swissmedic

- *Date:* 7 August 2024

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Libmeldy

International non-proprietary name: atidarsagene autotemcel

Pharmaceutical form: dispersion for infusion

Dosage strength(s): 2 - 10 x 10e6 cells/mL of viable CD34+ cells

Route(s) of administration: intravenous (i.v.) infusion

Marketing authorisation holder: SFL Pharma GmbH

Marketing authorisation no.: 68236

Decision and decision date: approved on 07.12.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for atidarsagene autotemcel in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 10 December 2020.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:
- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,
- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently, and before the onset of cognitive decline.

2.2.2 Approved indication

Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:
- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,
- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently, and before the onset of cognitive decline (see section "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The dose of Libmeldy to be administered is defined based on the patient's body weight at the time of infusion.
The minimum recommended dose of Libmeldy is 3 × 10e6 CD34+ cells/kg. In clinical studies, doses up to 30 × 10e6 CD34+ cells/kg have been administered.
The maximum volume of Libmeldy to be administered should remain < 20% of the patient's estimated plasma volume.
Libmeldy is intended for autologous use and should only be administered once.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	27 October 2022
Formal control completed	10 November 2022

Preliminary decision	10 March 2023
Response to preliminary decision	9 May 2023
Labelling corrections	7 August 2023
Response to labelling corrections	12 September 2023
Final decision	7 December 2023
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available report Libmeldy - EMA/584450/2020, published on 15 October 2020, issued by EMA

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Libmeldy - EMA/584450/2020, published on 15 October 2020, issued by the EMA

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Libmeldy - EMA/584450/2020, published on 15 October 2020, issued by the EMA

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Libmeldy - EMA/584450/2020, published on 15 October 2020, issued by the EMA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Libmeldy was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Libmeldy

Composition

Active substances

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.

Excipients

Dimethylsulfoxide (DMSO), sodium chloride and human albumin.
This medicinal product contains 3.5 mg sodium per mL and 55 mg DMSO per mL.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion. Intravenous (i.v.) infusion only.
A clear to slightly cloudy, colourless to yellow or pink dispersion.

Each patient-specific infusion bag of Libmeldy contains atidarsagene autotemcel at a batch-dependant 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 «Instructions for handling») to be administered, is presented in the Lot Information Sheet located inside the lid of the cryoshipper used for transport.

Indications/Uses

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 late infantile or early juvenile forms, without clinical manifestations of the disease,

- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline (see section «Properties/Effects»).

Dosage/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.

Dosage

Libmeldy is intended for autologous use (see section «Warnings and precautions») 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 x 10^6 $CD34^+$ cells/kg of body weight. In clinical studies, doses up to 30 x 10^6 $CD34^+$ cells/kg have been administered.
The maximum volume of Libmeldy to be administered should remain <20% of the patient's estimated plasma volume (see section «Warnings and precautions» and section «Instructions for handling»).
See the accompanying Lot Information Sheet (LIS) for additional information pertaining to dose.

- Traceability
To ensure traceability the name of the administered medicinal 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.

- 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 x 10^6 $CD34^+$ cells/kg, considering that the optimal range is between 20-30 x 10^6 $CD34^+$ cells/kg.
The minimum $CD34^+$ cell quantity may be achieved using one or more cycles of apheresis.

If, after medicinal product manufacturing, the minimum dose of Libmeldy of 3 x 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 «Properties/Effects»).

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 «Warnings and precautions»).
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 «Properties/Effects» for a description of the mobilisation regimen used in clinical studies).

- Recommended 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 «Warnings and precautions»).
A myeloablative conditioning is required before infusion of Libmeldy to promote efficient engraftment of the genetically modified autologous $CD34^+$ cells (see section «Properties/Effects» 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 an intravenous antihistamine (for example clemastine i.v.), or equivalent medicinal products be administered 15-30 minutes before the infusion of Libmeldy to reduce the possibility of an infusion reaction.

Special dosage instructions

Patients with hepatic disorders

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.

Patients with renal disorders

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.

Elderly patients

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

Children and adolescents

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.

Mode 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.
For instructions on preparation, accidental exposure and disposal of Libmeldy, see section «Instructions for handling».

- 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 « Warnings and precautions»).
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
Administer the product 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 200µm filter (see section «Instructions for handling»).
For detailed instructions on preparation administration, accidental exposure and disposal of Libmeldy, see section «Instructions for handling».

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section «Composition».

Previous treatment with haematopoietic stem cells gene therapy.

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

Warnings and precautions

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 to 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 patients’ age.
Prior to the commencement of cellular harvest, the treating physician should ensure that the patient has not clinically deteriorated. Thereafter, 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 should 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 create 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, approximately every ten minutes during the infusion and every hour, for 3 hours, after the infusion.

When more than one bag of Libmeldy is needed, it should be ensured prior to infusion that the volume of medicinal product to be infused is compatible with the recommended limit of DMSO, i.e. the total volume of DMSO administered should remain <1% of the patient’s estimated plasma volume. The maximum volume of Libmeldy to be administered should therefore remain <20% of the patient’s estimated plasma volume (see section «Instructions for handling»).

Also, when more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour.

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 «Dosage/Administration»).

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, haematological recovery after conditioning with busulfan was typically seen four to five weeks from the day of infusion of Libmeldy. In the clinical study with the cryopreserved (commercial) formulation, neutrophil engraftment occurred after a median (min, max) of 36.5 (31-40) days after gene-therapy. Patients should, therefore, be monitored for signs and symptoms of cytopenia for at least 6 weeks after infusion.
Red blood cells should be monitored according to medical judgment until engraftment of these cells and recovery are achieved. Supportive transfusion of red cells 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 six to seven 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 ≥20 x 10^9/L obtained on different days after Libmeldy infusion, with no platelet transfusion administered for 7 days immediately preceding and during the evaluation period (up to 60 days post gene therapy).
During the clinical development, 4/35 patients (11.4%) reported delayed platelet engraftment (median: 73.5 days, range 65-109 days) which was not correlated with an increased incidence of bleeding. As part of the standard of care/prophylaxis, all patients in the integrated safety set (N=29) received transfusion support with platelets. Platelets 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 a 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

During clinical development, anti-ARSA antibodies (AAA) were reported in 5 patients. Titers were generally low and resolved spontaneously or after treatment with rituximab (see section «Undesirable effects»). No impacts on the clinical efficacy or safety outcomes were observed.
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, 15 years post treatment. In a 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 «Interactions»). 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 5g/L to prevent potential late infections (occurring later than 100 days post therapy) associated with severe hypogammaglobinaemia, resulting from apheresis/bone marrow harvest 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.

Medical procedures to obtain haematopoietic stem cells

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.

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.

Interactions

No interaction studies have been performed.
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 «Warnings and precautions»).
No data is available on the use of Libmeldy in patients receiving hepatotoxic medicinal products or using hepatotoxic substances. The safety and efficacy of the use of Libmeldy in these patients hasn’t been demonstrated.

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 myeloablative conditioning, during Libmeldy treatment, and until haematological recovery following treatment.

Pregnancy, lactation

Human data on use during pregnancy or lactation and animal reproduction studies are not available.

Fertility

With regard to fertility, consult the professional information of the myeloablative conditioning medicinal product. 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.

Effects on ability to drive and use machines

Not relevant.

Undesirable effects

Summary of the safety profile

The safety of Libmeldy was evaluated in 35 patients with MLD.
The median duration of follow-up in the integrated safety data set, which included 29 patients treated with the fresh (investigational) formulation was 4.51 years (range: 0.64 to 8.85 years). Three patients died for reasons not deemed related to treatment with Libmeldy (1 presymptomatic EJ patient died due to cerebral ischemic infarction, 2 early symptomatic EJ patients died due to disease progression), and a total of 26 patients remained in the follow-up phase.
The median duration of follow-up in the 6 patients treated with the cryopreserved (commercial) formulation was 0.87 years (range: 0.0 to 1.47 years). All of them remained in the follow-up phase (see section «Properties/Effects»).
Preliminary safety data from Study 205756 with the cryopreserved formulation indicate that Libmeldy was well tolerated. The safety profile observed is consistent with the profile established in patients treated with the fresh formulation in terms of nature, time of onset and frequency of reported adverse events.

List of adverse reactions

The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows: "very common" (≥1/10), "common" (≥1/100, <1/10).

Table 1 Adverse reactions attributed to Libmeldy

System Organ Class	Very Common	Common
Immune system disorders	Antibody Test Positive (Anti ARSA Antibody) (14%)	

Table 2 Adverse reactions potentially attributed to myeloablative conditioning*

System Organ Class	Very Common	Common
Infections and infestations		Cytomegalovirus viraemia, Pneumonia, Staphylococcal infection, Urinary tract infection, Viral infection
Blood and lymphatic system disorders	Febrile neutropenia (79%), Neutropenia (17%)	Anaemia, Thrombocytopenia
Metabolism and nutrition disorders	Metabolic acidosis (28%)	Fluid overload
Psychiatric disorders		Insomnia
Nervous system disorders		Headache
Respiratory, thoracic and mediastinal disorders		Epistaxis, Oropharyngeal pain
Gastrointestinal disorders	Stomatitis (76%), Vomiting (24%)	Ascites, Diarrhoea, Gastrointestinal haemorrhage, Nausea
Hepatobiliary disorders	Hepatomegaly (21%), Veno-occlusive liver disease (10%)	Hypertransaminasaemia, Alanine aminotransferase increased, Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders		Skin exfoliation
Musculoskeletal and connective tissue disorders		Back pain, Bone pain
Renal and urinary disorders		Oliguria
Reproductive system and breast disorders	Ovarian failure (10%)	

System Organ Class	Very Common	Common
General disorders and administration site conditions		Pyrexia
Investigations		Aspergillus test positive

** Based on 29 patients who have undergone myeloablative conditioning by busulfan in the integrated data set.*

Description of specific adverse reactions and additional information

- Presence of Anti ARSA Antibodies

Five out of 35 patients tested positive for anti-ARSA antibodies (AAA) at various post-treatment time points and had the event “Antibody test positive / Presence of antibodies against arylsulfatase A” reported by the Investigator.

Antibody titres were generally low and resolved either spontaneously or after a short course of rituximab.

In all patients with positive AAA test results, no negative effects were observed in the post-treatment ARSA activity of peripheral blood or bone marrow cellular subpopulations nor in the ARSA activity within the cerebrospinal fluid.

Patients treated with Libmeldy should be regularly monitored for AAA (see section «Warnings and precautions»).

- Peripheral blood mobilisation and apheresis

During the clinical studies, haematopoeitic stem cell collection was performed either through bone marrow (BM) harvest or peripheral blood mobilisation. The safety profile of BM 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 BM harvest within the range of BM volumes harvested (median volume was 35.5 mL/kg; range: 15.1-56.4 mL/kg). In the Integrated Safety Set (n=29), one patient experienced bone pain, which was qualified as a grade 2 adverse event and deemed related to the BM harvest procedure, but unrelated to the volume harvested.

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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

A16AB21

Mechanism of action

Libmeldy is an *ex vivo* genetically modified autologous $CD34^+$ hematopoietic 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 as well as endoneural 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 persist for a longer period of time.

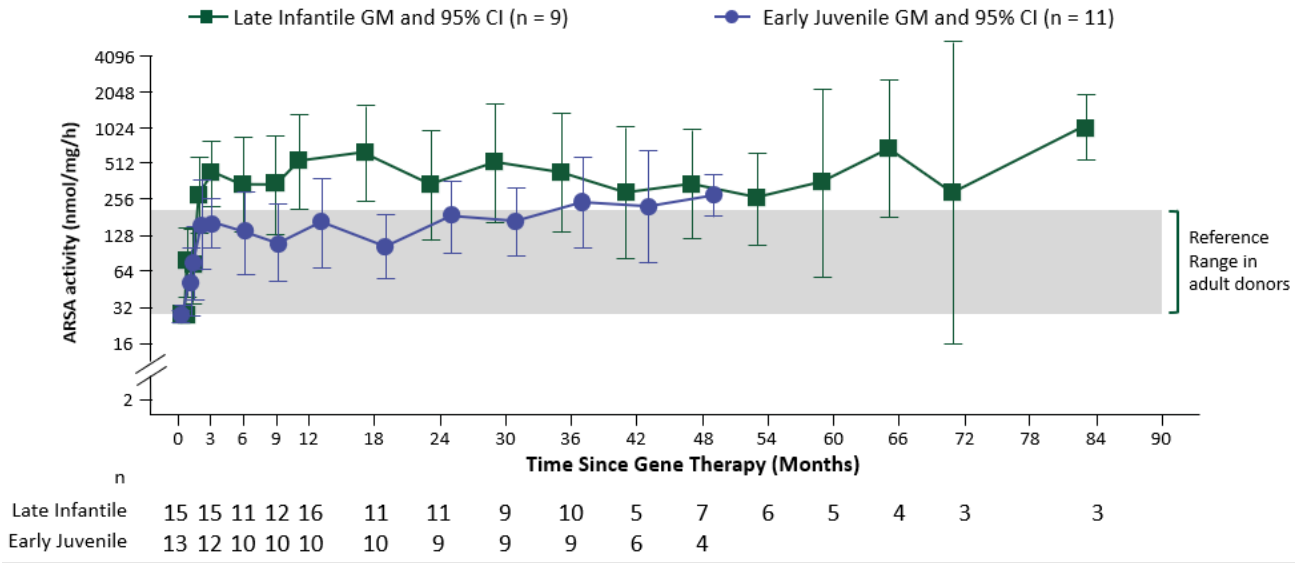
Pharmacodynamics

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

At Year 1 post-treatment, the proportion of BM-derived colonies harbouring the LVV genome ($\%LV^+$) in the overall treated population was 54.8% (range: 20.0% to 100%, [N=23]). The proportion of BM-derived colonies harbouring the LVV genome (%LV+) at Year 5 was 45.0% (range: 18.8% to 90.6% [n=6, 4 Late infantile (LI) and 2 Early Juvenile (EJ)]), indicative of stable engraftment over time in the treated population.

Reconstitution of ARSA activity in the hematopoietic system was observed in all MLD patients treated, with a progressive reconstitution of ARSA levels in Peripheral Blood Mononuclear Cells (PBMCs) which reached 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), by disease subtype (integrated efficacy set; N=29)



Note: Values < LLQ are imputed at LLQ. LLQ is 25.79 nmol/mg/h. GMs and 95% CIs are presented where there are at least 3 patients with non-missing data. ARSA: arylsulfatase A; CI: confidence interval; GM: geometric mean; LLQ: lower limit of quantification; PBMCs: peripheral blood mononuclear cells.

ARSA activity was also measured in cerebrospinal fluid (CSF) as a surrogate compartment of metabolic correction in the brain. The ARSA activity in CSF went from undetectable at Baseline to detectable in all evaluable patients by Month 6 post-treatment and reached reference range levels at Year 1 post-treatment. Thereafter, central reconstitution of ARSA enzymatic activity remained stable within the reference range.

Clinical efficacy

Clinical efficacy was based on the integrated analysis of results from 29 early-onset MLD patients treated with Libmeldy prepared as a fresh (non-cryopreserved) formulation. These results were generated in twenty (20) patients treated in the Registrational Study (Study 201222 - an open-label, non-randomized, single-arm safety and efficacy clinical trial) with a median duration of post-treatment follow-up of 4.0 years (range: 0.6 to 7.5 years) and nine patients treated in the context of 3 expanded access programs with a median follow-up of 1.5 years (range: 0.99 years to 2.72 years).
In addition, initial results from 9 patients treated in a further study with the commercial (cryopreserved) formulation of Libmeldy (Study 205756) are summarised below.

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. Pre-symptomatic Late Infantile (LI) or Early Juvenile (EJ) MLD patients and early symptomatic EJ MLD patients with biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity were included in the clinical development 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 forms (variants) 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 score is ≤1, and
  - If the patient's cognitive function has not started declining, which means that the patient's IQ is ≥85.

At time of inclusion in the clinical studies, out of the 29 early-onset MLD patients, 20 were pre-symptomatic and 9 were early symptomatic, 16 had a diagnosis of LI MLD and 13 had a diagnosis of EJ MLD. All LI study patients and some EJ 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 by symptomatic status at time of gene therapy and by disease subtype (Integrated efficacy set)

	Pre-symptomatic patients		**Early symptomatic patients**	
	Late Infantile subgroup (N=15)	**Early Juvenile subgroup (N=5)**	**Late Infantile subgroup (N=1)**	**Early Juvenile subgroup (N=8)**
Sex, n (%)				
Female	5 (33)	2 (40)	1 (100)	5 (63)
Male	10 (67)	3 (60)	0	3 (38)
Age at GT, in months				
Median	13.1	48.9	23.3	77.9
Min	7.6	11.4	23.3	38.8
Max	17.8	66.8	23.3	139.9

- Mobilisation and apheresis

During the clinical development, all (ten) patients for whom the decision was made to use mPB as the source material – and not to conduct a BM harvest - were administered G-CSF (10-12.5 µg/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 (0.24 mg/kg, subcutaneous) if clinically indicated depending on the white blood cells and $CD34^+$ cell count 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 apheresis.

- Pre-treatment conditioning
All patients received systemic conditioning with busulfan prior to treatment with Libmeldy.

Thirteen patients (45%) were treated with a sub-myeloablative conditioning (SMAC) regimen, defined as a target cumulative AUC of 67,200 µg*h/L. Sixteen patients (55%) were treated with a myeloablative (MAC) conditioning regimen, defined as a target cumulative AUC of 85,000 µg*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 IV 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 4800 µg*h/L (range: 4200 to 5600 µg*h/L), which corresponds to an expected total cumulative AUC of 67,200 µg*h/L (range 58,800 to 78,400 µg*h/L). The average, cumulative AUC in patients who received a SMAC regimen was higher than expected but remained within the target range (geometric mean 71,923.53 [95% CI: 68,751.04, 75,242.41]).

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 ≤1year; 120 mg/m^2/dose if >1 year) for a total of 4 doses, administered as a 3 hour IV 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 total cumulative AUC of 85,000 µg*h/L (range: 76,500 to 93,500 µg*h/L).

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.

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=29) were administered the medicinal product with a mean (min, max) cell dose of 10.81 x 10^6 (4.2, 25.9) $CD34^+$ cells/kg as an intravenous infusion.

- Integrated efficacy results (N=29)

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, 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 section «Pharmacodynamic Effects», Figure 1 and Table 4).

Early-onset MLD patients treated before the onset of overt symptoms showed normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction as measured by GMFM total score (%).

Using an ANCOVA model adjusted for age at GMFM assessment and treatment, the mean difference between treated pre-symptomatic LI patients and age matched untreated LI patients from the NHx study was 71.0% at Year 2 and 79.8% at Year 3 ($p<0.001$).

Similarly, the mean difference between treated pre-symptomatic EJ patients and aged matched untreated EJ patients was 52.4% at Year 2 and 74.9% at Year 3. These treatment differences were statistically significant ($p\leq0.008$) in favour of Libmeldy.

The difference in GMFM total score between treated early symptomatic EJ patients and aged matched untreated EJ patients was not statistically significant (28.7% at Year 2; $p=0.350$ and 43.9% at Year 3; $p=0.054$).

Deterioration of gross motor function was assessed from disease onset in EJ patients who were early-symptomatic at the time of gene therapy. By four years post disease onset, the estimated proportion of patients who survived and maintained locomotion and ability to sit without support (GMFC-MLD level 5 or higher) was 62.5% in the treated group compared to 26.3% in the untreated group, representing a delay in disease progression following treatment with Libmeldy.

A statistically significant increase in ARSA activity in PBMCs was also observed at Year 2 post-treatment compared to pre-treatment baseline in both pre-symptomatic patients (20.0-fold increase; p<0.001) and early symptomatic patients (4.2-fold increase; p=0.004) (see Table 4).

Table 4 ARSA activity measured in PBMCs (geometric mean) at Baseline and Year 2 after treatment in pre-symptomatic and early-symptomatic patients (integrated efficacy set).

	Geometric mean (%CVb) ARSA Activity in PBMCs		Fold Increase from Baseline to Year 2 *
	Baseline	Year 2	
Pre-symptomatic	26.923 (16.72) (n=19)	339.736 (270.85) (n=14)	20.0 (95% CI: 9.0, 44.0) p<0.001
Early-symptomatic	26.025 (2.72) (n=9)	134.056 (55.94) (n=6)	4.2 (95% CI: 1.6, 11.2) p=0.004

* 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

A secondary efficacy endpoint of the integrated efficacy analysis was measurement of IQ above 55 post-treatment with Libmeldy, the threshold for moderate mental retardation (DSM-IV), using neuropsychological tests. Intelligence Quotient/Development Quotient (IQ/DQ) measures, i.e. cognitive and language abilities, complement results from the GMFM and provide further evidence that the high levels of engraftment and enzymatic reconstitution translate into relevant treatment effects on key symptomatic domains in MLD patients.
In the LI subgroup (all pre-symptomatic at time of treatment except one), 12 out of 15 assessed patients had a fairly constant IQ/DQ, within the normal range (IQ/DQ score of 100+/-SD of 15) throughout follow-up. All but 2 of these patients (one pre-symptomatic, one early-symptomatic) remained above the threshold of severe mental disability (IQ/DQ>55) at chronological ages at which all 14 untreated NHx patients with neuropsychological assessments showed evidence of severe cognitive impairment (i.e. IQ/DQ below 55 and close to 0).
Of the 10 surviving EJ patients, all 4 pre-symptomatic patients and 4 out of 6 early-symptomatic patients showed normal IQ/DQ throughout follow-up. In contrast, 11 out of 12 NHx patients with neuropsychological assessments showed evidence of severe cognitive impairment during follow-up.

At the time of the integrated data analysis, i.e. at a median follow-up time of 3.035 years post-treatment (range 0.99 to 7.51), none of the 16 patients in the treated LI subgroup, all pre-symptomatic at time of treatment except one, had died (100% overall survival). Four pre-symptomatic LI patients were alive 6 or more years after treatment and 2 pre-symptomatic LI patients were alive 7 or more years after treatment. In comparison, 12 out of 19 (63.2%) untreated LI patients in the NHx study had died at the time of the analysis.

Comparable overall survival was observed in the treated and untreated EJ groups with a median follow-up time of 3.49 years post-treatment (range 0.64 to 6.55). One out of 5 (20%) EJ patients treated at pre-symptomatic stage died, due to cerebral ischemic infarction. There were 2 deaths among the 8 (25.0%) EJ patients treated at early-symptomatic stage, both due to disease progression. Similarly, 3 of the 12 (25%) untreated EJ patients in the NHx study had died at the time of the analysis.

A sensitivity analysis conducted to identify clinical factors, which could have influenced the level of treatment benefit with Libmeldy and optimize the recommended use of the treatment, identified 4 treatment failures:

- One 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 function and motor development.
- Three early symptomatic EJ patients treated 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 IQ<85 (82 and 58) at the time of treatment. Two out of the three patients showed deterioration between screening and baseline (onset of conditioning regimen) assessments.

- Study 205756 (cryopreserved commercial formulation)

Study 205756 is an open-label, single-arm study to evaluate the cryopreserved (commercial) formulation of Libmeldy in the treatment of pre-symptomatic LI and pre-symptomatic and early symptomatic EJ MLD patients. The cell dose range used in the first 9 patients in Study 205756 (10.45-30.0 x 10^6 $CD34^+$ cells/kg) is close to the range used in patients treated with the fresh (investigational) formulation of the medicinal product (4.2-25.9 x 10^6 $CD34^+$ cells/kg).

At the time of data cut, 6 patients (3LIs, 3EJs), all pre-symptomatic at the time of treatment, have been treated, with a median follow-up post-treatment of 0.87 year (range: 0.0 to 1.47 years). Preliminary efficacy data show levels of engraftment, Vector Copy Number, ARSA activity in PBMCs and CSF at different timepoints post-gene therapy within the range observed in the integrated data analysis of the patients treated with the fresh formulation of Libmeldy.

Paediatrics

Libmeldy has been studied in infants and children with an age range between 7.6 months and 11.6 years.

Pharmacokinetics

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.

Absorption

Not applicable.

Distribution

The biodistribution of Libmeldy was studied and distribution to hematopoietic tissues and disease target organs (including the brain) was demonstrated.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical 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 hematopoietic 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.

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).

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
Once thawed: maximum 2 hours at room temperature (20°C-25°C).

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 «Shelf life».

For detailed instructions for handling, see section «Instructions for handling» at the end of the information for professionals.

Authorisation number

68236 (Swissmedic)

Packs

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. [A - To be used in hospitals only according to Art. 26 para. 4 TPO]

Marketing authorisation holder

SFL Pharma GmbH, Basel

Date of revision of the text

December 2023

Instructions for handling

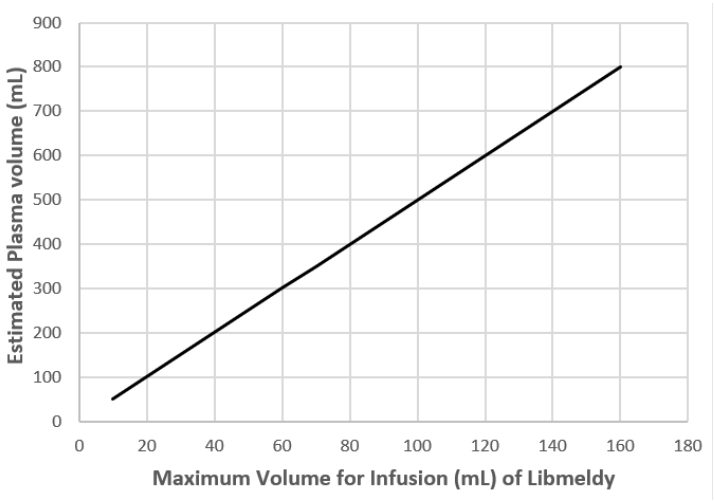
Precautions to be taken before handling or administering the medicinal product

- 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 «Dosage/Administration», 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.
- Careful consideration must be given to the volume of infusion in relation to age and weight of the patient. When the dose of Libmeldy to be infused represents more than one bag, it should be ensured prior to infusion that the volume of medicinal product to be infused is compatible with the recommended limit of DMSO, i.e. the total volume of DMSO administered should remain <1% of the patient's estimated plasma volume. Therefore, the maximum volume of Libmeldy to be administered should remain <20% of the patient's estimated plasma volume.
- The following graph is provided as a reference in order to determine the maximum volume of Libmeldy which can be infused to a patient based on their estimated plasma volume.

Figure 2 Guidance on DMSO safety limit: the maximum volume of Libmeldy to be administered should remain <20% of the patient's estimated plasma volume.



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 the marketing authorisation holder 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 200µm 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 for up to 3 hours following the infusion.
- 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 products and all material that has been in contact with Libmeldy (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.