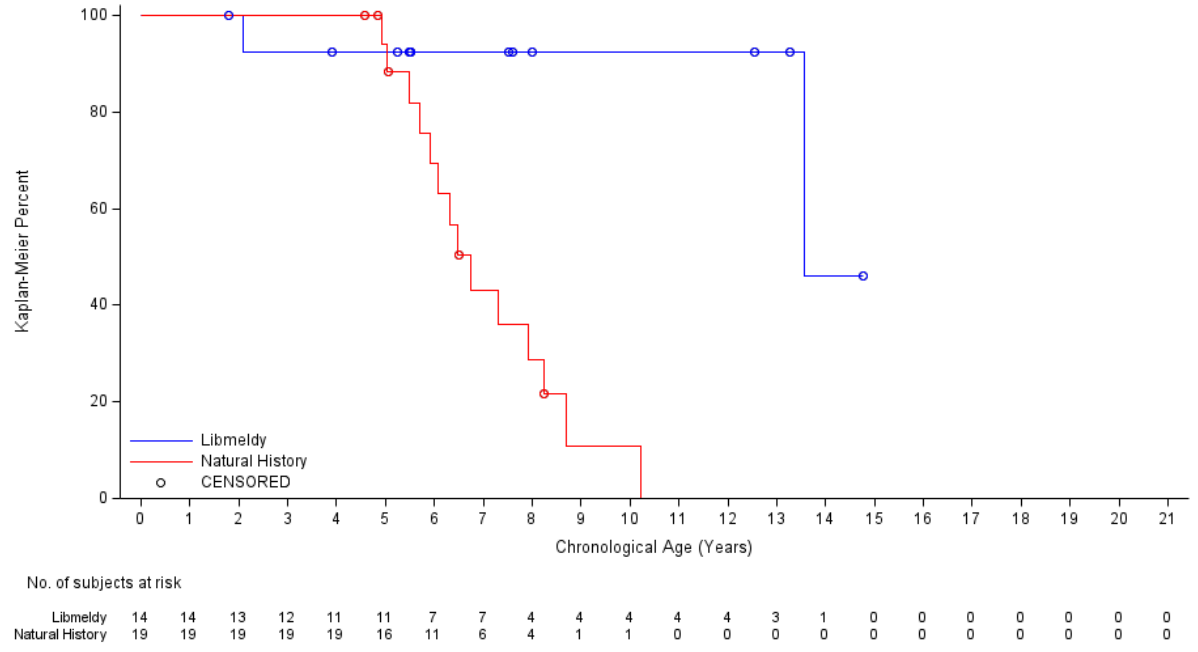
The risk of experiencing severe motor impairment (GMFC-MLD Level ≥5) or death was significantly reduced in the treated PSLI, PSEJ, and ESEJ patients versus MLD subtype-matched NHx patients (unstratified log rank test p<0.001 [PSLI], p=0.001 [PSEJ], p<0.001 [ESEJ]) (see Figure 2).

Figure 2: Kaplan-Meier Plot of Severe Motor Impairment-free Survival by Treatment in PSLI, PSEJ and ESEJ Treated Patients

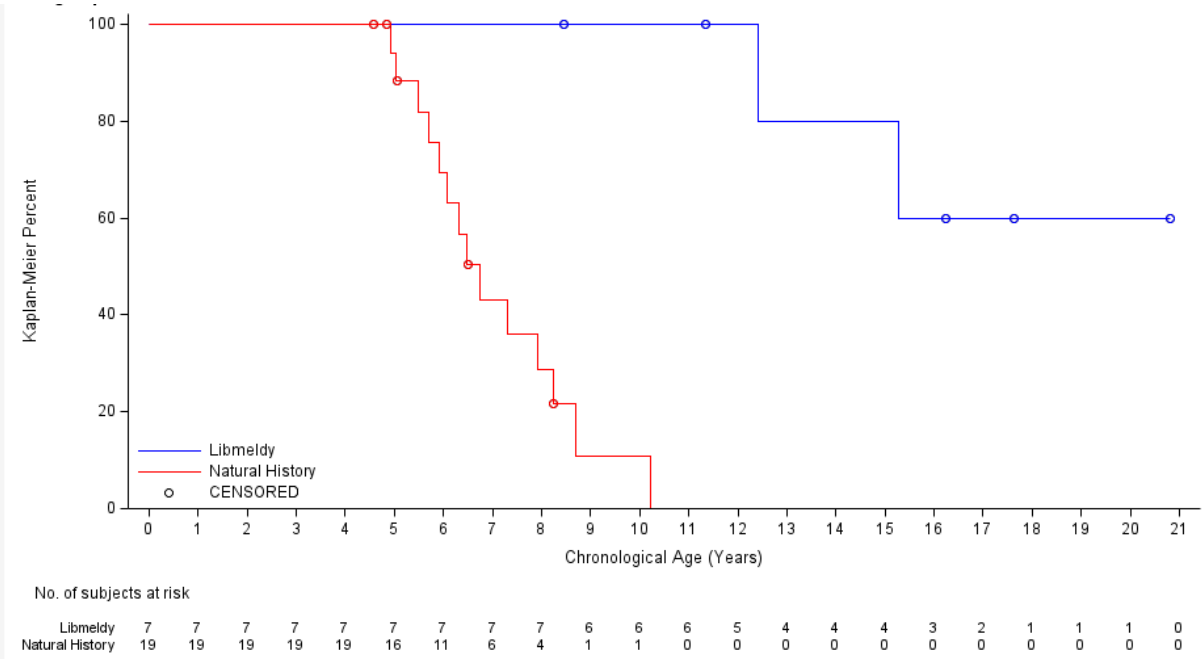
PSLI



PSEJ



ESEJ



Severe motor impairment-free survival is defined as the interval from birth to the earlier of loss of locomotion and sitting without support (GMFC-MLD Level 5 or higher) or death from any cause; otherwise, patient is censored at the last GMFC-MLD assessment date.

Cognition

Cognition was assessed in the integrated efficacy set (N=45) in PSLI, PSEJ and ESEJ patients. Cognitive function was defined as follows: normal cognitive function, IQ score ≥ 85; mild cognitive impairment, IQ score ≥ 70 and < 85; moderate cognitive impairment, IQ score > 55 and < 70; severe cognitive impairment, IQ score ≤ 55. Cognitive function was assessed on a regular basis by performance IQ (PIQ) as well as verbal IQ (VIQ).

For the PSLI group, data from 24 patients are available over a median period of 4.3 years (range 0.9 to 13.2 years) post-treatment. At last available follow up for the PIQ, a total of 17/24 scored ≥ 85, 5/24 patients scored ≥ 70 and < 85, 1/24 scored > 55 and < 70 and 1/24 scored ≤ 55. At last available follow-up, for the VIQ, 14/24 scored ≥ 85, 7/24 scored ≥ 70 and < 85 and 3/24 scored > 55 and < 70, indicating that the majority of treated PSLI patients had a normal or mildly impaired cognitive function. Untreated LI patients showed severe cognitive impairment, with most patients at the lowest levels of cognition.

For the PSEJ group, data from 10 patients are available over a median period of 3.5 years (range 1.9 to 9.2 years) post-treatment. At last available follow-up for the PIQ, all 10 patients scored ≥ 85. At last available follow-up for the VIQ, 9/10 scored ≥ 85, and 1/10 scored ≥ 70 and < 85, indicating that the majority of treated PSEJ patients had normal or mildly impaired cognitive function. For the ESEJ group, data from 5 patients, are available over a median period of 3.5 years (range 1.9 to 9.2 years) post-treatment. At last available follow-up for the PIQ, 2/5 scored ≥ 85, 3/5 scored ≥ 70 and < 85. At last available follow-up for the VIQ, 1/5 scored ≥ 85, 2/5 scored ≥ 70 and < 85, and 2/5 scored > 55 and < 70, indicating that the majority of treated ESEJ patients had normal or mildly impaired cognitive function. Untreated EJ patients showed severe cognitive impairment, with most patients at the lowest levels of cognition.

Overall survival

The risk of death was significantly reduced in PSLI patients compared with NHx LI patients (unstratified log rank test p<0.001). No treated PSLI patients have died and 6 of 24 patients

reached 10 years of age. In comparison, 20 of 31 NHx LI patients (65%) have died and the median actual age at death for the NHx LI patients was 5.9 years (range 3.5 to 13.4 years).

The risk of death for treated EJ patients (PSEJ and ESEJ) was similar to the risk for the NHx EJ patients (unstratified log rank test p=0.976 [PSEJ], p=0.153 [ESEJ]). The untreated NHx EJ patients all progressed to a severely debilitated state (see Figure 2) while EJ patients treated with Libmeldy maintained motor and cognitive abilities.

One out of 14 (7%) PSEJ patients died, due to cerebral ischemic infarction, not considered to be related to Libmeldy.

Of note, there were 2 other deaths due to disease progression among EJ patients from the registrational study (Study 201222), who had entered the rapidly progressive phase of the disease at time of treatment (see next section). Both deaths were not considered to be related to Libmeldy treatment.

Patients with advanced symptoms treated with Libmeldy during clinical development (n=4)

One LI and 3 EJ patients treated as part of the clinical studies were not included in the integrated efficacy population as their disease was too advanced at time of treatment.

- The LI patient experienced onset of disease-related symptoms between screening and administration of Libmeldy and was considered symptomatic at the time of treatment. The progression of this patient post-treatment was comparable to untreated NHx patients in both cognitive and motor functions.
- Three symptomatic EJ patients who had passed the early symptomatic stage and entered the rapidly progressive phase of the disease at time of treatment with Libmeldy showed deterioration in both motor and cognitive functions comparable to that observed in untreated NHx patients and progression of the disease led to death in two of them. Two out of the three patients showed deterioration between screening and baseline assessments (at onset of conditioning regimen) and had IQ < 85 (82 and 58) at baseline. The third patient had progressive motor impairment, impaired speech and multiple neurological abnormalities at the time of treatment.

Paediatric population

Libmeldy has been studied in infants and children with an age range between 0.6 and 11.6 years at time of treatment.
The European Medicines Agency has deferred the obligation to submit the results of studies with Libmeldy in the late juvenile subset of the paediatric population with metachromatic leukodystrophy (i.e. MLD patients aged between 7 and less than 17 years at time of disease onset) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Libmeldy is a gene therapy medicinal product consisting of autologous cells that have been genetically modified *ex vivo*. The nature of Libmeldy is such that conventional studies on pharmacokinetics, absorption, metabolism, and elimination are not applicable. The biodistribution of Libmeldy and progeny cells was nonetheless studied and evidence of biodistribution to haematopoietic tissues and disease target organs (including the brain) was observed.

5.3 Preclinical safety data

Due to the nature of Libmeldy, a standard toxicological assessment was not applicable and conventional mutagenicity, carcinogenicity and reproductive and developmental toxicity studies have not been conducted.
The pharmacology, toxicology and genotoxicity of Libmeldy were evaluated *in vitro* and *in vivo*. Integration site analysis (ISA) of mouse Lin- bone marrow cells and human $CD34^+$ cells transduced with ARSA LVV was conducted pre- and post-transplantation into mice and showed no enrichment

for insertion in or near cancer-related genes, or clonal dominance. A prototype lentiviral vector related to ARSA LVV did not induce *in vitro* transformation and sustained growth of transduced wild type mouse Lin- bone marrow cells due to insertional transformation. Lin- bone marrow cells from Cdkn2a-/- mice, a strain prone to cancer triggered by gamma-retroviral insertional mutagenesis, transduced with the same prototype lentiviral vector did not show genotoxic potential when transplanted into wild type mice.
Toxicity and oncogenesis (tumorigenicity) studies were performed in the mouse model of MLD. No evidence of toxicity due to ARSA overexpression and no abnormal or malignant growth of transplanted cells or haematopoietic tumours related to the integration of ARSA LVV were observed. ARSA overexpression in human HSPCs and in ARSA Tg mice did not impair the activation of other sulfatases dependent on the sulfatase activator SUMF-1, did not affect the proliferation and differentiation capacities of transduced cells and did not induce toxicity or functional impairment in ARSA Tg mice.
Additional studies with human $CD34^+$ cells transduced with ARSA LVV administered to immunodeficient, myeloablated mice demonstrated no toxicity, no vector mobilisation and bystander transduction of male gonads.
Molecular monitoring did not detect replication competent lentivirus (RCL).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylsulfoxide
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

6 months.

Once thawed: maximum 2 hours at room temperature (20 °C-25 °C).

6.4 Special precautions for storage

Keep the infusion bag(s) in the metal cassette(s).

Libmeldy must be stored in the vapour phase of liquid nitrogen (< -130 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Thawed medicinal product should not be refrozen.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mL ethylene vinyl acetate (EVA) infusion bag(s) with two available spike ports, packed in an EVA overwrap bag placed inside a metal cassette.

Libmeldy is shipped from the manufacturing facility to the treatment centre storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. Each metal cassette contains one infusion bag of Libmeldy.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains human blood cells. Healthcare professionals handling Libmeldy must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
- Libmeldy must remain at < -130 °C at all times, until the content of the bag is thawed for infusion.

Definition of the dose to be administered

- Considering the posology information provided in section 4.2, the dose to be infused and number of infusion bags to be used should be defined based on the total number of $CD34^+$ cells supplied indicated on the Lot Information Sheet (i.e. the 'supplied dose', calculated based on patient's weight at time of cell harvest). The dose of Libmeldy to be administered should also take into account the patient's weight at the time of treatment, and the fact that any bag used should be administered in its entirety.

Preparation prior to administration

- A patient may have multiple infusion bags. Each infusion bag is provided inside an overwrap bag, which is contained in a metal cassette.
- The overwrapped infusion bag(s) must be kept inside the metal cassette(s) in the vapour phase of liquid nitrogen at < -130 °C until ready to thaw and infuse.
- Account for all infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be available to prime the tubing prior to infusion, and to flush the infusion bag and tubing after infusion.

Checking prior to thawing

- Do not remove the metal cassette from cryogenic storage or thaw Libmeldy until the patient is ready to be infused. The timing of thaw of the infusion bag(s) containing Libmeldy and of the infusion should be coordinated. Confirm the infusion time in advance and adjust the start time for thaw so that the treatment is available for infusion when the patient is ready.
- Open the metal cassette and inspect the overwrap bag and infusion bag for any breaches of integrity before thawing. If an infusion bag is compromised, follow the local guidelines for handling of waste of human-derived material and contact Orchard Therapeutics immediately.
- Prior to thawing Libmeldy, it must be verified that the patient identity matches the unique patient information reported on the packaging labels and on the accompanying Lot Information Sheet. Libmeldy is intended solely for autologous use. Do not thaw or infuse Libmeldy if the information on the patient-specific label on the infusion bag does not match the intended patient.

Thawing

- After careful removal from the metal cassette, thaw the infusion bag in its sealed overwrap bag at 37 °C in a controlled thawing device until there is no visible ice in the infusion bag.
- Once thawing is complete, the bag should be removed immediately from the thawing device.
- The overwrap bag should be carefully opened to remove the infusion bag which should be kept at room temperature (20 °C-25 °C) until infusion.
- Gently massage the infusion bag to resuspend the cells. The content of the infusion bag should be inspected for any remaining visible cellular aggregates. Small clumps of cellular material should disperse with gentle manual mixing. Do not shake the bag.

- The infusion bag should not be washed, spun down, sampled and/or resuspended in new media prior to infusion.
- Libmeldy should not be irradiated as irradiation could lead to inactivation of the product.
- If more than one infusion bag is provided for the patient treatment dose, the next bag should only be thawed after the content of the preceding bag has been fully infused.

Administration

- Libmeldy should be administered as an intravenous infusion via a central venous catheter, per the administration site's standard procedures for cell therapy products.
- The recommended administration set consists of a blood transfusion set equipped with a 200 µm filter.
- Each bag should be infused by gravity within 2 hours of thaw, including any interruption during the infusion, to maintain maximum product viability.
- The maximum infusion rate is 5 mL/kg/h, and the content of each bag should be infused within approximately 30 minutes.
- When more than one bag of Libmeldy is needed, only one bag of product should be infused per hour.
- Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored prior to the start of the infusion, during the infusion and after the infusion of each Libmeldy bag as per institution guidelines.
- At the end of the infusion, flush all Libmeldy remaining in the infusion bag and any associated tubing with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that as many cells as possible are infused into the patient. Careful consideration must be given to the volume of infusion in relation to the age and weight of the patient.

Measures to take in case of accidental exposure

- In case of accidental exposure local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Libmeldy must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

- Unused medicinal product and all material that has been in contact with Libmeldy (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.

7. MARKETING AUTHORISATION HOLDER

Orchard Therapeutics (Netherlands) B.V.
Bargelaan 200,
2333 CW Leiden,
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/20/1493/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2020

Date of latest renewal: 21 November 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AGC Biologics S.p.A.
Zambon Scientific Park
Via Meucci 3
20091 Bresso (MI)
Italy

Name and address of the manufacturer responsible for batch release

AGC Biologics S.p.A.
Zambon Scientific Park
Via Meucci 3
20091 Bresso (MI)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Libmeldy in each Member State, the MAH will agree about the content and format of the educational 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
- The Guide for healthcare professionals
- The Guide for handling and method of administration.

- **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 oncogenesis, 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 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 to handling and method of administration for healthcare professionals** shall contain the following key elements:

    - Guidance that Libmeldy must be administered in a Qualified Treatment Centre 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.

The patient information pack should contain:
- The Package leaflet
- The Patient and parent/carer guide
- The Patient alert card.

- **The patient and parent/carer guide** shall contain 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.

- **The patient alert card** shall contain 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.

The MAH shall ensure that, in each Member State where Libmeldy is marketed, a system aimed to control its distribution beyond the level of control ensured by routine risk minimisation measures is implemented. The following requirements need to be fulfilled before the product is prescribed, manufactured, dispensed and used:
Libmeldy will only be available through treatment centres qualified by the MAH to ensure traceability of the patient's cells and manufactured drug product between the treating hospital and manufacturing site. The selection of the treatment centres will be conducted in collaboration with national health authorities as appropriate. The healthcare professionals will receive training on the physician educational materials as part of the centre qualification process.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
In order to further characterise the long-term efficacy and safety of Libmeldy in children with late infantile or early juvenile forms of MLD, the MAH shall	Interim reports to be submitted in accordance with the RMP

conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Final study report: March 2046

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE INTERMEDIATE PACKAGING

METAL CASSETTE AND OVERWRAPPING BAG

1. NAME OF THE MEDICINAL PRODUCT

Libmeldy 2-10 x 10^6 cells/mL dispersion for infusion
atidarsagene autotemcel ($CD34^+$ cells)

2. STATEMENT OF ACTIVE SUBSTANCE

An 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. This medicine contains cells of human origin.

3. LIST OF EXCIPIENTS

Also contains dimethylsulfoxide, human albumin and sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
10-20 mL per infusion bag
See Lot information sheet for number of infusion bags and $CD34^+$ cells per bag for this patient.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP
Shelf life after thawing: 2 hours at room temperature (20 °C-25 °C)

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen (< -130 °C). Keep infusion bag in the metal cassette until ready for thaw and administration. Do not unseal the overwrap bag until after thaw. Once thawed do not re-freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchard Therapeutics (Netherlands) B.V.
Bargelaan 200,
2333 CW Leiden,
The Netherlands

12. MARKETING AUTHORISATION NUMBER

EU/1/20/1493/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

First name:
Last name:
Patient DOB:
DIN:
COI ID:
Lot:
Bag ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Libmeldy 2-10 x 10^6 cells/mL dispersion for infusion
atidarsagene autotemcel ($CD34^+$ cells)
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

First name:
Last name:
Patient DOB:
DIN:
COI ID:
Lot:
Bag ID:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10-20 mL of cell dispersion per bag.

See Lot information sheet for number of infusion bags and $CD34^+$ cells per bag for this patient.

6. OTHER

For autologous use only.

PARTICULARS TO APPEAR ON THE LOT INFORMATION SHEET (LIS) INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

An 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.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT, AND DOSE OF THE MEDICINAL PRODUCT

INFORMATION ON SUPPLIED LOT(S)

The following lot(s) is (are) included in the shipment:

Lot number	**Bag ID**	**Volume of dispersion for infusion** (mL)	**Strength** (x 10^6 cells/mL)	**Total $CD34^+$ cells** (x 10^6)	**Expiry date** (DD-MMM-YYYY)

Total number of bags:
Total number of $CD34^+$ cells (x 10^6):

The ***supplied dose*** (calculated based on patient's weight at time of cell harvest) is:
_____ × 10^6 $CD34^+$ cells/kg.

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.

4. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

5. OTHER SPECIAL WARNINGS, IF NECESSARY

SAVE THIS DOCUMENT AND HAVE IT AVAILABLE WHEN PREPARING FOR ADMINISTRATION OF LIBMELDY.

For autologous use only.

6. SPECIAL STORAGE CONDITIONS

INSTRUCTIONS FOR STORAGE AND USE

Store and transport frozen (< -130 °C). Keep infusion bag in the metal cassette until ready for thaw and administration. Do not unseal the overwrap bag until after thaw. Once thawed do not re-freeze.

Shelf life: 6 months at < -130 °C. Shelf life after thawing: 2 hours at room temperature (20 °C-25 °C).

7. EXPIRY DATE AND OTHER BATCH SPECIFIC INFORMATION

Information is presented in the table in section 3 above.

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

9. BATCH NUMBER, DONATION AND PRODUCT CODES

SEC:
First name:
Last name:
Patient DOB:
Weight at first collection (kg):
DIN:
COI ID:

Information related to batch number and Bag ID is presented in the table in section 3 above.

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchard Therapeutics (Netherlands) B.V.
Bargelaan 200,
2333 CW Leiden,
The Netherlands

11. MARKETING AUTHORISATION NUMBER

EU/1/20/1493/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient or carer

Libmeldy 2-10 × 10^6 cells/mL dispersion for infusion
atidarsagene autotemcel ($CD34^+$ cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or nurse.
- Your child's doctor or nurse will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when your child sees them or if your child goes to hospital.
- If your child gets any side effects, talk to your child's doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Libmeldy is and what it is used for

What Libmeldy is

Libmeldy (atidarsagene autotemcel) is a type of medicine called **gene therapy**. It is made specially for your child from your child's own blood cells.

What Libmeldy is used for

Libmeldy is used to treat a serious condition called metachromatic leukodystrophy (MLD):
- in children with the 'late infantile' or 'early juvenile' forms of the disease who have not yet developed any signs or symptoms,
- in children with the 'early juvenile' form of the disease who have started developing symptoms but whose symptoms are not yet worsening rapidly.

People with MLD have a fault in the gene to make an enzyme called arylsulfatase A (ARSA). This leads to a build-up of substances called *sulfatides* in the brain and nervous system, causing damage to the nervous system and progressive loss of physical skills and, later, mental ability, ultimately leading to death.

How does Libmeldy work?

Cells called *stem cells* are collected from your child's blood. They are then modified in a laboratory to insert a working gene for making ARSA. When your child is given Libmeldy, which is made up of these modified cells, the cells will start making ARSA to break down the sulfatides in the nerve cells and other cells of your child's body. This is expected to slow down the progression of the disease and improve your child's quality of life.

Libmeldy is given by a drip (*infusion*) into a vein (*intravenously*). For more information on what happens before and during treatment, see section 3, *How Libmeldy is given*.

If you have any questions about how Libmeldy works or why this medicine has been prescribed to your child, ask your child's doctor.

2. What you need to know before your child is given Libmeldy

Your child must not be given Libmeldy

- if your child is allergic to atidarsagene autotemcel or any of the ingredients of this medicine (listed in section 6). If you think your child may be allergic, ask your doctor for advice.
- if your child has previously had gene therapy made from his/her blood stem cells.
- if your child is allergic to - or if your doctor thinks your child would get unacceptable side effects from - any of the ingredients in the medicines your child will be given before treatment with Libmeldy (see section 3).

Warnings and precautions

Talk to your doctor before your child is given Libmeldy.

- Information about cell-based medicinal products, like Libmeldy, must be kept for 30 years at the hospital. The information kept about your child will be their name and the batch number of Libmeldy they received.

- Libmeldy is made from your child's own stem cells and should only be given to your child.

Before the treatment with Libmeldy

- Evaluation of your child by their doctor to confirm that they have MLD and assess for symptoms and effects of their disease will take place before decision to use Libmeldy is made. Your child may not be showing any physical signs of the disease at the time of initial evaluation.
  If your child's MLD has progressed and has worsened before the initiation of the treatment, their doctor may determine that their disease has reached a 'rapidly progressive phase'. If this happens, your child may not gain benefit from the treatment and your child's doctor may decide not to give Libmeldy.

- Central venous catheters are thin, flexible tubes, that are inserted by a doctor into a large vein to access the bloodstream of your child. The risks of these lines are infections and the formation of blood clots. The doctor and nurses will monitor your child for any central venous catheter complications.

- Libmeldy is tested for the presence of infectious microbes before it is administered to your child. There is a small risk of infection. Your child's doctors and nurses will monitor them throughout the infusion for signs of infection and provide treatment if needed.

- The doctor will check your child's thyroid gland. The thyroid gland is in the neck and it makes hormones that are important to help the body function normally. It will also be monitored after treatment if needed.

After the treatment with Libmeldy

- After the treatment, your child may be asked to enrol in a **follow up study** for up to 15 years to better understand the long-term effects of Libmeldy.

- If your child requires a blood transfusion within the first 3 months after they have received Libmeldy, blood products should be irradiated. This means the white blood cells, called lymphocytes, have been reduced to minimise the risk of a reaction to the transfusion. The doctor will monitor your child for any blood transfusion reaction.

- Your child's blood cells will be low for a period of time after the treatment with Libmeldy. This affects infection fighting blood cells called neutrophils that can be measured with a simple blood test. If your child's neutrophils are still low after 60 days, this may be called 'engraftment failure'. In such case, your child's doctor may decide to return the previously collected rescue cells to your child (see section 3). The rescue cells do not have the working ARSA gene added to them and will not produce the ARSA enzyme.

- After receiving the conditioning medicine, your child may have a low number of platelets in their blood. This means that your child's blood may not be able to clot normally and your child may be prone to bleeding for some time after the treatment. The doctor will monitor your child's platelet count with simple blood tests and provide your child with treatment if required. This may include a transfusion of platelets to help increase their platelet count.

- Metabolic acidosis may occur. It is a condition where the level of acid in the blood rises. There can be many different reasons for this, and the condition is more common in patients with MLD. Symptoms of metabolic acidosis include feeling breathless, rapid breathing, nausea (feeling sick) and vomiting. The doctor will monitor your child for signs and symptoms of metabolic acidosis.

- Inserting a new gene into the stem cells could theoretically cause blood cancers (leukaemia and lymphoma). After the treatment, your doctor will monitor your child for any signs of leukaemia or lymphoma.

- During the clinical studies, some patients developed antibodies to the ARSA enzyme, called anti-ARSA antibodies (see side effects of Libmeldy in section 4). This resolved on its own or after treatment with an appropriate medicine. Your child's doctor will monitor their blood for anti-ARSA antibodies and give treatment if needed.

- After your child has received Libmeldy, they will be monitored with regular blood tests. This will include measurement of antibodies, known as immunoglobulins, in their blood. If their level is low, your child may require immunoglobulin replacement therapy. Your child's doctor will discuss this with you if needed.

- Libmeldy is prepared using parts of the human immunodeficiency virus (HIV), which have been altered so that they cannot cause infection. The altered virus is used to insert the ARSA gene into your child's stem cells. Although this medicine will not give HIV infection to your child, having Libmeldy in their blood may cause a false positive HIV test result with some commercial tests (so-called "PCR-based tests") that recognise a piece of HIV used to make Libmeldy. If your child tests positive for HIV after Libmeldy treatment, please contact your child's doctor or nurse.

- After a treatment with Libmeldy, your child will not be able to donate blood, organs, tissues or cells. This is because Libmeldy is a gene therapy product.

Before your child is given Libmeldy the doctor will:

- Check your child's lungs, heart, kidney, liver, as well as blood pressure.
- Look for signs of infection; any infection will be treated before your child is given Libmeldy.
- Check for hepatitis B, hepatitis C, human T-cell lymphotropic virus (HTLV), HIV or mycoplasma infection.
- Check if your child had a vaccination in the previous 6 weeks or if one is planned in the next few months.

When Libmeldy treatment cannot be completed

Before receiving Libmeldy your child will be given a conditioning medicine to remove cells from their bone marrow.

If Libmeldy cannot be given after your child has had the conditioning medicine, or if the modified stem cells do not take hold *(engraft)* in your child's body, the doctor may decide to return the previously collected rescue cells to your child by infusion (see also section 3, *How Libmeldy is given*). The rescue cells do not have the working ARSA gene added to them and will not produce the ARSA enzyme. For more details, please contact your child's doctor.

Other medicines and Libmeldy

Tell your doctor if your child is taking, has recently taken or might take any other medicines.

- Your child should not take any **medicines for HIV infection** from at least one month before your child is given the mobilisation medicines, until at least 7 days after Libmeldy infusion (see also section 3, *How Libmeldy is made and given*).
- Your child must not be given vaccines called **live vaccines** for 6 weeks before they are given the conditioning medicine to prepare for Libmeldy treatment, nor after treatment while your child's immune system (the body's defence system) is recovering.

Libmeldy contains sodium and dimethylsulfoxide (DMSO)

This medicine contains 35-560 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 2 to 28% of recommended maximum daily dietary intake of sodium for an adult.

If your child has not previously come into contact with DMSO (a substance used to preserve frozen cells), the doctor or nurse should watch your child closely for any reactions during and after the infusion of each bag.

3. How Libmeldy is given

Libmeldy will always be given to your child by a doctor in a qualified treatment centre and will only be given once.

When	What happens	Why
About 2 months before Libmeldy infusion	Mobilisation medicine is given	To move the blood stem cells from your child's bone marrow into the blood stream.
About 2 months before Libmeldy infusion	Blood is collected	To make Libmeldy and to serve as replacement cells if needed.
5 days before Libmeldy infusion	A conditioning medicine is given for 3–4 days in a hospital	To prepare your child's bone marrow for treatment by destroying cells in the bone marrow so they can be replaced

		with the modified cells in Libmeldy.
15 to 30 minutes before Libmeldy infusion	A medicine called an antihistamine may be given	To help prevent an allergic reaction to the infusion.
Start of Libmeldy treatment	Libmeldy is given by a drip (infusion) into a vein. This will be in a hospital and will take about 30 minutes for each infusion bag. The number of bags will vary by patient.	To add stem cells containing the ARSA gene into your child's bone marrow.
After Libmeldy treatment	Your child will remain in the hospital for about 4–12 weeks	To recover and be monitored to check if your child's treatment is working and help if they have any side effects until the doctor is satisfied that it is safe for your child to leave the hospital.

Other medicines your child will be given before Libmeldy

Your child may be given medicines known as **mobilisation medicine** and **conditioning medicine** (see section 4 for more information on possible side effects of these medicines).

Since Libmeldy is made from your child's own stem cells, your child's blood will be drawn from a vein and collected to prepare the medicine about 2 months before treatment.

- Your child will first be given a mobilisation medicine to move the blood stem cells from your child's bone marrow into their blood stream.
- The blood stem cells can then be collected by a machine that separates blood components *(apheresis machine)*. It may take more than 1 day to collect enough blood stem cells to make Libmeldy.

The stem cells collected from the blood will be divided into:

- The **treatment sample**, which will be sent away to make Libmeldy, by inserting a working copy of the ARSA gene into the stem cells in the sample.
- The **backup sample**, which will be frozen and stored, to be given to your child as replacement stem cells if Libmeldy cannot be given or does not work (see 'When Libmeldy treatment cannot be completed' in section 2). Of note, the back-up cells may alternatively be collected from your child's bone marrow. In such a case, your child will be given medicines to relax and prevent pain or make them unconscious before the procedure. The doctor will collect your child's bone marrow using a special syringe.

How your child is given Libmeldy

- Libmeldy will be given to your child in a qualified treatment centre and by doctors trained in using this type of medicine.
- The doctors will check that the Libmeldy infusion bags are all identified as being made from your child's own sample.
- Libmeldy is a one-time treatment. It will not be given to your child again.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects are related to the conditioning medicine used to prepare your child's bone marrow for treatment with Libmeldy.

Talk with your child's doctor about side effects of the conditioning medicine. You may also read the package leaflets for that medicine.

Side effects of the conditioning medicine

➔ **Tell the doctor or nurse immediately** if your child gets any of the following side effects after receiving the conditioning medicine. They usually happen between the first few days and several weeks after receiving the conditioning medicine but can also develop much later.

Very common side effects (may affect more than 1 in 10 people)

- blood tests showing low level of white blood cells without or with a fever
- mouth sores, inflammation of the mouth
- being sick (*vomiting*)
- enlarged liver
- loss of function or decreased function of ovaries

Common side effects (may affect up to 1 in 10 people)

- viral and bacterial infections
- chest infection (*pneumonia*)
- runny nose
- extreme response to an infection
- low level of red blood cells (*anaemia*) or white blood cells
- abnormal bleeding or bruising - may be caused by low level of blood platelets, reducing the ability of blood to clot
- metabolic acidosis, a condition where the acid levels in the blood are high
- excess fluid in body
- trouble sleeping
- headache
- infection of the organs involved in excretion of urine (such as the bladder and urinary tract)
- nosebleeds
- pain in the mouth and throat
- build-up of fluid in the abdomen
- diarrhoea
- bleeding in the digestive tract
- feeling sick (*nausea*)
- constipation
- indigestion
- increase in liver enzymes (transaminases and aminotransferases) seen in blood tests
- decrease in liver enzyme (albumin) seen in blood test
- pain in the right upper abdomen (belly) under the ribs, yellowing of eyes or skin, rapid weight gain, swelling of arms, legs and abdomen, and trouble breathing. These may be signs of a serious liver condition called *veno-occlusive disease*
- skin peeling
- nappy rash
- itchy skin
- skin inflammation

- back pain
- bone pain
- pain in joints
- decreased urine production
- fever
- inflammation of the digestive tract
- positive test for Aspergillus (fungus that may cause lung disease)

Side effects of Libmeldy

The following side effects have been reported with Libmeldy.

Very common side effects (may affect more than 1 in 10 people)
- positive test for antibodies against ARSA. Antibodies are the body's natural defence against anything that the body thinks is foreign.

Reporting of side effects

If your child gets any side effects, talk to your child's doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Libmeldy

The following information is intended for doctors only.

As this medicine will be given in a hospital, the hospital is responsible for the correct storage of the medicine before and during its use, as well as for its correct disposal.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer container and infusion bag labels.

Do not use this medicine if you notice that the infusion bag is damaged or leaking.

Store at < -130 °C for up to 6 months. Do not thaw the product until it is ready to be used. Once thawed, keep at room temperature (20 °C-25 °C) and use within 2 hours. Do not refreeze.

This medicine contains genetically-modified human cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling human-derived material.

6. Contents of the pack and other information

What Libmeldy contains

- The active substance consists of your child's own stem cells that contain working copies of the ARSA gene. The concentration per bag is 2–10 × 10^6 cells per millilitre.

- The other ingredients are a solution used to preserve frozen cells and sodium chloride (see section 2, *Libmeldy contains sodium*).

This medicine contains genetically modified human blood cells.

What Libmeldy looks like and contents of the pack

Libmeldy is a clear to slightly cloudy, colourless to yellow or pink dispersion of cells that is supplied in one or more clear infusion bags, each packed in a pouch inside a closed metal container.

Your child's name and date of birth, as well as coded information identifying your child as the patient, are printed onto each infusion bag and each metal container.

Marketing Authorisation Holder

Orchard Therapeutics (Netherlands) B.V.
Bargelaan 200,
2333 CW Leiden,
The Netherlands

Manufacturer

AGC Biologics S.p.A.
Zambon Scientific Park
Via Meucci 3
20091 Bresso (MI)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Libmeldy.

Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains human blood cells. Healthcare professionals handling Libmeldy must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
- Libmeldy must remain at < -130 °C at all times, until the content of the bag is thawed for infusion.

Defining the dose to be administered

- The dose to be infused and number of Libmeldy infusion bags to be used should be defined based on the total number of $CD34^+$ cells supplied indicated on the Lot Information Sheet (i.e. the 'supplied dose', calculated based on patient's weight at time of cell harvest). The dose of Libmeldy to be administered should also take into account the patient's weight at the time of treatment, and the fact that any bag used should be administered in its entirety.

Preparation prior to administration

- A patient may have multiple infusion bags. Each infusion bag is provided inside an overwrap bag, which is contained in a metal cassette.
- The overwrapped infusion bag(s) must be kept inside the metal cassette(s) in the vapour phase of liquid nitrogen at < -130 °C until ready to thaw and infuse.
- Account for all infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be available to prime the tubing prior to infusion, and to flush the infusion bag and tubing after infusion.

Checking prior to thawing

- Do not remove the metal cassette from cryogenic storage and thaw Libmeldy until the patient is ready to be infused. The timing of thaw of the infusion bag(s) containing Libmeldy and of the infusion should be coordinated. Confirm the infusion time in advance and adjust the start time for thaw so that Libmeldy is available for infusion when the recipient is ready.
- Open the metal cassette and inspect the overwrap bag and infusion bag for any breaches of integrity before thawing. If an infusion bag is compromised, follow the local guidelines on handling of waste of human-derived material and contact Orchard Therapeutics immediately.
- Prior to thawing Libmeldy, it must be verified that the patient identity matches the unique patient information reported on the packaging labels and on the accompanying Lot Information Sheet. Libmeldy is intended solely for autologous use. Do not thaw or infuse Libmeldy if the information on the patient-specific label on the infusion bag does not match the intended patient.

Thawing

- After careful removal from the metal cassette, thaw the infusion bag in its sealed overwrap bag at 37 °C in a controlled thawing device until there is no visible ice in the infusion bag.
- Once thawing is complete, the bag should be removed immediately from the thawing device.
- The overwrap bag should be carefully opened to remove the infusion bag which should be kept at room temperature (20 °C-25 °C) until infusion.
- Gently massage the infusion bag to resuspend the cells. The content of the infusion bag should be inspected for any remaining visible cellular aggregates. Small clumps of cellular material should disperse with gentle manual mixing. Do not shake the bag.
- The infusion bag should not be washed, spun down, sampled and/or resuspended in new media prior to infusion.
- Libmeldy should not be irradiated as irradiation could lead to inactivation of the product.
- If more than one infusion bag is provided for the patient treatment dose, the next bag should only be thawed after the content of the preceding bag has been fully infused.

Administration

- Libmeldy should be administered as an intravenous infusion via a central venous catheter, per the qualified treatment centre's standard procedures for cell therapy products.
- The recommended administration set consists of a blood transfusion set equipped with a 200 µm filter.
- Each bag should be infused by gravity within 2 hours of thaw, including any interruption during the infusion, to maintain maximum product viability.
- The maximum infusion rate is 5 mL/kg/h, and the content of each bag should be infused within approximately 30 minutes.
- When more than one bag of Libmeldy is needed, only one bag of product should be infused per hour.
- Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be

monitored prior to the start of the infusion, during the infusion and after the infusion of each Libmeldy bag as per institution guidelines.

- At the end of the infusion, flush all Libmeldy remaining in the infusion bag and any associated tubing with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that as many cells as possible are infused into the patient. Careful consideration must be given to the volume of infusion in relation to the age and weight of the patient.

Measures to take in case of accidental exposure

- In case of accidental exposure local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Libmeldy must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

- Unused medicinal product and all material that has been in contact with Libmeldy (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.