FINOSE Joint HTA
Fimea NoMA TLV

FINOSE joint assessment report

Libmeldy (autologous CD34+ cells encoding ARSA gene)

Dispersion for infusion

Assessed 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 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

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Case number Fimea: 2020/006120

FINOSE

The Nordic collaboration FINOSE offers effective and transparent evaluations of pharmaceutical products with a view to reimbursement or procurement in the three countries Finland, Norway and Sweden. The collaborating agencies are the Finnish Medicines Agency (Fimea), the Norwegian Medicines Agency (NoMA) and Sweden's Dental and Pharmaceutical Benefits Agency (TLV).

Joint assessments of pharmaceutical products include both relative effectiveness and health economics. The evaluation reports are designed to support the decision processes in the three countries, according to the legal standards and procedures of each country. The three agencies take turns at the different tasks of the evaluation; this leads to higher joint quality and a more time efficient procedure. In the present FINOSE report, Fimea and NoMA acted as authors and TLV performed a reviewer role.

The present report presents a joint assessment of an Advanced Therapy Medicinal Product (ATMP) with a small target population. Joint assessments for this type of products, with very few patients in each country might potentially facilitate patient access to products through the following mechanisms:

- A joint view on the products' benefits and costs could facilitate the practical organisation of patients who might need to travel between countries for treatments.
- A joint view may also facilitate potential future joint negotiations. However, procurement is not within the FINOSE team's remit.
- For smaller companies with limited organisations in each country, a submission for a joint FINOSE assessment could reduce the administrative burden.

Many of these potential benefits of producing joint assessments for products with small target populations also apply to products with larger target populations so we see benefits in assessing those jointly as well of course in order to facilitate access to the patients.

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The clinical experts have been consulted on current clinical praxis and in interpretation of the clinical material. The FINOSE group is not bound to the statements of the experts, interpretations and opinions on which the cost-effectiveness analysis should be based on.

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Case number NoMA: 21/17217
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Summary

- Metachromatic leukodystrophy (MLD) is a rare inherited metabolic disease caused by mutations in the Arylsulfatase A (ARSA) gene and lack of its corresponding enzyme. This causes accumulation of sulfatides, particularly in the cells of the nervous system but also in other organs, which leads to a progressive loss of motor function and cognitive ability and, eventual death.
- Libmeldy is indicated for the treatment of metachromatic leukodystrophy characterized by mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with late infantile (LI) or early juvenile (EJ) forms, without clinical manifestations of the disease, and in children with the early juvenile form, with early clinical manifestations of the disease (ES-EJ), who still have the ability to walk independently and before the onset of cognitive decline.
- In Libmeldy treatment, autologous hematopoietic stem cells (CD34+), transduced with functional copy of an ARSA gene, are administered to the patient after a conditioning myeloablative treatment. The genetically modified cells can secrete a functional ARSA enzyme, which breaks down and prevents the build-up of harmful sulfatides.
- Currently, the patients are treated with multi-disciplinary supportive care and home care, including paediatric neurologist, physiotherapist, neuropsychologist, occupational therapist, speech therapist, assistive device, and symptomatic medicines.
- FINOSE agrees with the company that best supportive care is the relevant comparator as there are no disease modifying or curative treatments available.
- The clinical evidence base of Libmeldy consists of single arm trials (201222, 205756), compassionate use programs and hospital exemptions.
- All treated LI patients were alive at the end of the follow-up (median of 3.5 years), whereas in the untreated population several patients had died between 4–6 years of age. All untreated siblings of the LI patients had died before the age of 7 years. The result was less clear for EJ patients because of a short follow-up time (median of 3 years for PS-EJ, and 4 years for ES-EJ), and a small number of patients.
- Treated patients had higher gross motor function measure (GMFM) in all subgroups of disease subtype compared to untreated patients. Out of 15 treated LI patients, [––––––] remained at gross motor function class MLD (GMFC-MLD) level 0, which corresponds to normal level of gross motor function. Compared to the untreated population at the same age, the GMFC-MLD levels were higher for 14 out of 15 treated patients at the end of the follow-up. [––––––––––] evaluable pre-symptomatic EJ (PS-EJ) patients [––] remained at GMFC-MLD level 0. Compared to the natural history cohort and matched siblings, the treated patients seemed to have higher GMFC-MLD levels. At end of the follow-up, [––––] early-symptomatic EJ (ES-EJ) patients had progressed from the level they were at time of treatment.
- FINOSE finds that there is an uncertainty regarding the company assumption on the comparability of the treated and untreated populations. The disease progression seems slower in the treated population already before the treatment-start. Another uncertainty due to the short follow-up time, is that the risk of long-term adverse

events has not been evaluated. Also, common adverse events might be missed, because of the very limited number of treated subjects. The only adverse event attributed to Libmeldy was development of antibodies to ARSA. Most of the adverse events are related to busulfan conditioning regimen.

- Treatment with Libmeldy is aimed at preventing, or slowing, the clinical manifestation of disease.
- The company has chosen to model the effect of Libmeldy primarily through the secondary end point in the registrational study 201222, which was improvement of the categories gross motor function measure score, specifically for MLD-patients (GMFC-MLD). The total GMFC-MLD score compared to the historical control MLD population, was evaluated 24 months after treatment. These response categories were not applied in the study itself but were used to model long term efficacy through the health economic model, by assuming a degree of stabilization.
- The price used in the health economic model for Libmeldy, as applied by the company, is 30 074 576 NOK, which is applied as a one-off drug cost in the same year as a treatment eligible patient is identified. This should be compared to extensive at-home and care costs and hospitalizations for untreated patients over a lifetime.
- FINOSE has calculated two scenarios, one combined scenario, and several additional analyses with the aim of highlighting the main uncertainties in the health economic model. The first scenario concerns patients with too short follow-up time to yet conclude on response-status. These patients are reclassified according to FINOSEs criteria of necessary follow-up time (scenario 1). The second scenario uses the same patient response-status as in the company's base case. However, the duration of the modelled effect is shortened to 15 years. After 15 years the treated patients have the same rate of disease progression as untreated patients in the natural history cohort (scenario 2).
- For FINOSE scenario 1 the cost per QALY gained for the combined population eligible for treatment with Libmeldy is 3 225 418 NOK, and in FINOSE scenario 2 the cost is 3 151 472 NOK per QALY gained. Results for each subgroup is also presented. The results when combining the alterations from scenario 1 and scenario 2 into one combined scenario, the cost per QALY gained is 6 359 681 NOK.
- Assumptions regarding grouping of responders and subsequent sustained long-term efficacy, and the drug cost of Libmeldy are the key drivers for the cost effectiveness.
- FINOSE has performed several one-way sensitivity analyses to explore how changes in individual parameter inputs affect the results. The main parameter affecting the results according to FINOSE is the company's assumption that patients who have not experienced a progression or onset of disease during study follow-up time, will stabilize in a given GMFC-MLD stage for the lifelong time horizon. The sensitivity analysis shows a range in ICERs between 843 000 to 25.7 million NOK, suggesting the model is very sensitive to alterations.
- FINOSE has identified the following main uncertainties in the modelling of the cost-effectiveness analysis of Libmeldy: 1) the assumption that for certain patients who have not experienced a progression or onset of disease during the follow-up time, these will stabilize in a given GMFC-MLD stage, which is sustained over the lifelong time horizon, 2) the duration of a potential disease stabilization, 3) Relative efficacy of

Libmeldy compared to untreated patients in a real world setting, and 4) the QALY values accrued in each health state.

- In summary, the limited number of patients observed in the clinical trials and the early access programs, limited follow-up time and non-randomized studies without a control arm contribute to the uncertainties.

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Abbreviations

AAA	Anti ARSA antibody
AE	Adverse event
ARSA	Arylsulfatase A
CFS	Cerebrospinal fluid
CNS	Central nervous system
CUP	Compassionate use program
DQ	Development quotient
EJ	Early juvenile
ES	Early-symptomatic
GMFC	Gross Motor Function Classification
GMFC-MLD	Gross Motor Function Classification in MDL
GMFM	Gross Motor Function Measure
GT	Gene therapy
HE	Hospital exemption
HSCT	Haematopoietic stem cell transplantations
ICER	Incremental cost-effectiveness ratio
LI	Late infantile
LV	Lentiviral vector
MAC	Myeloablative
MLD	Metachromatic Leukodystrophy
MRI	Magnetic resonance imaging
NCV	Nerve conduction velocity
PBMC	Peripheral blood mononuclear cells
PS	Pre-symptomatic
SAE	Serious adverse events
sCMFS	Severe cognitive and motor impairment-free survival
SMAC	Sub-myeloablative

1 Scope

This report is a FINOSE joint assessment of autologous CD34+ cells encoding ARSA gene (Libmeldy) for the treatment of patients with 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

The assessment is primarily based on the documentation presented by Orchard Therapeutics.

The aim of this FINOSE report is to inform national policy decision regarding the use Libmeldy in Finland, Norway and Sweden. The primary focus of this report is to assess the relative effectiveness, the safety and the cost effectiveness of Libmeldy. The FINOSE reports may be complemented with national versions of the report with additional or local information and conclusions.

P (population)	Patients with late infantile or early juvenile forms of MLD, without clinical manifestations of the disease and patients with the early juvenile form of MLD, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.
I (intervention)	Libmeldy
C (comparison, comparators)	Supportive care without haematopoietic stem cell transplantations (HSCTs)
O (outcomes)	• Gross motor function as measured by Gross Motor Function Measure (GMFM) and Gross Motor Function Classification (GMFC) • Cognitive function as measured by IQ and Developmental Quotient (DQ) • ARSA activity • Overall survival • Adverse events • Health-related quality of life • Costs • Incremental cost-effectiveness ratio (ICER) • Budget impact

2 Medical background

2.1 Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) is a rare inherited metabolic disease. The disease is caused by mutations in the arylsulfatase A (ARSA) gene that result in lack of the corresponding ARSA enzyme. The lack of active ARSA enzyme causes a toxic accumulation of sulfatides, particularly in the cells of the nervous system but also in other organs. The damage caused by this leads to a progressive loss of motor function and cognitive ability and, eventual death. (1)

Even though there is no universally accepted classification system for MLD phenotypes, the disease can be classified into four main phenotypes (late infantile [LI], early juvenile [EJ], late juvenile [LJ], and adult phenotypes) based on age of onset. Historically juvenile phenotypes (EJ and LJ) have often been combined into one group. Genetic mutations leading to MLD, can be functionally divided into 2 broad groups: null (0) alleles associated with no enzymatic activity and residual (R) alleles encoding for ARSA with some residual enzymatic activity. Figure 1 displays a simplified version of the relationship and boundaries between genotype/phenotype of MLD variants. (1,2).

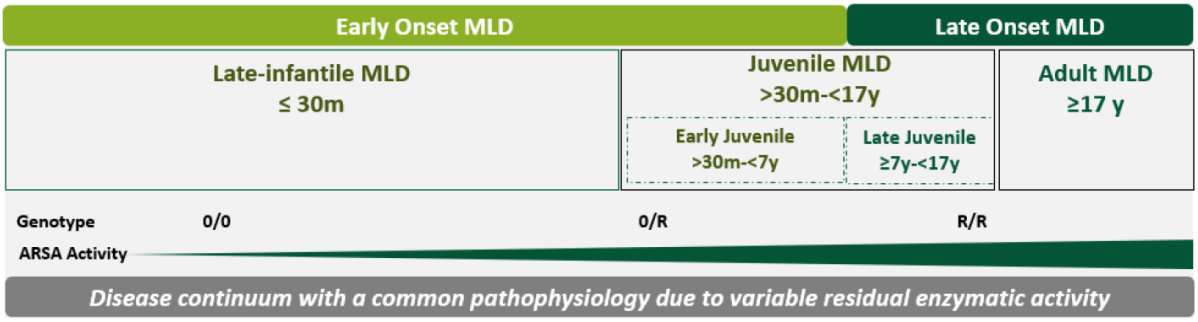


Figure 1. Simplified MLD Genotype-Phenotype Relationship. (1 fig.1)

Late infantile MLD (LI-MLD) patients usually carry 2 null alleles (0/0 genotype) and hardly express any residual ARSA activity (1–4). Therefore, symptoms are seen before 30 months of age. LI-MLD is the most prevalent MLD variant constituting approximately 40 to 60 percent of all MLD cases (5,6). LI-MLD is also the most aggressive form of the disease with a highly predictable and severe disease course, characterized by progressive decline in motor and cognitive function and an early death. A retrospective analysis of 98 LI-MLD patients since 1921 reported a 5-year survival of 25 percent and a 10-year survival of zero (7). When the same analysis considered only cases reported after 1990, the 5-year survival was 52 percent. Recent publication describing the natural history of the patient population (22 patients since 2000) report similar 5-year survival (56%) but a higher 10-year survival (40%) than the retrospective study including patients from 1921 (8) (1–8).

Early juvenile MLD (EJ-MLD) patients carry either one null allele and one residual allele (0/R genotype), or less frequently two residual alleles (R/R genotype). They have symptom onset between the ages of 30 months and 6 years (before their 7th birthday), and tend to have a slower and more variable initial disease progression (1–4,6). Since 1921 reported 5-year survival for all juvenile forms (EJ+LJ) was 70.3 percent based on 78 patients and in cases reported after 1990 it was 100 percent (7). Recently reported 5 year-survival was 90 percent and 10-year-survival 80 percent based on 14 EJ-MLD patients since 2000 (1–4,6–8).

The clinical course of the disease can be broadly divided into a pre-symptomatic stage, an early-symptomatic stage, a progressive phase and a decerebrated state (1,2,9–12). The pre-symptomatic stage with normal motor and cognitive development is followed by onset of first symptoms. The early-symptomatic stage, is short in early onset forms and longer and more variable in late onset forms. In the progressive phase there is rapid loss of motor and cognitive function in all forms. The disease inevitably ends in a decerebrated state and eventually death. The deterioration of gross motor function classification rate across the GMFC-MLD scale is illustrated in Figure 2.

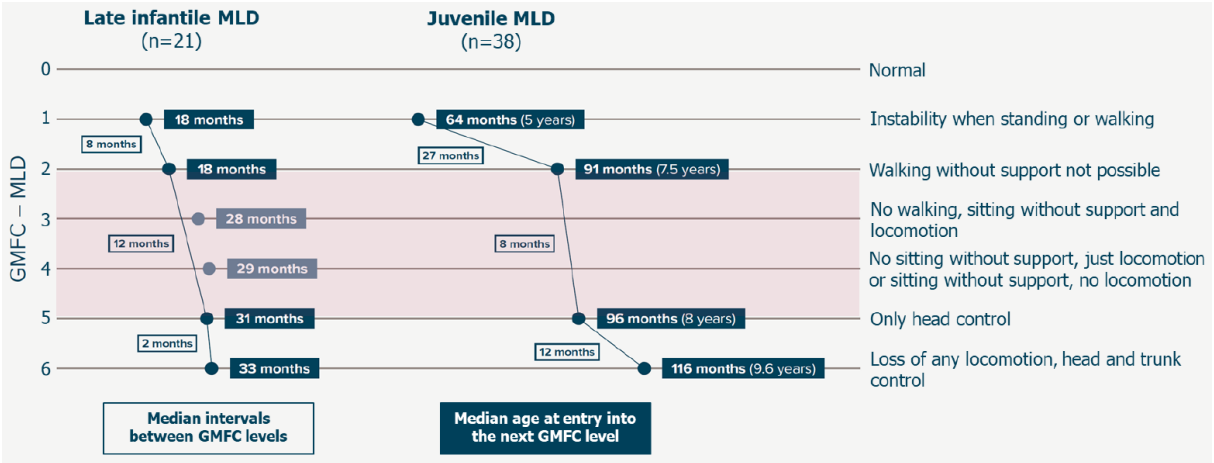


Figure 2. Rate of deterioration of motor function on GMFC-MLD scale in late infantile and juvenile MLD. (2,9) GMFC = Gross Motor Function Classification.

Currently there are no studies that have directly measured the health-related quality of life (HRQoL) of MLD over the course of the disease.

At the time of orphan designation, MLD affected less than 0.5 in 10,000 people in the European Union (EU) (13). The incidence of all MLD variants has been estimated to be 1.1 cases per 100,000 livebirths in the EU (1). The exact prevalence and incidence in Finland, Norway and Sweden is unknown. However, it has been estimated based on international literature to be 1-2 present cases per 100,000 people in Sweden and 1-4 new cases per 100,000 livebirths in Norway (14–16). Furthermore, it has been estimated that around 60 percent of patients have the late infantile variant and 20 percent to 30 percent have the juvenile variant (early juvenile + late juvenile). According to the company (2) it could be estimated to be around one new MLD patient per year in Sweden and one every other year in Finland and Norway (1,2,13–16).

2.2 Libmeldy

2.2.1 Therapeutic indication

Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by 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 Mechanism of action

Libmeldy is an ex vivo genetically modified autologous CD34+ haematopoietic stem and progenitor cell gene therapy. Autologous CD34+ haematopoietic stem and progenitor cells are collected from patient bone marrow harvest or from mobilised peripheral blood and transduced with a lentiviral vector, which inserts one or more copies of the ARSA gene into the cell's genome so that genetically modified cells become capable of expressing the functional ARSA enzyme. When administered to the patient the genetically modified cells engraft and are able to repopulate the haematopoietic compartment. A subpopulation of the infused cells 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. These genetically modified cells can produce and secrete supraphysiological levels of the ARSA enzyme, which can be taken up by surrounding cells and used to break down or prevent the build-up of harmful sulfatides. (1)

2.2.3 Posology and method of administration

The minimum recommended dose of Libmeldy is 3×10^6 CD34+ cells/kg. The maximum volume of Libmeldy to be administered should remain < 20 percent of the patient's estimated plasma volume (17).

Libmeldy is intended for autologous use and should only be administered once. It must be administered in a qualified treatment center with experience in Haematopoietic Stem Cell Transplantation (HSCT). Currently, there are five treatment centers in Europe that are certified or in the process to be certified for administration of Libmeldy. These centers are located in Italy, France, Germany, UK and the Netherlands. Initial assessment and diagnosis can be done locally. The company has informed FINOSE that opening a qualified treatment center within the Nordic region will be considered after decisions on reimbursement in the Nordic countries (2,17).

Libmeldy is manufactured using autologous CD34+ cells, which are isolated from bone marrow harvest or mobilized peripheral blood. Collecting the cells from peripheral blood requires mobilization with granulocyte colony-stimulating factor with or without plerixafor followed by apheresis. One or more cycles of apheresis may be required to obtain enough cells. The collected stem cells are divided into backup and treatment samples. A back-up collection of HSPC 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. The treatment sample is transduced with a working copy of the ARSA gene (17).

Five days before Libmeldy infusion, a myeloablative (MAC) or sub-myeloablative (SMAC) conditioning medicine is given for 3–4 days in a hospital. It is required to promote efficient engraftment of the genetically modified autologous CD34+ cells. Busulfan is the recommended conditioning medicine. 15–30 minutes before Libmeldy infusion, a pre-medication with antihistamine is given to the patient to reduce the possibility of an allergic reaction related to Libmeldy infusion. Libmeldy is administered intravenously via a central catheter. Infusion of one bag takes approximately 30 minutes. The number of bags vary by patient. Patients will remain in the hospital for about 4–12 weeks after Libmeldy infusion.

Monitoring of anti-ARSA antibodies (AAA) is recommended prior to treatment, between 1 and 2 months after treatment, and then at 6 months, 1 year, 3 years, 5 years, 7 years, 9 years, 12 years, 15 years post treatment.

2.3 Current treatment options

2.3.1 Treatment guidelines for MLD

There are currently no national guidelines for the treatment and management of MLD in Finland, Norway, or Sweden. The Global Leukodystrophy Initiative consortium has published guidelines (18,19) on the preventive and symptomatic care of patients with leukodystrophies, including MLD. As these guidelines are for all leukodystrophies, they do not identify subgroups of MLD or make specific recommendations for their treatment. Details of the guidelines are summarized in Appendix Table 39 (2).

According to clinical experts, late infantile and early juvenile forms of MLD is mainly treated with supportive care.

Finland
Multi-disciplinary supportive care includes pediatric neurologist, physiotherapist, neuropsychologist, occupational therapist, speech therapist, assistive device, symptomatic medicines (baclofen, analgesics etc.), patient and family psychosocial support, dietician, genetic counselling etc. Allogenic HSCT may be an option in later-onset disease especially in pre-symptomatic phase, but it is associated with greater risks and uncertain evidence. For early-onset patients (late infantile MLD) it is not an option.

Norway
All forms of MLD are treated with supportive care only. Management depends on the principles for best supportive care as outlined internationally. A multisystem care approach is generally available with special attention given to the following: physiotherapy and avoidance of contractures, spasticity, respiratory problems, nutrition-PEG due to swallowing difficulties, OT and speech and swallowing maintenance therapy, constipation, and pain. While a diagnosis is made in a specialty/university hospital, supportive care and follow up are done in local/district hospitals. This is because there is no available disease modifying treatment to be offered at this time. When the diagnosis is established, patients could be considered for HSTC if the disease is in a fase/disease type where this may be an option. The local habilitation team must be involved. Palliative pediatric teams exist in many places to support the local level of care.

Sweden
LI and EJ forms of MLD is treated with supportive care only. HSCT is an option for LJ and adult forms of MLD, if the diagnosis is pre-symptomatic or with minimal motor and/or psychiatric symptoms (20).

2.3.2 Comparator

The company uses best supportive care (BSC) as comparator to Libmeldy, because there is currently no disease modifying or curative treatments available. Supportive therapies include physical therapy to maintain mobility, muscle relaxant medications to reduce spasticity, pain management, management of skeletal deformity, respiratory physiotherapy to manage pulmonary infections, anti-convulsant drugs to control seizures, and anti-psychotic medications to control psychiatric symptoms, as well as dietary support, enteral nutrition through a feeding tube in cases of dysphagia, and family and psychological counselling (2).

The clinical experts agree that HSCT is not a treatment option for the LI-MLD and EJ-MLD patient populations that are included in the Libmeldy indication.

The chosen comparator is in line with Finnish, Norwegian and Swedish treatment practices.

FINOSE conclusion: FINOSE agrees with the company that best supportive care is the relevant comparator as there are no disease modifying or curative treatments available.

3 Clinical efficacy and safety

3.1 Clinical evidence

The assessment of clinical efficacy and safety is mainly based on the evidence included in the submission dossier prepared by the company. The authoring team has checked the information retrieval included in the company's submission dossier for completeness against

- a search in ClinicalTrials.gov and PubMed
- the studies included in the European public assessment report (EPAR)

3.2 Clinical trials

The evidence on the safety and efficacy of Libmeldy in treatment of early-onset MLD is based on one phase 1/2 registrational study (201222, NCT01560182) where patients were treated with a fresh formulation, one phase 2 clinical study where patients were treated with the commercial cryopreserved formulation (205756, NCT03392987) and three expanded access programs. The efficacy data generated were compared with data from a natural history cohort TIGET NHx study (204949). The clinical trials and expanded access programs are descripted in Table 1 and more details are reported in Appendix Table 40–Table 42 (1,2).

In the trials, the MLD diagnosis was based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles. The details of the eligibility criteria in the trials are reported in Appendix Table 40–Table 42.

Table 1. Summary of relevant trials (1,2).

Study NCT-number [publications]	**Study Design**	**Treated study Population**	**Intervention**	**Primary efficacy endpoints**
Registrational study 201222 NCT01560182 (21,22)	- phase 1/2 - open label - single arm - single centre	9 LI-MLD, all pre-symptomatic (8 pre-symptomatic at time of infusion) 11 EJ-MLD, 4 were pre-symptomatic at time of infusion. 2 EJ-MLD withdrawn before treatment	Libmeldy non-commercial fresh formulation	- Improvement of the total GMFM score compared to the historical control MLD population, evaluated 24 months after treatment. - Increase of residual ARSA activity. Measured in the PBMC at two years as compared to pre-treatment values.
205756 NCT03392987	- phase 2 - open label - single arm - single centre	6 pre or early onset MLD patients	Libmeldy commercial cryopreserved formulation	- Change in GMFM score
Expanded access programmes CUP 207394 HE 205029 CUP 206258	- CUP and HE were used for patients when study 201222 had closed for enrolment. Study design was similar than defined for study 201222.	CUP 207394: 1 symptomatic EJ-MLD HE 205029: 3 pre-symptomatic LI-MLD CUP 206258: 4 LI-MLD and 1 EJ-MLD, all pre-symptomatic	Libmeldy non-commercial fresh formulation	- Similar outcomes were observed as those defined for study 201222
TIGET NHx study 204949 NCT01560182	- Natural history study following patients with MLD.	Untreated patients: 19 LI-MLD 12 EJ-MLD	Untreated patients without intervention	- The study comprises prospective and retrospective data.

		Of which 11 were untreated siblings to Libmeldy-treated patients		

EJ = early juvenile; LI = late infantile. PBMC = peripheral blood mononuclear cells; GMFM=Gross Motor Function Measure; CUP= Compassionate use programs; HE= Hospital exemption

3.2.1 Registrational study 201222

Registrational study 201222 was a single arm, single centre, open label Phase 1/2 study. In total, 20 early-onset MLD (LI or EJ variants) subjects were treated with Libmeldy. Eligible subjects must have either an older sibling affected by MLD, whose age of symptom onset was ≤ 6 years of age, or if MLD was diagnosed in a pre-symptomatic child without an older affected sibling, the subject was approved by the Orchard Therapeutics medical monitor.

The LI variant was defined based on the age at onset of symptoms (≤ 30 months) in the older sibling(s), two null (0) mutant ARSA alleles and/or peripheral neuropathy detected by electroneurography. Two out of three of these criteria were to be met. Similarly, for the EJ variant, the criteria were age at onset of symptoms (in the patient or in the older sibling) between 30 months and 6 years, one null (0) and one R mutant ARSA allele(s) and/or peripheral neuropathy.

Pre-symptomatic clinical status was defined as subjects without neurological impairment (disease- related symptoms), with or without signs of the disease revealed by instrumental evaluations (electroneurography and brain magnetic resonance imaging (MRI)). Early-symptomatic clinical status (for the EJ variant) was initially defined as subjects identified within 6 months from the first reported symptoms (two EJ subjects were enrolled using this definition). Subsequently, early-symptomatic EJ subjects were defined as subjects meeting the following two criteria: IQ ≥70 and the ability to walk independently for ≥10 steps. The rationale for this change was to prevent enrolment of subjects who had a rapidly progressive form of the disease as identified at the time of treatment. All LI subjects and some pre-symptomatic EJ subjects were identified after an older sibling had developed symptoms and received an MLD diagnosis, prompting testing in other family members.

Clinical efficacy endpoints

One of the two co-primary efficacy endpoints was the total gross motor function measure (GMFM) score two years after treatment, compared to age-matched natural history patients. The GMFM score was designed to measure children's gross motor function based on 88 items, grouped in five dimensions (1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing, and 5) walking, running and jumping), which each have four levels (0=cannot do; 1= initiates; 2= partially completes; 3=task completion). The other co-primary endpoint was the ARSA activity in peripheral blood mononuclear cells (PBMC) two years after treatment, compared to the ARSA activity at baseline.

Secondary endpoints included nerve conduction velocity, brain MRI, gross motor function classification (GMFC-MLD), neuropsychological tests, neurological evaluations, survival, engraftment (lentiviral vector transduced cells, vector copy number).

The GMFC-MLD classification system (23) was used to classify the motor function of patients. It consists of 7 levels, ranging from level 0 (normal gross motor function) to level 6 (loss of any locomotion and any head and trunk control) (Table 2). GMFC-MLD is age independent and should be applied only after the age of independent walking is achieved (18 months or older).

Table 2. Gross Motor Function Classification in MLD (GMFC-MLD) (23).

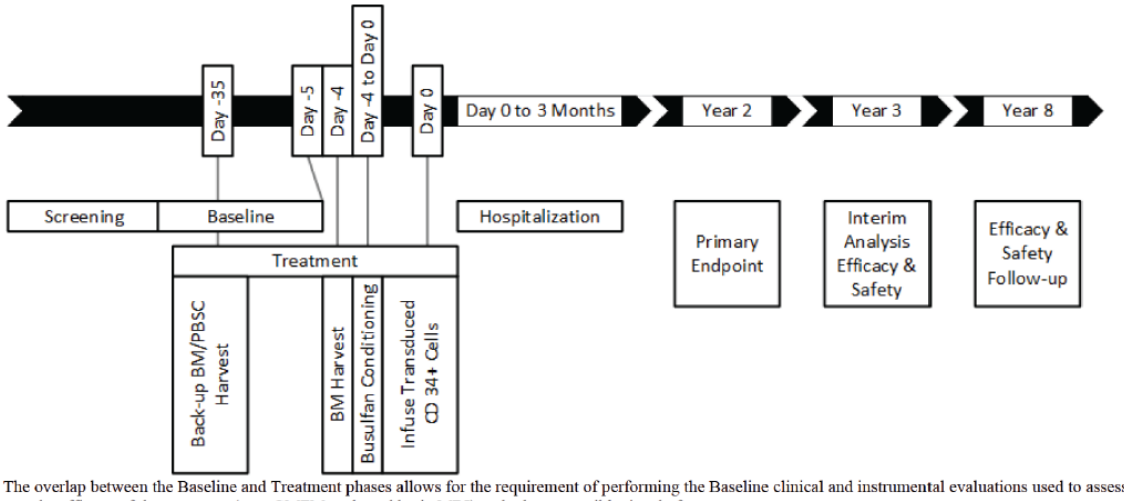
Level	Description
0	Walking without support with quality of performance normal for age
1	Walking without support but with reduced quality of performance, i.e., instability when standing or walking
2	Walking with support. Walking without support not possible (fewer than five steps)
3	Sitting without support **and** locomotion such as crawling or rolling. Walking with or without support not possible
4	(a) Sitting without support but no locomotion, **or** (b) Sitting without support not possible, but locomotion such as crawling or rolling
5	No locomotion nor sitting without support, but head control is possible
6	Loss of any locomotion as well as loss of any head and trunk control

The primary safety endpoints were conditioning regimen-related safety and short-term and long-term safety of lentiviral vector-transduced cell infusion.

The study consisted of 4 phases:

1) Screening phase (evaluation of inclusion and exclusion criteria),
2) Baseline phase,
3) Treatment phase: cell harvest for investigational drug product manufacture on day -4, busulfan conditioning day -4 to day -1, administration of Libmeldy on day 0
4) Follow up phase (8 years), see Figure 3.

Detailed information of the study is reported in Appendix Table 40.



The overlap between the Baseline and Treatment phases allows for the requirement of performing the Baseline clinical and instrumental evaluations used to assess the efficacy of the treatment (e.g., GMFM scale and brain MRI) at the latest possible time before treatment.

Figure 3. Study diagram of 201222.

Early access Programmes

One early-symptomatic early juvenile (ES-EJ) MLD patient was treated under a compassionate use scheme (CUP 207394), after the enrolment in study 201222 was closed to EJ patients. No formal inclusion or exclusion criteria were established for this CUP; however, this patient met all the eligibility criteria defined for Study 201222 but was symptomatic for 8 months prior to treatment (not ≤ 6 months from onset of symptoms). The efficacy endpoints were similar to study 201222.

Because Study 201222 was closed for enrolment and no other clinical trials with Libmeldy were open for recruitment, three pre-symptomatic patients were treated under a Hospital Exemption (HE) programme 205029. The enrolment criteria, study design and efficacy endpoints were similar to those defined for study 201222.

Following the HE, a new CUP 206258 was initiated, and five pre-symptomatic patients were treated. The enrolment criteria, study design and efficacy endpoints were similar to those defined for Study 201222; however, the maximum dose was increased to the level 30 × 106 cells/kg. More details of these three expanded access programs are reported in Appendix Table 41.

Commercial formulation 205756

Study 205756 is a single arm, single centre, open label study for pre-symptomatic subjects with early-onset MLD. This study was initiated to enable continued controlled access to Libmeldy using the intended commercial cryopreserved formulation. Detailed information is reported in Appendix Table 42.

Comparator population, TIGET NHx study 204949

A non-concurrent comparator group from the TIGET NHx study 204949 was used for the evaluation of treatment effects in the analyses of clinical trial and expanded access program data. In addition to prospective data collection following enrolment in the NHx study, retrospective data available prior to enrolment were also collected with the objective of reconstructing the disease progression of these subjects as much as possible.

The age and disease variant-matched data included 19 LI-MLD subjects and 12 EJ-MLD subjects from the NHx study. In addition, a matched-sibling analysis was also undertaken when the data were available, as eight LI subjects and four EJ subjects treated with Libmeldy had untreated siblings enrolled in the NHx study. The matched sibling analysis set included 12 subjects treated with fresh formulation of Libmeldy (OTL-200-f) and 11 corresponding untreated siblings from the TIGET NHx Study.

The age matching was done at the population level for example for the comparison of measurements at 2 years after the treatment. This means that all untreated patients, within the age range of treated patients at 2 years after the treatment, were selected for the analysis. Individual patient matching was not performed.

3.2.2 Other ongoing and planned trials

Late onset MLD

There is an ongoing phase 3 study to evaluate the efficacy and safety of the cryopreserved formulation of Libmeldy in the LJ-MLD patients (OTL-200-07; NCT04283227). The interim report date is planned to be in 2028 and the final study report date 30 June 2032 (1).

LongTERM-MLD study

As part of the conditional marketing authorisation, it is mandatory to continue monitoring long-term safety and efficacy outcomes data from patients treated with Libmeldy. The dataset should cover patients treated previously in clinical trials and new patients treated with Libmeldy in post-authorisation setting. The planned follow-up is 15 years post treatment (1).

3.3 Patient populations

3.3.1 Efficacy population

The efficacy population was constructed using participants from the registrational study 201222 (n=20), the compassionate use programs 207394 (n=1) and 206258 (n=5) and three patients treated under hospital exemption (HE 205029) (Figure 4). Four of these patients were excluded from the efficacy analysis (n=25) because of a rapid disease progression between the screening and treatment (n=1) or because they did not meet the approved indication at screening (n=3). The 6 patients treated with cryopreserved formulation were not included because of limited data available. The efficacy results are presented for 25 patients, 15 with PS-LI, 5 with PS-EJ and 5 with ES-EJ-MLD (1,2).

Mean age of LI patients and EJ patients was 12 months and 66 months at first contact, respectively (ranges: 8–18 months and 11–140 months). Mean duration of follow-up was 3.8 years for LI patients (range: 1.0-7.5 years) and 3.6 years for EJ patients (1.0–5.2 years).

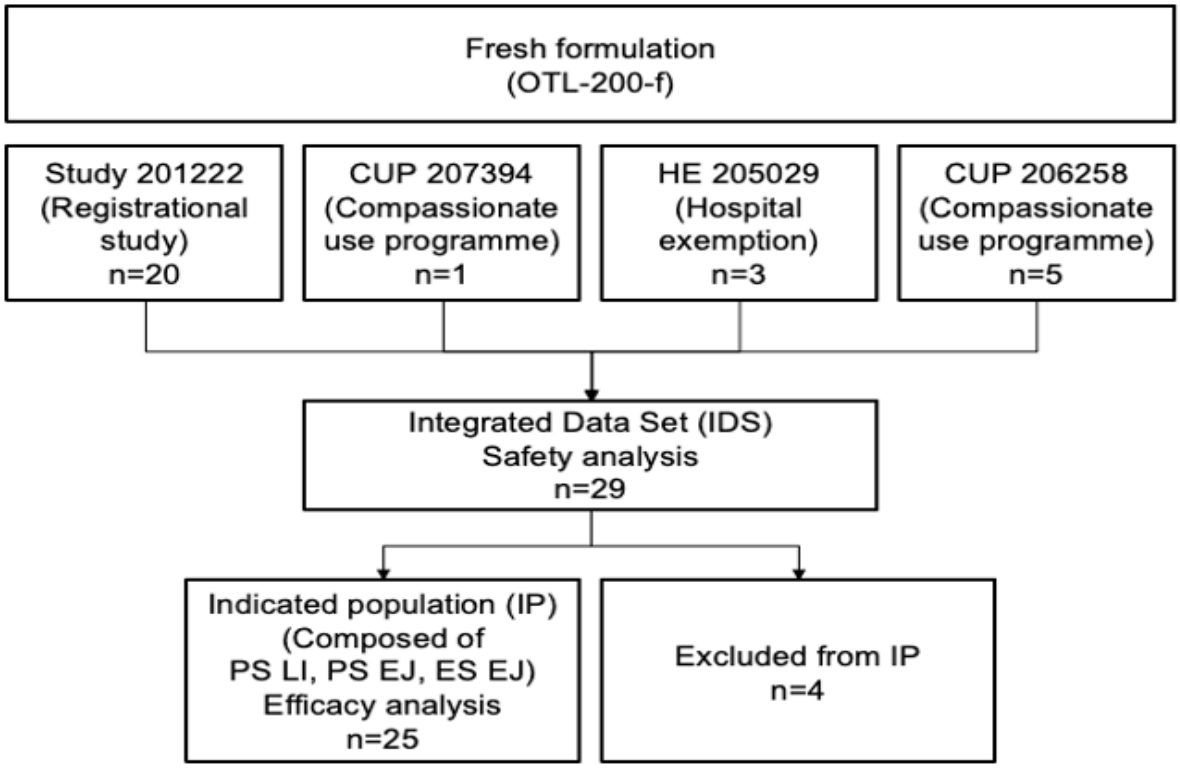


Figure 4. Construction of efficacy and safety populations. PS LI = pre-symptomatic late infantile; PS EJ = pre-symptomatic early juvenile; ES EJ = early-symptomatic early juvenile.

3.3.2 Safety population

All 29 patients who received fresh formulation of Libmeldy were included in the safety population. 16 patients received myeloablative conditioning regimen (MAC) and 13 patients sub-myeloablative conditioning regimen (SMAC).

3.3.3 Comparator population

Among the 31 subjects included in the comparator group from the 204949 (TIGET NHx) study, 19 subjects were LI-MLD and 12 subjects were EJ-MLD. 11 patients were matched siblings with Libmeldy-treated clinical trial patients. The comparator group does not include all patients reported by Fumagalli et al. (8).

Mean age of LI patients and EJ patients in the comparator group was 21 months and 52 months at first contact, respectively (ranges: 10–28 months and 20–74 months). Mean duration of follow-up was 6.8 years for LI patients (range: 1.8-14.2 years) and 8.6 years for EJ patients (2.5–16.1 years).

3.4 Results for clinical efficacy

The registrational study 201222 had two co-primary endpoints: improvement of GMFM score by 10 percent compared to the untreated population and increase in the ARSA activity by twice the standard deviation compared to the base line, at 2 years after the treatment. The GMFM score exceeded the pre-defined threshold of a difference of 10 percent in all patient groups. The ARSA activity in PBMC increased at levels higher than reported for healthy subjects and at two years post treatment there were a statistically significant increase in ARSA activity for both LI and EJ subgroups compared to baseline. However, the information available does not allow conclusions on whether the co-primary endpoint related to ARSA activity was met in the study 201222 (1,2). Based on the data and results provided, it is not possible to conclude whether the differences are larger than 2 times SD (SD of ARSA activity not available/shown) which was the prespecified criteria for meeting this endpoint.

Unless otherwise specified, the source of the following information is the material submitted by the marketing authorization holder.

3.4.1 Overall survival

PS-LI patients

Kaplan-Meier plots of overall survival of PS-LI patients in the efficacy (n=15) and comparator (n= 19) populations are shown in

Figure 5. All treated patients were alive at the time of data cut-off in March 2018. Median follow-up time in the treatment population was 3 years.

In the comparator population, several patients died between 4–6 years of age (

Figure 5). Out of 19 untreated patients in the NHx study, seven were alive at the time of data cut-off in March 2018. Median age of death was 11.2 years. Median duration of follow-up was 4.5 years.

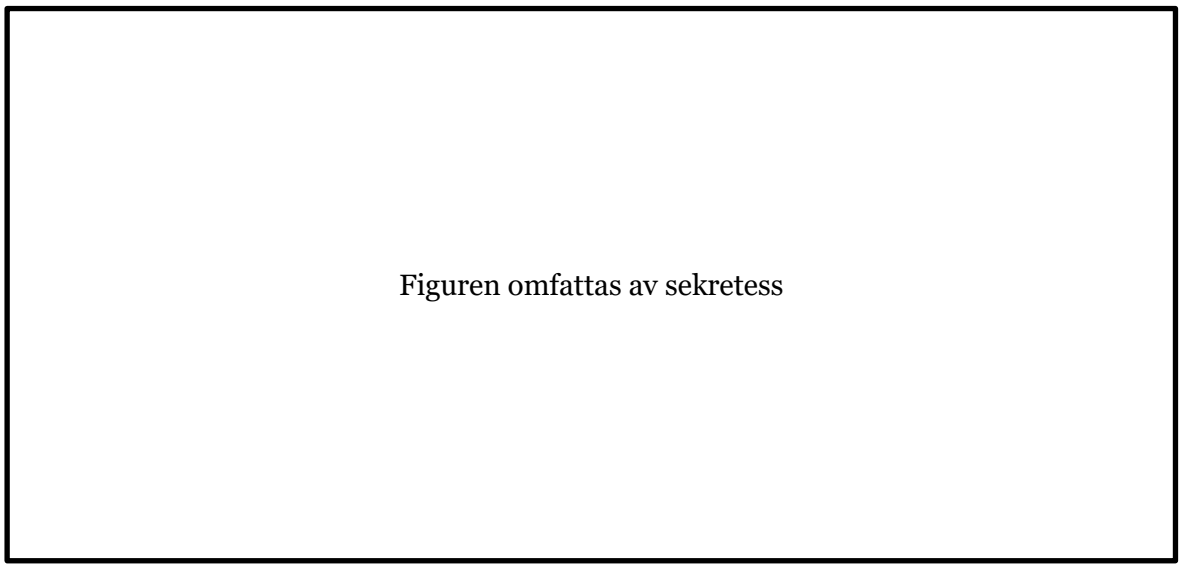


Figure 5. Kaplan-Meier plot of overall survival (OS) for PS-LI patients treated with Libmeldy (red) or BSC (black). OTL-200-f= fresh formulation of Libmeldy. Pre-Symp = Pre-symptomatic; LI = Late Infantile.

Treated LI patients (n=7) were also compared with untreated siblings in the TIGET NHx study (n=6). Kaplan-Meier plot of the comparison is shown in Figure 6. All treated patients were alive at the time of data cut-off. All untreated siblings died before the age of 7 years.

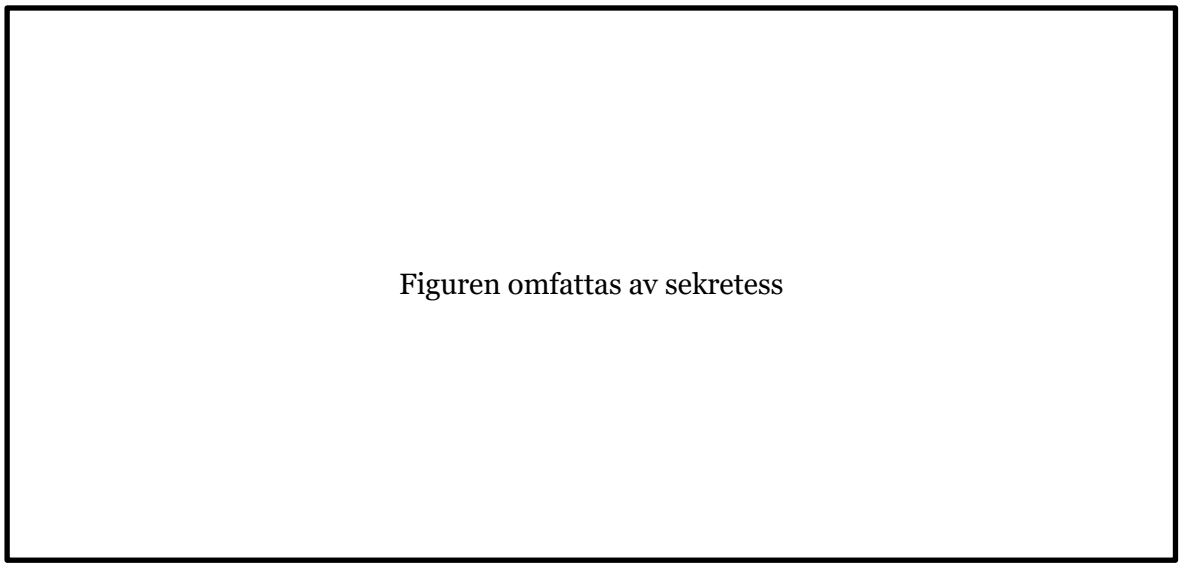


Figure 6. Kaplan-Meier plot of overall survival (OS) for LI patients treated with Libmeldy (red) with comparison to sibling treated with BSC (black). OTL-200-f= fresh formulation of Libmeldy.

EJ patients

Kaplan-Meier plots of overall survival of treated PS-EJ patients (n=5), treated ES-EJ patients (n=5) and untreated EJ patients (n= 12) are shown in Figure 7.

All treated ES-EJ patients were alive at the time of data cut-off in March 2018. One treated PS-EJ patients had died of cerebral ischaemic infarction deemed unrelated to MLD or the Libmeldy treatment. Two untreated EJ patients had died at the time of data cut-off. Median follow-up times were 3 and 4 years for treated PS-EJ and ES-EJ patients, respectively, and 7 years for untreated EJ patients.

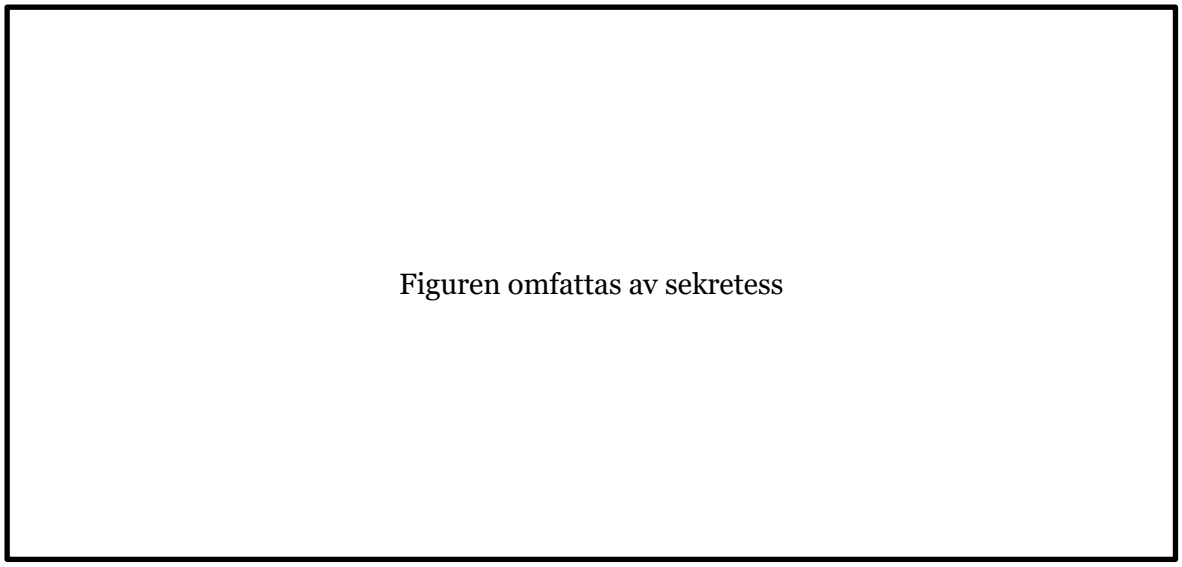


Figure 7. Kaplan-Meier plot of overall survival (OS) for PS-EJ (red) and ES-EJ (blue) patients treated with Libmeldy with comparison to BSC (black). OTL-200-f= fresh formulation of Libmeldy. Pre-Symp= Pre-symptomatic; Symp= Symptomatic; EJ= Early juvenile.

3.4.2 Severe cognitive and motor impairment-free survival (sCMFS)

Severe cognitive and motor impairment-free survival (sCMFS) was defined as the interval from birth to severe cognitive impairment (DQ Performance ≤55) and loss of locomotion and loss of sitting without support (GMFC Level 5 or higher) or death from any cause.

PS-LI

Kaplan-Meier plots of sCMFS of PS-LI patients in the efficacy (n=15) and comparator (n= 19) populations are shown in Figure 8. All treated patients remained alive and free of severe cognitive and motor impairment at the time of data cut-off in March 2018. On the contrary, in the comparator population the number of patients alive and free of severe cognitive and motor impairment rapidly declined between three and six years of age. In the matched sibling analysis, none of the patients in the comparator population was event free at the age of six years (Figure 9).

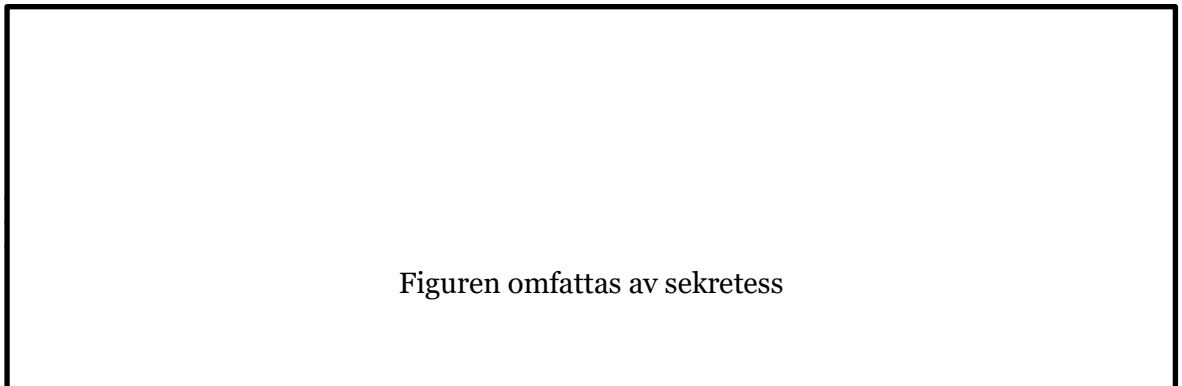


Figure 8. Kaplan-Meier plot — age at severe cognitive and motor impairment or death of treated PS-LI subjects (red) with comparison to NHx data (black). OTL-200-f = fresh formulation of Libmeldy; PSymp at GT= Pre-symptomatic at Gene Therapy; LI = Late Infantile.

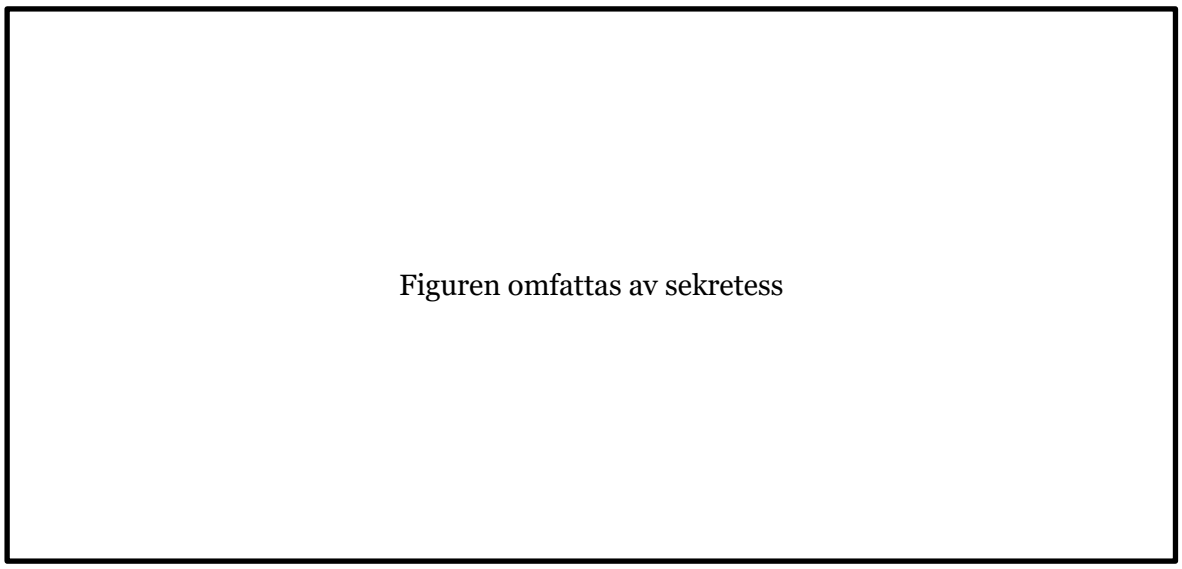


Figure 9. Kaplan-Meier plot — age at severe cognitive and motor impairment or death of treated LI subjects with comparison to untreated siblings. OTL-200-f = fresh formulation of Libmeldy; LI = Late Infantile.

EJ patients

Kaplan-Meier plots of sCMFS of treated PS-EJ patients (n=5), treated ES-EJ patients (n=5) and untreated EJ patients (n= 12) are shown in Figure 10. All treated ES EJ patients were event free at the time of data cut-off in March 2018. One treated PS EJ patient had died of cerebral ischaemic infarction deemed unrelated to MLD or the Libmeldy treatment. In the comparator population the number of patients alive and free of severe cognitive and motor impairment rapidly declined between 6 and 10 years of age. Similar result is seen in the matched sibling analysis (Figure 11).

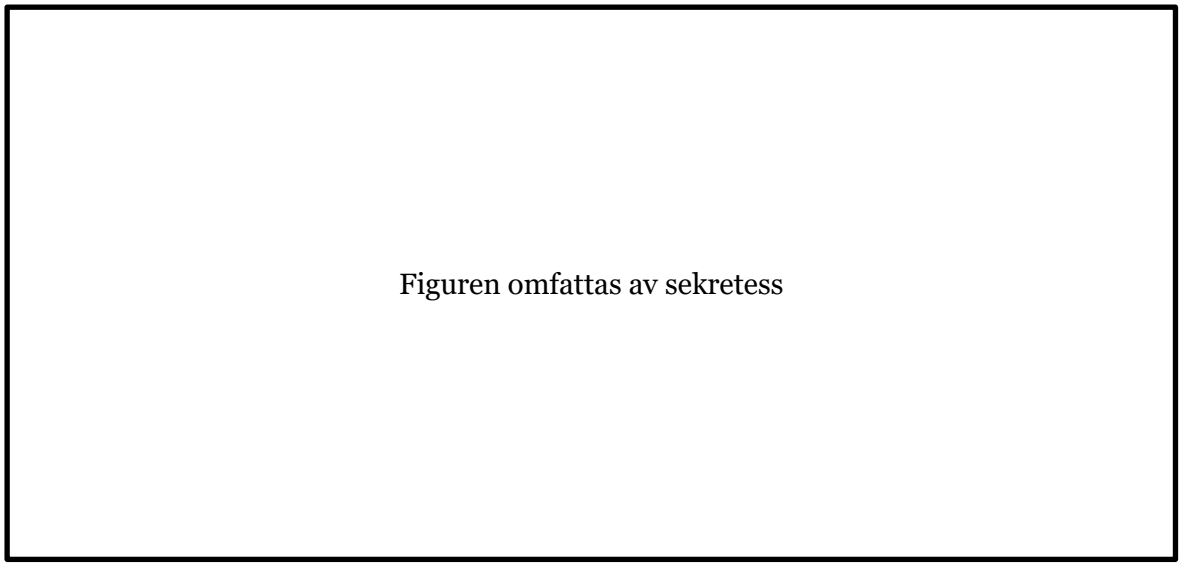


Figure 10. Kaplan-Meier plot — age at severe cognitive and motor impairment or death of treated EJ subjects with comparison to NHx data. OTL-200-f= fresh formulation of Libmeldy; PSymp at GT= Pre-symptomatic at Gene Therapy; Symp at GT= Symptomatic at Gene Therapy; EJ= Early juvenile.

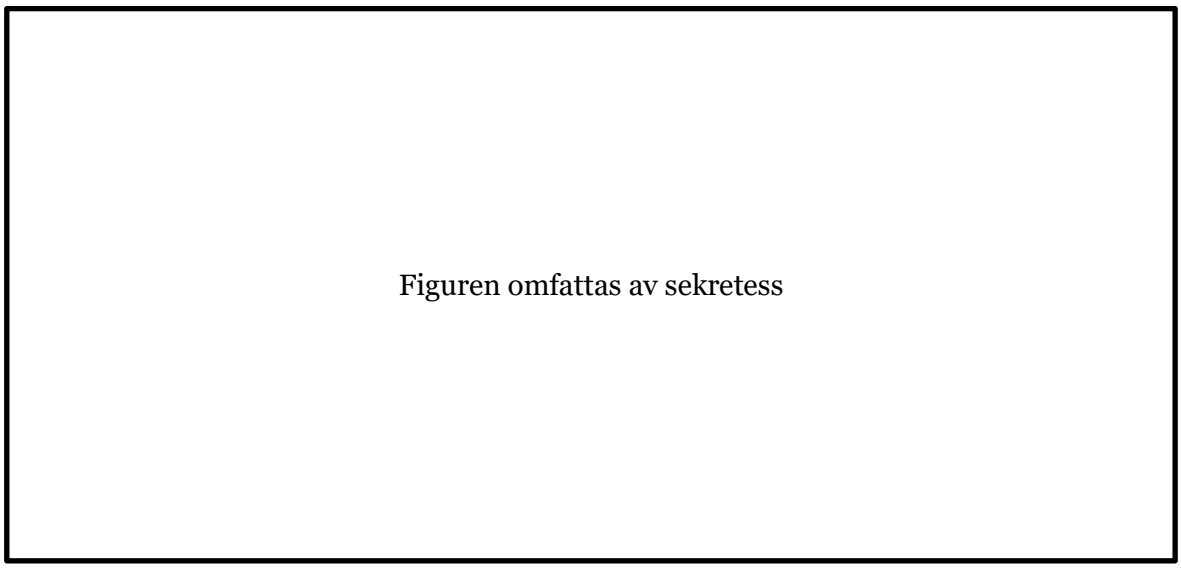


Figure 11. Kaplan-Meier plot — age at severe cognitive and motor impairment or death of treated EJ subjects with comparison to untreated siblings. OTL-200-f= fresh formulation of Libmeldy; EJ= Early juvenile.

3.4.3 Gross motor function measure (GMFM)

The results of GMFM measurements are presented as least square means and difference from an ANCOVA analysis, adjusted for age and treatment (Table 3). TIGET NHx Study subjects were age and disease subtype matched to the subjects treated with Libmeldy. Data were not available for CUP 206258 patients (n=5) because they were not yet followed to Year 2 at the time of the data cut-off for the integrated analyses. The treatment differences were statistically significant in Year 2 in favour of Libmeldy for PS-LI and PS-EJ patients, but not for ES-EJ patients.

Table 3. Gross Motor Function (GMFM) total score (%) 2 years and 3 years after the treatment.

	Libmeldy, % (n)	untreated, % (n)	difference, %, p
PS-LI			
Year 2	79.5 (10)	8.4 (8)	71.0 (<0.001)
Year 3	82.6 (9)	2.8 (9)	79.8 (<0.001)
PS-EJ			
Year 2	96.7 (4)	44.3 (8)	52.4 (0.008)
Year 3	93.2 (4)	18.2 (9)	74.9 (<0.001)
ES-EJ			
Year 2	74.2 (5)	29.8 (10)	44.4 (0.073)
Year 3	69.4 (5)	15.5 (10)	53.8 (0.015)

3.4.4 Arylsulfatase (ARSA) activity

Arylsulfatase (ARSA) activity in peripheral blood mononuclear cells (PBMC) at year 2 (2 years after treatment) compared to pre-treatment values was a co-primary endpoint in the study 201222. ARSA activity was measured also in bone marrow and cerebrospinal fluid (results not shown). A statistically significant increase in ARSA activity in PBMCs was observed at year 2 post-treatment compared to pre-treatment baseline in PS-LI, PS-EJ and ES-EJ patients (Table 4).

Table 4. ARSA activity in PBMC. Adjusted mean, nmol/mg/h.

Subgroup	Baseline	Year 2	Year 3
PS-LI	26.3 nmol/mg/h (95% CI 14.4, 48.0) n=14	632.4 nmol/mg/h (95% CI 263.1, 1520.2) p<0.001 vs Baseline n=9	1165.9 nmol/mg/h (95% CI 472.5, 2876.5) p<0.001 vs Baseline n=8
PS-EJ	26.3 nmol/mg/h (95% CI 8.9, 78.1) n=5	232.5 nmol/mg/h (95% CI 67.8, 797.4) p=0.003 vs Baseline n=4	471.4 nmol/mg/h (95% CI 124.4, 1786.5) p<0.001 vs Baseline n=3
ES-EJ	26.3 nmol/mg/h (95% CI 9.7, 71.7) n=5	101.8 nmol/mg/h (95% CI 34.8, 298.0) p=0.031 vs Baseline n=4	253.8 nmol/mg/h (95% CI 92.7, 695.1) p<0.001 vs Baseline n=5

3.4.1 Gross Motor Function Classification in MLD (GMFC-MLD)

The motor function of patients was classified using Gross Motor Function Classification in MLD (GMFC-MLD) classification system (23). It consists of 7 levels, ranging from level 0 (normal gross motor function) to level 6 (loss of any locomotion and any head and trunk control) (Table 2). GMFC-MLD is age independent and should be applied only after the age of independent walking is achieved (18 months or older).

PS-LI patients

Out of 15 treated PS-LI patients, [–––]

[redacted] In the NHx study, there are no observations of patients in GMFC-MLD levels [redacted]. Individual development of comparator patients cannot be inferred based on Figure 12.

Table 5. GMFC-MLD levels of LI patients (n=15) at the end of the follow-up.

Tabellen omfattas av sekretess

Figuren omfattas av sekretess

Figure 12. Panel plot of GMFC-MLD levels by age in LI patients treated with Libmeldy, in comparison to NHx data. The boxplots display the 10th, 25th 50th, 75th, and 90th percentiles. OTL-200-f = Libmeldy fresh formulation; [1] = TIGET NHx study.

EJ-patients

Out of 5 treated PS-EJ patients, [–––] (Table 6, Figure 13). [––]

Matched sibling analysis was also presented for [––––––––––––––] (Figure 13). All of the untreated siblings [––]

Table 6. GMFC-MLD levels of PS-EJ patients (n= 5) and ES-EJ patients (n= 5) at the end of the follow-up.

Tabellen omfattas av sekretess

Figuren omfattas av sekretess

Figure 13. Panel plot of GMFC-MLD levels by age in EJ patients treated with Libmeldy, in comparison to NHx data. The boxplots display the 10th, 25th 50th, 75th, and 90th percentiles. OTL-200-f = Libmeldy fresh formulation; [1] = TIGET NHx study.

3.4.2 Treatment effect on cognitive function

The developmental quotient (DQ) is a measure of a patient's cognitive function. It reflects the individual's developmental age in relation to their chronological age, where DQ=100 means that the developmental age equals the chronological age. As such, DQ scores are age-independent and do not develop with increasing age. Multiple tests were used for DQ measurements. Normal cognitive development was defined as a DQ of 85 or more, mild cognitive impairment as a DQ of 70-85, moderate cognitive impairment as a DQ of 55-70, and severe cognitive impairment as a DQ ≤55.

LI patients

The DQ scores for all the LI patients were above [–––––––] (Table 7). The adjusted mean DQ score for treated PS-LI patients at year 2 was [––––––––] for untreated patients (difference: [–––]) At year 3, the scores were [–––––], respectively (difference: [–––]). Three LI patients had [–––––––––––––––––––] at year 2. Two of them later improved, but one of them declined below [–––––––––––––––––––––––––––––] (Figure 14).

Table 7. Development quotient (DQ) adjusted mean score.

Tabellen omfattas av sekretess

Figuren omfattas av sekretess

Figure 14. DQ profiles of LI subjects treated with Libmeldy (blue), in comparison to NHx data (orange). OTL-200-f = fresh formulation of Libmeldy. GT = gene therapy.

In all treated PS-EJ patients, DQ scores remained above [–––––––] (Figure 15). The adjusted mean DQ score at year [–––––––] for treated PS-EJ patients and [–––] for untreated patients (difference: [–––]) (Table 7). At year 3, the scores were [–––––––], respectively (difference: [–––]).

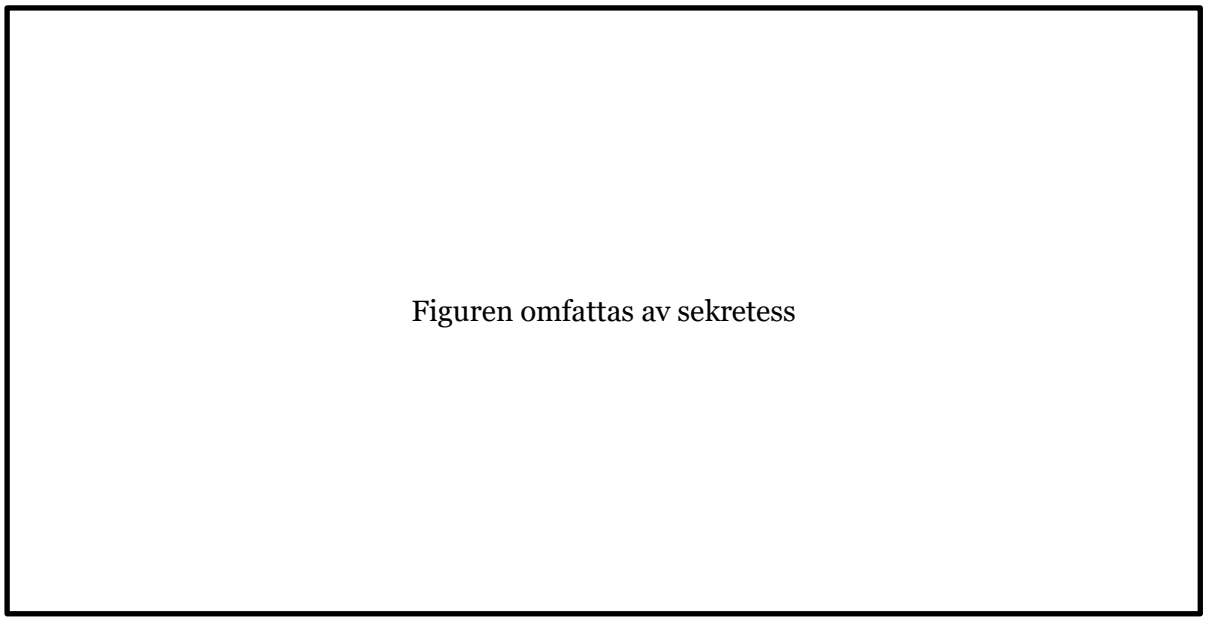


Figure 15. DQ profiles in PS-EJ patient treated with Libmeldy (blue), in comparison to NHx data (orange). OTL-200-f = fresh formulation of Libmeldy. GT = gene therapy.

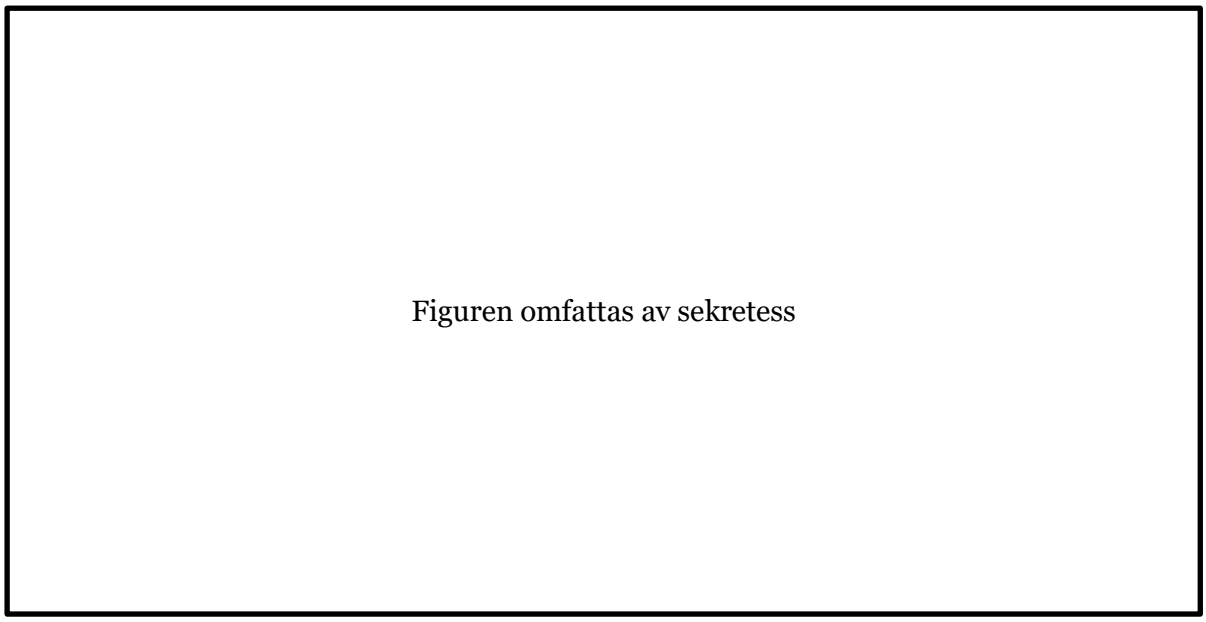


Figure 16. DQ profiles in ES-EJ patients treated with Libmeldy (blue), in comparison to NHx data (orange). OTL-200-f= fresh formulation of Libmeldy. GT= gene therapy.

In all treated ES-EJ, DQ scores remained above [––––––] (Figure 16). However, one patient declined to [––––––––––––––––––––––] of age. The adjusted mean DQ score at year 2 was [–––] for treated PS-EJ patients and [–––] for untreated patients (difference: [––}) (Table 7). At year 3, the scores were [––––––––––], respectively (difference: [––]).

All treated patients [–––.

3.4.3 Engraftment

The presence of lentiviral vector sequences in the genomic DNA was detected using quantitative polymerase chain reaction and expressed as vector copy number, which corresponds to the average number of copies of the transduced gene per cell.

Engraftment was estimated as the percentage of lentiviral vector positive cells (LV+ cells) in bone marrow-derived chlorogenic progenitor cells. Engraftment above 4 percent of cells at year 1 after treatment was a secondary endpoint in the study 201222, determined as vector copy number per cell ≥0.04, equivalent to 4 percent of cells assuming one vector copy per cell.

The percentage of LV+ cells in bone marrow derived colonies at year 1 after treatment was [––––––––––––––––––––––––––] At year 5, the same proportion was [–––––––––––––––––––––––––––] The percentages seemed to be higher in the LI subgroup (n=12) than in the EJ subgroup (n=12) at all timepoints (Figure 17). The vector copy number values in PBMCs in LI and EJ subgroups remained stable during the follow-up after initial increase (Figure 18). The vector copy number in LI subgroup was approximately was [–––––––––––––––––––––––––––––––] These results are for integrated efficacy data set used for marketing authorization. (1)

Figuren omfattas av sekretess

Figure 17. Percentage of lentiviral vector transduced cells in bone marrow over time.

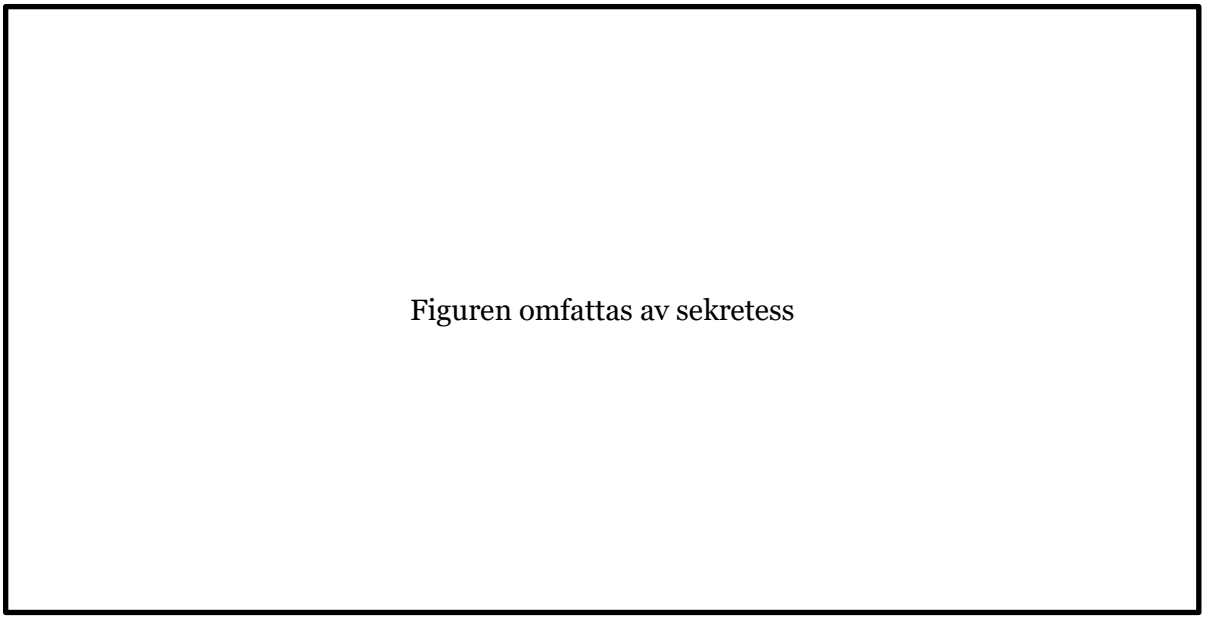


Figure 18. Vector copy number profile in total PBMC and subpopulations, for all visits by disease subtype and symptomatic status at gene therapy (GT).

3.4.4 Brain MRI and nerve conduction velocity

Brain MRI scores

The effect of Libmeldy treatment on the progression of white matter demyelination and atrophy in the central nervous system was assessed using brain MRI. Improvement in the MRI total score 2 years after the treatment was a secondary endpoint of the study 201222. Brain MRI was performed and interpreted at a single institution by an independent neuroradiologist. Quantification of MRI abnormalities was performed by adapting and optimizing the Loes' scoring system previously used for adrenoleukodystrophy and MLD (10,22,24). The adapted MRI score ranges from 0 (normal) to 31.5 (markedly abnormal), and a score of > 0 is considered abnormal.

The adjusted mean MRI total scores in the PS-LI (n=8) and PS-EJ (n=4) populations at year 2 were lower than in the untreated NHx population (Appendix Table). In the ES-EJ population, there was no significant difference at year 2.

Nerve conduction velocity (NCV)

Peripheral neuropathy, characterised by severe slowing of motor and sensory nerve conduction, often precedes the CNS manifestations of MLD, particularly in LI-MLD and contributes to the gross motor impairment observed in this MLD variant. Nerve conduction velocity (NCV) from electroneurography ENG recordings was measured and interpreted at a single institution by the same neurophysiologist.

Improvement in the NCV index at 2 years after the treatment was a secondary outcome measure in study 201222. NCV index at year 2 for PS-LI patients was significantly higher for treated than for untreated patients (Appendix Table). In contrast, treated ES-EJ patients had lower NCV index than untreated patients. There was no significant difference between treated and untreated PS-EJ patients at year 2.

3.5 Results for safety

The information presented in this section includes integrated safety data from all 29 patients treated with fresh formulation of Libmeldy in the registrational study (n=20) (study 201222) and expanded access programs (n=9) (CUP 207394, HE 205029, CUP 206258). Of the 29 patients, 16 patients had LI-MLD variant, and 13 patients had EJ-MLD variant. Additionally, some results are provided from four patients included in the Study 205756 of the cryopreserved commercial formulation.

The data cut-offs for safety are as follows: 30 March 2018 (study 201222), 5 January 2018 (CUP 207394), 5 December 2018 (HE 205029) and 5 December 2018 (CUP 206258).

Patient exposure

For the safety population (n=29), the median (min–max) follow-up time was 3.16 (0.64–7.51) years. Median duration of follow-up was 3.04 years in the LI subgroup and 3.49 years in the EJ subgroup. Two patients in the LI subgroup had more than seven years of follow-up.

In the safety analysis pre-treatment phase was defined as prior to the first day of the conditioning regimen (screening and baseline). Treatment phase was defined as from the first day of the conditioning regimen to the date of gene therapy (GT) infusion. Follow-up phase comprises the whole post-GT period. Follow-up phase was divided in acute[1], 3-month post-GT[2], short-term[3] and long-term phases[4]. At the time of cut-offs, only 16 patients were in the long-term phase. (1)

Summary of adverse events

Adverse events (AEs) are summarized in Table 8. All patients (100%) experienced at least one grade 3 or higher adverse event. The most frequently reported grade 3 events were febrile neutropenia (79%), gait disturbance (52%), and stomatitis (41%). Four patients (14%) experienced grade 4 events, including dysphagia in two patients, metabolic acidosis in one patient, and veno-occlusive disease and atypical hemolytic uremic syndrome in one patient (1).

Twenty patients (69%) experienced serious adverse events (SAEs) during the follow-up post-GT phase. SAEs were most frequently reported in the gastrointestinal disorders (31%), infections and infestations (28%), and nervous system disorders (21% of patients) system organ classes. Two patients (7%) experienced SAEs of device-related infection in the pre-treatment phase, and two patients (7%) infection in the follow-up phase. None of the SAEs were deemed as related to Libmeldy by the investigator. They were all consistent with the known safety profile of busulfan or symptoms of MLD (1).

In the treatment phase 17 patients (59%) experienced any adverse event. The most common adverse events were metabolic disorders (14%), hepatomegaly (7%), head injury (3%), respiratory tract infection (3%) and rash erythematous (3%) (1).

In the total follow-up phase all patients experienced adverse event. In the acute phase 3 patients (10%), in the 3-month post-GT 28 patients (97%), in the short-term 28 patients (97%) and in the long-term 13 patients out of 16 patients (81%) experienced adverse event. The most common adverse events in the follow-up phase were infections and infestations (90%), blood and lymphatic system disorders (79%), gastrointestinal disorders (79%), investigations (79%),

[1] 48 hours after gene therapy infusion.
[2] From 48 hours after the end of infusion up to day 100 (day 100 included).
[3] From day 101 till the end of day 1097.
[4] After day 1098.

general disorders and administration site conditions (76%), hepatobiliary disorders (55%), and nervous system disorders (52%) (1).

Four patients (14%) had positive anti ARSA antibody (AAA) test and these were the only adverse events that were deemed related to Libmeldy. All patients with positive antibody tests had LI-MLD and they were from expanded access programmes. For one patient this event resolved spontaneously, for the other three the events resolved following a course of rituximab treatment (1).

A higher percentage of subjects with EJ-MLD (85%) than subjects with LI-MLD (38%) experienced adverse events during the treatment phase. Subjects with LI-MLD experienced fewer serious adverse events during the follow-up phase compared with subjects with EJ-MLD (63% vs 77%) (1).

Table 8. Overall summary of adverse events for different phases. Pooled results from study 201222, CUP 207394, HE 205029, CUP 206258 (1).

Parameter	Pre-treatment	Treatment	Total follow-up post-GT
Number of subjects with adverse event, n (%)			
At least one AE	29 (100)	17 (59)	29 (100)
At least one serious AE	2 (7)	0 (0)	20 (69)
At least one grade 3 or higher AE	7 (24)	8 (28)	29 (100)
At least one AE leading to death	0 (0)	0 (0)	3 (10)
At least one AE leading to withdrawn	NA	0 (0)	3 (10)
Number of subjects with treatment-related adverse event, n (%)			
At least one AE	NA	0 (0)	4 (14)
At least one serious AE	NA	0 (0)	0 (0)

NA: Not Applicable. GT: Gene Therapy. CUP= Compassionate Use Program, HE= Hospital Exemption. Source: (1)

Deaths

Three deaths have been reported during the clinical trials or expanded access programs. All of these occurred after patients had received the treatment and all were deemed unrelated to Libmeldy. Two of these occurred during the registrational study (study 201222) and were associated with rapid progression of the underlying disease. In both cases the subjects would not be eligible for treatment in the post-market authorisation settings given the approved indication (1,2).

One patient's death in the expanded access program (CUP 206258) was due to left hemisphere cerebral ischemic stroke. The patient was pre-symptomatic at the time of treatment and asymptomatic at the time of ischemic stroke. The cause of the event is unknown, but the investigator assessed that there was not sufficient information to establish a causal relationship between the event and gene therapy. Therefore, the event of ischemic cerebral infarction was deemed unrelated to Libmeldy or MLD (1,2).

Adverse events of special interest

European Medicines Agency has concluded that the market authorization holder marks the following adverse events as events of special interest: renal tubular acidosis / metabolic acidosis, hepatobiliary disorders, elevations in IgE and elevations in ferritins (1).

In the integrated safety data, renal tubular acidosis or metabolic acidosis was reported in 16 patients prior to treatment with Libmeldy and in 19 patients in total. Two patients who experienced AEs of renal tubular acidosis prior to the treatment subsequently experienced SAEs of metabolic acidosis. The events occurring post-GT were considered to be related to the underlying disease and not Libmeldy (1,2).

No hepatic impairment was reported prior treatment with Libmeldy (1). During the follow-up, 16 patients experienced hepatobiliary adverse event. After excluding events related to the gallbladder, 11 subjects (38%) had events in the hepatobiliary disorders system organ class. European Medicines Agency has concluded that hepatic ARSA and hepatomegaly are known safety concerns related to busulfan conditioning (25).

Increased IgE was reported in 4 subjects (14%) before treatment with Libmeldy and in 13 patients (45%) during the follow-up phase. Investigator assessed them to be unrelated to Libmeldy (1).

Six patients (21%) had adverse events of serum ferritin increased. All were reported in the 3-month post-GT phase and they were likely related to repeated transfusions during this time period. Investigator assessed them to be unrelated to Libmeldy (1).

Safety of busulfan

Gene therapy with Libmeldy represents an autologous HSCT and exposes patients to short- and long-term adverse effects of myeloablative busulfan-therapy. Severe short-term consequences of busulfan therapy may, for example, include veno-occlusive disease and infections. Busulfan can impair fertility and ovarian suppression (26).

Most common grade 3 adverse events attributed to busulfan were febrile neutropenia (79%), stomatitis (41%), mucosal inflammation (31%) and veno-occlusive disease (10%) (2).

16 patients received myeloablative conditioning regimen (MAC) and 13 patients sub-myeloablative conditioning regimen (SMAC). More neutropenia and stomatitis were observed in patients who received MAC regimen compared to patients who received SMAC regimen (1).

Busulfan has been classified as a human carcinogen, and a causal relationship between busulfan exposure and cancer has been observed. For example, leukaemia patients treated with busulfan developed many different cytological abnormalities, and some developed carcinomas (26).

Safety of commercial formulation of Libmeldy

In Study 205756, four patients (100%) experienced a total of 19 grade 3 adverse events. No grade 4 or grade 5 adverse events were reported during any of the study phases in Study 205756. In the study, a total of 4 serious adverse events were reported in two patients. None of the serious adverse events were considered by the investigator to be related to Libmeldy (1).

European Medicines Agency has concluded that the evidence of cryopreserved (commercial) formulation is too limited to draw any conclusion. However, they conclude that there is no apparent difference in safety between fresh and cryopreserved formulations (1).

Updated safety results

Orchard Therapeutics submitted updated safety results upon request for FINOSE. In the updated safety results the median (min–max) follow-up time was 4.5 (0.64–8.85) years. There were no significant changes in the safety evidence between the data cut-offs.

3.6 FINOSE discussion

Clinical evidence

The evidence base is composed of one single-arm registrational study (n=20) and multiple early access schemes with 1—5 patients. Altogether, 29 patients have been treated with Libmeldy, and the safety results are presented for these patients. Four or the treated patients would not be eligible for the treatment according to the approved indication and thus, are excluded from the results of efficacy. There was no comparator arm in the trial. However, results from a natural history cohort, from the same treatment center as the treated patients were presented. These patients were selected based on their age, disease variant and disease stage (symptomatic or pre-symptomatic) for comparison. Matching on individual level was not conducted. This approach was used also for the marketing authorization application.

Efficacy

The results of overall survival proved difficult to quantify, even though it seems clear that the Libmeldy treatment had a favourable effect on overall survival of LI patients. LI patients with treatment were all alive at the end of the follow-up (median of 3.5 years), whereas in the untreated population, several patients had died between 4–6 years of age. All untreated siblings of the LI patients had died before the age of 7 years.

The overall survival result was less clear for EJ than for LI patients because of a short follow-up time (median of 3 years for PS-EJ, and 4 years for ES-EJ), and a small number of patients in the EJ group (Figure 7). The two untreated EJ patients who died were between 9–11 years of age, but only 5 out of 10 treated EJ patient have been followed after 9 years of age.

Treated patients had higher GMFM in all subgroups of disease subtype compared to untreated patients. The differences at year 2 were 71 percent, 52 percent and 44 precent in PS-LI, PS-EJ and ES-EJ patient groups, respectively. The differences between partly unmatched treated and non-treated cohorts were statistically significant in favour of Libmeldy for PS-LI and PS-EJ patients, but not for ES-EJ patients. In the registrational study 201222 the aimed effect size was 10precent. The differences seem to be larger at year 3 compared to year 2, which may result from decline of GMFM scores of untreated patients over time. The differences are greatest in PS-LI patients because of the earlier onset of the disease in these patients and a more rapid decline of GMFM score in untreated patients compared to other disease subtypes.

Out of 15 treated PS-LI patients, [——]

[——] Compared to the natural history cohort and matched siblings of the same age, the treated PS-EJ patients had higher GMFC-MLD levels. While the treated patients were on levels 0–1 at the end of the follow-up, the untreated population and matched siblings were mostly on levels 2–6 at the same age.

At end of the follow-up, [–––] Because of the short follow-up, it is difficult to say whether some of the patients had stabilized or whether they will move to lower levels later.

For all treated ES-EJ patients, the GMFC-MLD levels at the end of the follow-up were higher than for untreated patients at the same age. However, for 4/5 of the treated ES-EJ patients, the GMFC-MLD levels were higher than in the comparator population already before treatment (Figure 13). In addition, the mean age of the first contact was 52 months for untreated EJ patients and 66 months for the patients treated with Libmeldy. This may be a sign of a disease type with slower progression in the treated population, because the first symptoms seem to appear later.

[––]. These findings question the comparability of the treated and untreated populations and the ability of the matched sibling analysis to provide a valid comparison. It should be kept in mind that the registrational study was single arm, and only patients with no symptoms or at least sufficient cognitive and motor function (ES-EJ patients, equals to GMFC-MLD level 0 or 1) at the time of treatment were included.

The company refers to a case report of an identical triplet with LI-MLD (7) to justify the use of untreated siblings as comparators, because the triplet had similar disease progression. However, it is unclear whether this finding can be extrapolated to unidentical siblings. Elgün et al. have shown that the age of onset may vary between siblings and the variability in the age of onset is similar in sibling pairs and unrelated patients (12). In juvenile MLD, 80 precent of the siblings had more than one year between the disease onset and 40 precent more than 2 years. Another study shows that the onset of symptoms can vary several years within MLD EJ patients with same genotypes (8). Thus, the chronological age of patients may not be a reliable point of comparison for treated and untreated patients, not even when comparing with an untreated sibling, because the onset of symptoms has a considerable variation, also within patients with same genetic background.

There was a clear difference in the cognitive function measured with DQ between treated and untreated patients. In general, the DQ score for untreated patients after 3 and 7 years of age (LI and EJ patients, respectively) was very low, while the scores for treated patients were mostly at normal levels. However, one PS-LI patient and one ES-EJ patient developed severe cognitive impairment 4–5 years after the treatment.

Engraftment of transduced cells was estimated measuring average vector copy number from bone marrow derived cells and assuming that each cell contains no more than one copy of the gene. The proportion of these cells was 54.8 precent (range: 20% to 100%, n=23) at year 1 and 45.0 precent (range 18.8 to 90.6%, n=6) at year 5. As pointed out in EPAR, the downwards trend over time could be interpreted as a possible indicator for time-dependent decrease in treatment effect, considering that also the ARSA activity levels in individual CSF profiles seem to decrease over time. The averages of the proportion of modified cells are higher in every point of measure in LI patients compared to EJ patients, which may result from different proportions of MAC and SMAC conditioning regimens in these subgroups. The switch to MAC regimen may also explain the downwards trend of average vector copy number described above, even though there is no evidence that the use of MAC leads to higher engraftment levels (1).

Current clinical evidence indicates that the outcomes of the treatment cannot be predicted reliably for individual patients. ARSA enzyme activity in PBMC and CSF was found to be at higher level 2 years after the treatment as compared to pre-treatment baseline and the ARSA activity in CNS was within or above the normal range. However, no correlation between the ARSA activity and clinical outcomes (GMFM, GMFMC-MLD, DQ, MRI) was observed. In addition, the brain MRI results do not correspond with the motor function or other clinical outcomes, and thus MRI on its own cannot be used to determine the efficacy of Libmeldy. However, the possibility to use ARSA activity in CSF as a predicting factor for treatment success will be further elucidated in a post marketing setting (1).

The company also provided an updated data analysis, which was based on the same December 2019 data cut that was used for the results presented above (See Appendix 10). In the updated analysis the follow-up times were at least 5 years for all patients in the pivotal study (201222) and in one of the compassionate use programs (CUP 207394). The updated analysis did not change the overall conclusions on the evidence.

Safety

The limitations of Libmeldy's safety data include limited sample size, single-arm study design and limited long-term follow-up. Due to the short follow-up time, the risk of long-term adverse events has not been evaluated. Both common and rare adverse events might be missed, because of the very limited number of treated subjects.

The only adverse events attributed to Libmeldy were anti-ARSA antibody test positive. Most of the adverse events appear related to busulfan conditioning regimen. Some adverse events were related to the underlying condition MLD.

Gene therapy with Libmeldy exposes patients to adverse events related to conditioning with busulfan. The risks associated with conditioning include secondary malignancies, veno-occlusive disease and impairment of fertility. Based on the duration of follow-up, long-term toxicity of the conditioning regimen cannot be determined, such as the occurrence of second primary malignancies. EMA has concluded that the safety profile of the busulfan conditioning regimen is as expected and substantial but manageable. The incidences are higher in the MAC vs SMAC regimen for febrile neutropenia and stomatitis as well as serum ferritin increase.

So far, the only patients treated with cryopreserved commercial formulation of Libmeldy are six patients in the phase 2 study 205756. Currently there are no signs that the safety of cryopreserved formulation differs from the safety of the fresh formulation.

FINOSE conclusion: The registrational study 201222 had two co-primary endpoints: improvement of GMFM score by 10 percent compared to the untreated population and increase in the ARSA activity by twice the standard deviation compared to the base line, at 2 years after the treatment. The GMFM score exceeded the pre-defined threshold in all patient groups. The ARSA activity in PBMC increased at levels higher than reported for healthy subjects and at two years post treatment there were a statistically significant increase in ARSA activity for both LI and EJ subgroups compared to baseline. However, the information available does not allow conclusions on whether the co-primary endpoint related to ARSA activity was met in the study 201222.

FINOSE concludes, that the company has demonstrated Libmeldy's effects based on pooled results of single arm study and early access programs. Based on the results, it seems clear that the treated patients mostly stay alive and do not develop severe symptoms of MLD during the follow-up. These effects are not typically seen in the comparator population in TIGET NHx

study or in the natural course of the disease. However, it remains unclear whether the effect will remain over time. Due to the short follow-up time and limited number of treated patients, the risk of long-term adverse events has not been evaluated and also common adverse events might be missed.

The size of the treatment effects compared to untreated population of the TIGET NHx study cannot be concluded based on the data presented by the company. This is mainly since the motor and cognitive ability of the treated population is much higher at the start of the follow-up compared to the natural history cohort of similar age. Consequently, the prognosis is likely to differ between the treated patients and the historical controls. This bias remains despite the age adjustment because of a large variation in the age of onset of the disease, also between siblings. These issues are most evident in the EJ group of patients.

4 Cost-effectiveness analysis

The following chapter is based on the dossier sent in by the company. All assumptions described are based on the application if not otherwise stated. The conclusions boxes after each section gives a short assessment of the choices related to key parameter inputs, used methods, simplifications and scientific judgements made by the company. The results of the FINOSE scenario analyses are presented in section 5.2.

The positive approval by EMA, implies that EMA's advisory committee, the CHMP, indicates that the benefits of the drug outweighed the risks. EMA notes that the benefits of Libmeldy in patients with MLD who had not yet developed symptoms were clear, and during the study period patients maintained similar function as healthy subjects. Benefit was less marked and more variable in those with early juvenile MLD who already experienced symptoms, so use in this group was restricted to those who can still walk and have not developed decline in mental function. Although benefit with Libmeldy lasted several years it is not yet clear whether it will persist life-long, and extended follow-up is needed. According to EMA, because MLD is a rare disease, the studies are necessarily small and the amount of data available on side effects is limited and will also need long-term follow-up. The company has submitted a cost-effectiveness model in which patients who have been treated with Libmeldy are compared with patients who have received best supportive care in a partly retrospective and prospective study (NHx-Study). The NHx-study mostly consisted of untreated siblings of patients enrolled in the clinical trial for Libmeldy. The economic model is based on a partitioned survival model with a Markov structure. The modelled population consists of the following three patient groups that were pre-defined and included in the Libmeldy-clinical trial:

- Pre-symptomatic Late-Infantile (PS-LI): Children with a confirmed diagnosis of late infantile MLD without clinical manifestations of the disease,
- Pre-symptomatic Early-Juvenile (PS-EJ): Children with a confirmed diagnosis of early juvenile MLD without clinical manifestations of the disease,
- Early-symptomatic Early-Juvenile (ES-EJ): Children with early-juvenile MLD who have early clinical manifestations of the disease, with the ability to walk independently (GMFC-MLD ≤ 1) and before the onset of cognitive decline (IQ ≥ 85).

The combined model population presented in the company base case results is a weighted average of each eligible disease cohort, i.e., PS-LI, PS-EJ, and ES-EJ. The model also assesses the three subgroups mentioned above separated. Proportions of the combined MLD model population (Table 9) were derived from a convergence of a structured expert elicitation process compiling the input from Scandinavian clinical experts with experience in the management of patients with MLD that have been treated with Libmeldy as well as best supportive care. An overview of the model structure is depicted in Figure 19, and explained further below.

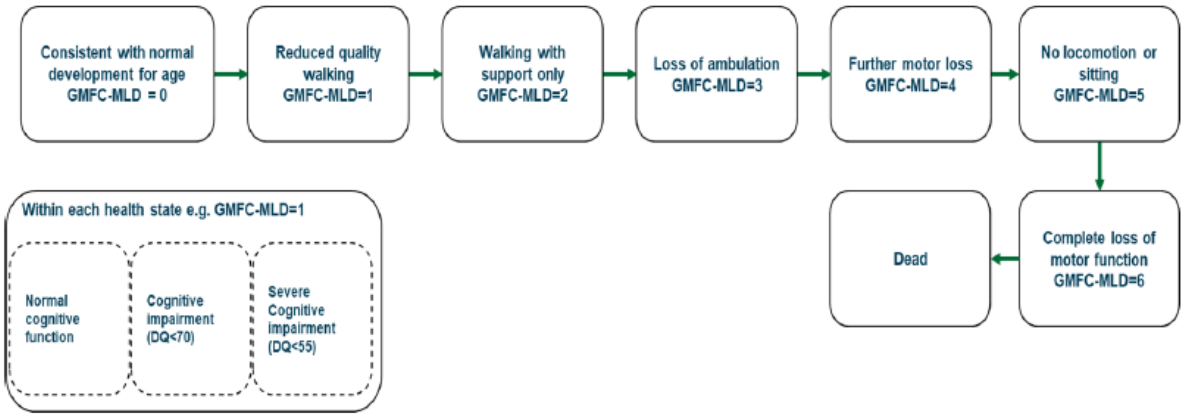


Figure 19. Partitioned survival model (PSM) for modelling the costs and effect of Libmeldy. GMFC-MLD: Gross Motor Function Classification – Metachromatic Leukodystrophy.

At model entry, the overall patient population is distributed across PS-LI, PS-EJ and ES-EJ subgroups according to Table 9.

Table 9. MLD Combined Eligible Patient population breakdown by disease cohort e.g., combined patient population.

MLD Disease Cohort	Percentage of model cohort
PS-LI	72,5%
PS-EJ	15,1%
ES-EJ	12,3%

The age at model entry for each of the disease variants is based on the mean age at treatment in the Libmeldy clinical trial (PS-EJ and ES-EJ) or the earliest age at which the GMFC-MLD score can be used (PS-LI). The PS-LI patients begins at 18 months of age because GMFC-MLD scores are only validated for use in patients older than 18 months of age as GMFC-MLD 0 is based on an un-impacted patient's ability to achieve walking without support within the range of normal development.

Table 10. Age and Health state of MLD patients at model entry.

Disease Variant	GMFC-MLD Stage at Model Entry	Patient Age at Model Entry
PS-LI	100% GMFC-MLD 0	18 months
PS-EJ	100% GMFC-MLD 0	45 months
ES-EJ	40% GMFC-MLD 0 60% GMFC-MLD 1	80 months

Table 10 also presents the baseline health state distribution. At baseline, all pre-symptomatic patients (PS-LI and PS-EJ) are in GMFC-MLD 0, where they remain until they first experience clinical onset of disease, defined by progression beyond GMFC-MLD 0. Early symptomatic patients (ES-EJ only) enter the model either in GMFC-MLD 0 (40% of patients) or in GMFC-MLD 1 (60% of patients) based on the distribution of Libmeldy treated patients at entry into the Orchard Therapeutics clinical trials.

The economic model consists of eight health states (Figure 19). A monthly model cycle length has been applied. The health states are based on the progression of GMFC-MLD, which are divided into 7 (0-6) different severities/levels, and death. GMFC-MLD was an important secondary endpoint in the Libmeldy clinical trial. In each cycle, patients can either stay in the same health state, transition into the next GMFC-MLD health state, or transition to death. Individuals can only progress to the next GMFC-MLD stage (e.g., from GMFC-MLD 1 to GMFC-

MLD 2) and cannot improve (patients cannot transition from GMFC-MLD 1 to GMFC-MLD 0), and there are no backward transitions.

In addition to the eight health states, the model consists of sub-states within each main health state. In PS-LI-MLD, cognitive decline occurs at a similar rate to motor function decline. In contrast, for PS-EJ and ES-EJ-MLD, cognitive decline can occur before or after motor function loss. For each of the GMFC-MLD stage for EJ patients, three cognitive sub-states were also included to reflect the cognitive progression of MLD, and hence enable the capture of the combined effects of cognitive decline and motor function loss on patients.

Additionally, the GMFC-MLD 6 health state captures the portion of patients that will require inpatient hospitalization. Whilst the health states are broadly defined by the motor function and cognitive status, each health state also captures the likely associated symptoms and complications of MLD, such as painful muscle spasms, swallowing difficulties requiring the placing of a gastrostomy tube, breathing difficulties, neuropathic pain, etc.

A lifetime time horizon was applied in this analysis, using a Norwegian health care payer perspective (option included to use Swedish and Finish perspective). An annual discount rate of four percent was used for both costs and health effects for the first 39 years, followed by a three percent for year 40-74 and two percent from year 75 to the end of the time horizon.

FINOSE discussion
Orchard has chosen to use one of the secondary endpoints (GMFC-MLD) from the clinical study to model the effect of Libmeldy and stabilization over time. Orchard could have used the co-primary endpoint GMFM to model the effect of Libmeldy, however GMFM is given as a percentage of age-dependent standardized measure, and it may not reflect disease progression over time.

FINOSE conclusion: The economic evaluation is based on a partitioned survival model with eight health states, with cost and benefits reflecting disease progression and management of the disease MLD over a lifetime. The chosen modelling approach implies that most inputs, parameters, and costs could easily be altered for the purpose of testing and exploring alternative scenarios.

FINOSE agrees that chosen endpoint (GMFC-MLD) to model the effect of Libmeldy is suitable. However, FINOSE would point out that a simpler modelling approach could have been constructed for the purpose of a cost/effectiveness analysis.

4.1 Effectiveness

4.1.1 Clinical effectiveness

No additional baseline characteristics from the clinical trial for Libmeldy were included in the economic analysis, except the age and distribution of the patient population as described above. The modelled effect of Libmeldy is based on gross motor function classification (GMFC-MLD), as well as the inclusion of engraftment success (lentiviral vector transduced cells, vector copy number) and neurological evaluations (DQ-scores) for the EJ-patient population.

Treatment response (Libmeldy)
Treatment with Libmeldy is aimed at preventing, or slowing, the clinical manifestation of disease. These benefits will vary across individuals depending on their status at the time of treatment. Patients are classified as “full responders” or “partial responders” depending on the observed clinical benefits with regards to the GMFC-MLD-endpoint at the latest data cut (see

Table 5, Table 6, Figure 12 and Figure 13). The criteria for full and partial responders are described below, and as such they were implemented in the model as assumptions regarding the clinical efficacy of Libmeldy:

- Patients are assumed to be full-responders if they were pre-symptomatic at the time of treatment and demonstrated broad disease stabilization throughout the clinical trial follow-up period, i.e. did not progress past GMFC-MLD 0 or have decline in cognitive function, illustrating that treatment has been able to prevent irreversible damage and halt disease progression.
- Stable partial responders are assumed to be those patients who after an initial period of decline following treatment, then stabilize at either GMFC-MLD 1, 2, 3 and 4 for the remainder of follow-ups during the clinical time period; or who were symptomatic at time of treatment and remained in that GMFC health state at follow-up time points.
- Unstable partial responders are assumed to be as those patients who continue to have disease progression despite treatment, but at a slower rate than natural history.

With the rationale given above, the following classifications of responders were implemented in the model (Table 11).

Table 11. The company's model base case for full, partial and unstable responders by disease variant, treated with Libmeldy.

Tabellen omfattas av sekretess

The classifications of responders as grouped above, is also depicted in Appendix 5.

Time to disease progression

The "time to progression" parameter was implemented for responders from the Libmeldy study, to simulate the potential impact of Libmeldy treatment on preventing onset of clinical symptoms. Libmeldy would prevent MLD disease progression in full-responder patients and these patients would remain in GMFC-MLD 0 for the duration of the "time to progression" value. The progression parameter was calculated on the basis of the observed progression time between the GMFC-MLD levels from those patients who experienced disease progression in the clinical studies. For the model base case, for patients who were classified as "full responders", the duration of effect of Libmeldy was assumed to be life-long, which was simulated by setting the "time to progression"-to lifetime. Input values for the progression parameters and mean times to transition for each disease variant are presented in Table 12, Table 13 and Table 14, for patients who did not achieve full response, i.e. patients categorized as unstable partial responders, but which progress at a slower rate than NHx-cohort.

For the comparator-arm the amount of time a patient spends in each health state is derived from data from the age and disease subtype matched NHx cohort which was used as the comparator for the Libmeldy-trials, where available, and supplemented with published literature and expert clinical opinion. Mean time to transition model inputs for each modelled disease variant for the BSC-arm are presented in conjunction with the Libmeldy-transitions in Table 12, Table 13 and Table 14. The numbers used for the validation is found in Appendix 7.

By nature of it being a natural history study, patients only entered the TIGET NHx study once they were symptomatic (with all patients entering in GMFC-MLD level 1 or higher). To align with the pre-symptomatic Libmeldy treated LI and EJ populations in the model, the average time from GMFC-MLD 0 to GMFC-MLD 1 was derived from the difference between the age at model entry and the average age at entry into GMFC-MLD 1 in the Libmeldy Indicated Population dataset, for the LI and EJ cohorts respectively. The numbers in the tables are noted as total months in each state, but for calculations in the health economic model, these are converted into monthly probabilities of progression, as the model uses a monthly cycle length.

Table 12. Pre-symptomatic late-infantile (PS-LI) mean time to transition inputs for the unstable partial responders.

	Mean time to transition (months)	
GMFC-MLD Transitions	**Libmeldy calculation; base case**	**BSC: TIGET NHx**
from 0 to 1	3.3	3.3
from 1 to 2	[-----]	3.7
from 2 to 3	[-----]	3.0
from 3 to 4	[-----]	3.0
from 4 to 5	[-----]	3.0
from 5 to 6	[-----]	9.6
from 6 to death	[-----]	57.3

Table 13. Pre-symptomatic early-juvenile (PS-EJ) mean time to transition inputs for the unstable partial responders.

	Mean time to transition (months)	
GMFC-MLD Transitions	**Libmeldy calculation; base case**	**BSC: TIGET NHx**
from 0 to 1	9.4	9.4
from 1 to 2	[-----]	18.3
from 2 to 3	[-----]	4.4
from 3 to 4	[-----]	4.4
from 4 to 5	[-----]	4.4
from 5 to 6	[-----]	27.7
from 6 to death	[-----]	56.5

Table 14. Early-symptomatic early-juvenile (ES-EJ) mean time to transition inputs for the unstable partial responders.

	Mean time to transition (months)	
GMFC-MLD Transitions	**Libmeldy calculation; base case**	**BSC: TIGET NHx**
from 0 to 1	9.4	9.4
from 1 to 2	[-----]	18.0
from 2 to 3	[-----]	4.4
from 3 to 4	[-----]	4.4
from 4 to 5	[-----]	4.43.7
from 5 to 6	[-----]	27.7
from 6 to death	[-----]	56.5

Cognitive decline

To reflect the cognitive decline that can occur before or after motor function loss in EJ patients, cognitive sub-states were developed for each GMFC-MLD stage. For each EJ cohort, patients were distributed into one of the three cognitive sub-states for each of the GMFC-MLD stages. The distribution was based upon the observed data for the cohort (via the Orchard Therapeutics clinical trial DQ performance data) and clinical expert feedback obtained via structured expert elicitation. Clinical experts also expected that cognitive loss could occur prior to gross motor decline, i.e. in GMFC-MLD 0. This is supported by data that show that ES-EJ patients can present with either cognitive impairment or motor function as the first signs of MLD symptoms.

The GMFC-MLD 0 cognitive distributions were stratified into 2 groups:

- "GMFC-MLD 0: Before cognitive decline" to simulate the cognitive distribution of patients entering the model.
- "GMFC-MLD 0: After cognitive decline" to simulate the initial cognitive loss prior to gross motor function decline.

A "time until cognitive decline" parameter was then applied for each EJ cohort to simulate the length of time that would elapse before patients remaining in GMFC-MLD 0 would experience a cognitive decline, implemented as a transition from "Before cognitive decline" to "After cognitive decline".

At each cycle, the patients in each GMFC-MLD stage were distributed into the cognitive sub-states based on the cognitive distributions for the cohort (Table 15).

Table 15. Cognitive sub-state distribution by GMFC-MLD stage in EJ natural history.

Cognitive Sub-state distribution	Normal/mild Cognitive Function*	Moderately Cognitive Impairment**	Severe Cognitive Impairment***	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	100%	0%	0%	12*
After Cognitive Decline: GMFC-MLD 0	73%	27%	0%	NA
GMFC-MLD 1	54%	38%	9%	NA
GMFC-MLD 2	33%	43%	25%	NA
GMFC-MLD 3	25%	35%	40%	NA
GMFC-MLD 4	16%	28%	55%	NA
GMFC-MLD 5	8%	21%	71%	NA
GMFC-MLD 6	0%	14%	86%	NA

* (DQ ≥ 70) ** (70 > DQ ≥ 55) *** (DQ < 55)

Overall survival

In the TIGET NHx study, death from MLD is preceded by loss of all motor function (GMFC-MLD 6), i.e., 100% of patient's progress to GMFC-MLD 6 before death. Therefore, it was assumed that transitions to death due to MLD is only possible from GMFC-MLD 6. This assumption was validated with clinical experts who confirmed that patients will progress through all GMFC-MLD stages prior to death due to MLD. In addition, to also capture all-cause mortality, country specific general population mortality was applied to GMFC-MLD 0 through GMFC-MLD 6. In the model, all-cause mortality is not included in the health state transition probabilities but are applied on top of these as an age-dependent background mortality risk.

Survival in each health state was informed by observed clinical trial data, either the comparator NHx-study or the Libmeldy-study. While the model assumes that patients are required to transition to GMFC-MLD 6 to experience death due to MLD-related mortality, patients were able

to transition to death from all GMFC-MLD states based on all-cause mortality in the population. Patients in GMFC-MLD 0-5 used the general population all-cause mortality rate to transition to death. Norwegian life tables were used to inform the FINOSE joint model.

Mortality of patients in the GMFC-MLD 6 state is modelled using time-dependent increasing hazards, to reflect the increased probability of dying the longer time spent in the health state, as observed in natural history studies. In the model, patients in GMFC-MLD 6 transition to death at time-dependent rates based on a parametric survival curve. The resulting MLD-related mortality estimates are applied to patients in GMFC-MLD 6, given that all NHx patients transitioned to GMFC-MLD 6 prior to death from MLD. Meanwhile, all-cause mortality was also included, given the assumption informed by the TIGET NHx data that MLD patients would progress to GMFC-MLD 6 prior to progressing to disease related death.

The parametric survival curve applied in the model for transitions from GMFC-MLD 6 to death, was generated by fitting seven parametric curves (Fitted Distributions: Exponential, Weibull, Log-normal, Log-logistic, Generalized Gamma, Gompertz and Gamma) to the survival data (time from entry at GMFC-MLD 6 to death) from the TIGET NHx study for the LI and EJ patient populations (Figure 20 and Figure 21). The Weibull curve, which provided the best fit to the observed data and was considered conservative, was used as the base case parametric curve in the model and was extrapolated over the model time horizon.

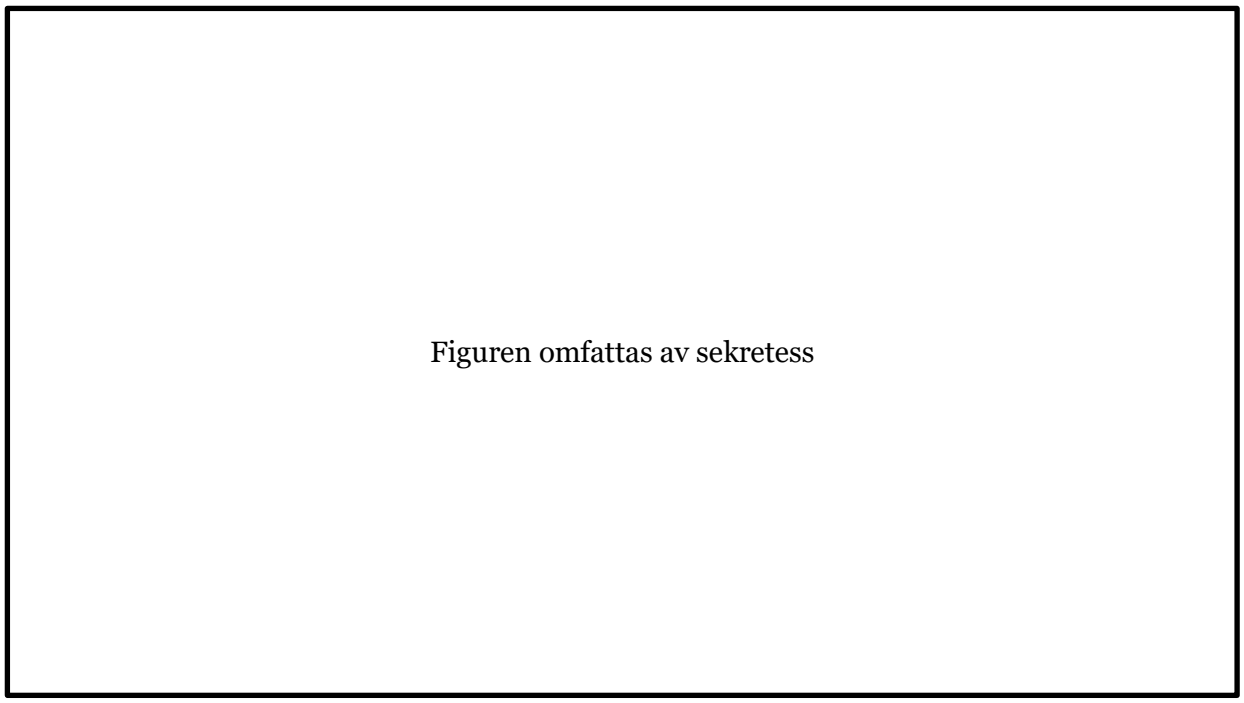


Figure 20. Extrapolations of time-to-event data for the historical control arm, for time from GMFC-MLD 6 to death for the PS-LI patient population.

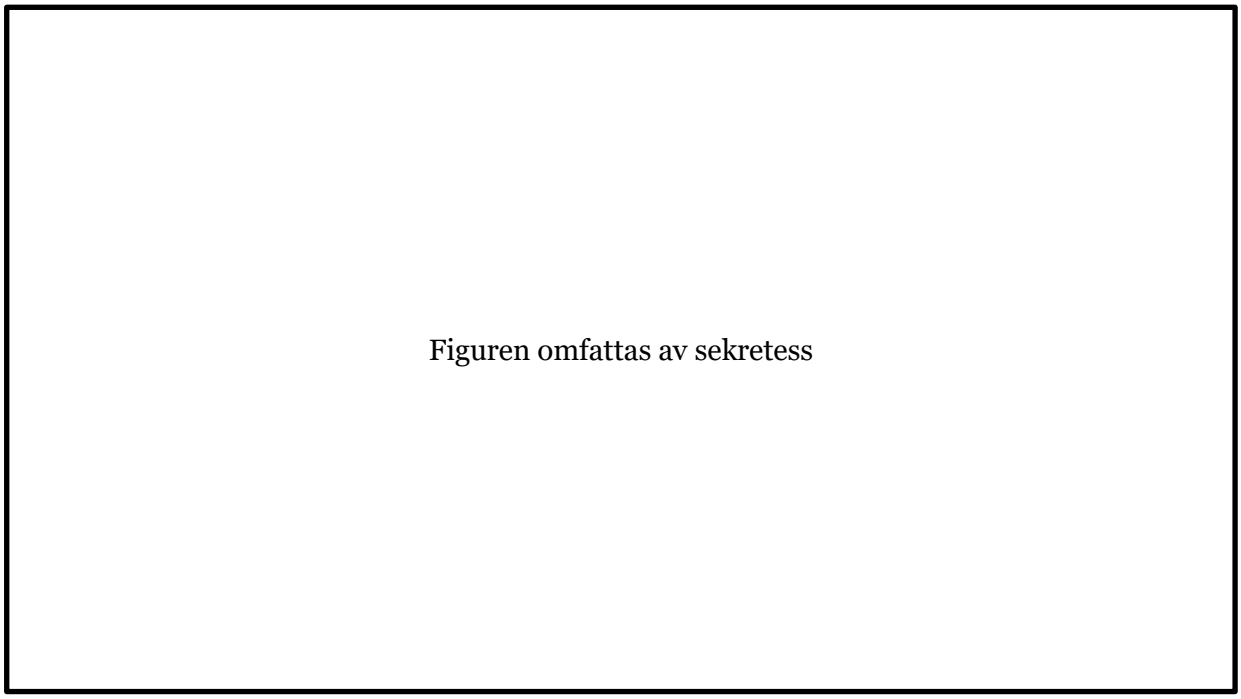


Figure 21. Extrapolations of time-to-event data for the historical control arm, for time from GMFC-MLD 6 to death for the EJ-patient population.

The mean age at death for the PS-LI, PS-EJ and ES-EJ BSC model arms, extracted from the model engine as the time point where 50 percent of the baseline cohort remains alive, was validated against published mean age at death values (Table 16).

Table 16. Comparison of mean age at death in the model and published literature by disease variant.

Disease Variant	Modelled Mean Age at Death (BSC)[1]	Published Mean Age at Death
PS-LI	10.5 years	9.4 years[2]
PS-EJ	16.6 years	17.4 years[3]
ES-EJ	19.0 years	17.4 years[3]

1 Timepoint in model when <50% of the cohort remains alive
2 Mean age at death for LI MLD, sourced from the recent publication by Fumagalli et al 2021 [13]
3 Mean age at death for all juvenile (early and late juvenile) MLD patients, sourced from Mahmood et al, 2010 [14]

Slight differences were observed between the published median age at death for the ES-EJ population and modelled mean age at death, which is likely due to the modelling framework in which ES-EJ patients starting at GMFC-MLD 0 spend the same amount of time in this health state as PS-EJ patients, which wouldn't be the case in the real setting.

FINOSE discussion

The company has chosen to model the effect of Libmeldy primarily using GMFC-MLD, which was a secondary end point in the registrational study 201222. For the purposes of the economic modelling, the company has grouped the patients based on their GMFC-MLD levels in the latest data cut into different categories of response. However, when grouping individual patients into the different GMFC-MLD-groups, the company has taken into account several clinical parameters (ARSA-levels, DQ-scores etc.). These grouping categories were not pre-specified for the study itself but were created post hoc to model long term efficacy through the health economic model, by assuming a degree of stabilization. FINOSE emphasize that the company's chosen modelling approach and corresponding structure, while it might capture the natural history of the disease, lead to an unreasonable estimation of benefit for patients treated with Libmeldy. The build of the model relies on "either/or" classifications of lifelong response. As a

consequence, small adjustments or alterations in the modelled responder's status have a large impact on the cost-effectiveness results. This is due to a model with many health states, and relatively few patients to inform each health state, in conjunction with the assumption that patients who had not progressed during the follow-up time will remain in the same health state for the rest of the modelled time horizon.

The company's definition of response relies on assumptions about long-term stabilization of disease symptoms. This was based on Libmeldy's mechanism of action, which the company argues supports long-term stabilization. That is, after successful engraftment, gene-corrected hematopoietic stem and progenitor cells provide a steady supply of gene-corrected cells for the patient's lifetime. The company explains this with that HSCT has shown an ongoing lasting effect for metabolic disease beyond 30 years and has been used for over 50 years to successfully treat other diseases. Even so, stabilization assumptions should according to FINOSE be based on Libmeldy evidence rather than inferred from other technologies used for other conditions. With regards to uncertainty, EMA has highlighted several points in their assessment of Libmeldy. On a general note, EMA states that the duration of follow-up is considered limited for this type of gene therapy, and this precludes to draw definite conclusions on the long-term efficacy. With the current evidence it is difficult to estimate an appropriate rate of progression and the GMFC-MLD health state in which patients could potentially stabilize. The progression parameters were calculated based on the observed progression time between the GMFC-MLD levels from those patients who experienced disease progression in the clinical studies. However, the calculations of disease progression rates are based on very few observations due to few patients and limited follow-up time in the studies. The company's assumptions and cost-effectiveness results with regards responder status should therefore be interpreted as the best-case scenario for treatment with Libmeldy. With the possibility that some patients would progress and possibly stabilize for a longer period in lower GMFC-MLD (e.g., 5-6) states than in the company's base case, this would substantially reduce Libmeldy´s modelled treatment benefit. As stated in Chapter 3.6 the company also provided an updated data analysis, which was based on the same December 2019 data cut as used for the results presented above (See Appendix 10). The new data does not strengthen the hypothesis of persisting stabilization at any specific point in time after treatment, as new data shows that decline in GMFC-MLD level may occur after as much as 6 years of stability [----------] (Appendix 10). This increases the uncertainty in the overall conclusion and analysis. FINOSE concludes that a determinant and conclusive relative treatment effect compared to untreated population of the TIGET NHx study, cannot be precisely estimated. The updated analysis did not change the overall conclusions on the evidence or FINOSES reclassification of response in the economic model and have not altered the grouping of responders in the scenarios (cut-off 30 months for LI-patients and 3 years for EJ-patients at the time of submission). However, based on the results, it seems clear that the treated patients mostly stay alive and do not develop severe symptoms of MLD during the follow-up. These effects are not typically seen in the comparator population in TIGET NHx study or in the natural course of the disease. One conclusive ICER could therefore not be calculated, and different scenarios will therefore be presented together with extensive sensitivity analysis.

FINOSE conclusion: The FINOSE evaluators do not agree with the company's modelled grouping of clinical effect, i.e., classifying patients as responders, partial responders and unstable partial responders depending on their latest data-cut. FINOSE evaluators argue that the observation period is too short to conclude on which group of response some of the patients might be in. FINOSE presents a scenario (scenario 1) where patients are reclassified according to FINOSEs criteria of necessary follow-up time. Distribution of the response-grouping and the adjacent criteria used in the FINOSE scenario is shown in Appendix 5.

The overall follow-up time is too short to conclude on the long-term effect of Libmeldy, especially given the patients young age at the time of treatment and the lifelong time horizon in which the effect is supposed to take place. While a few patients have been followed for up to 8 years, other patients have a very short follow-up period and subsequently limited number of observations. To address the uncertainty related to long-term effects of Libmeldy, FINOSE presents a scenario where patients in the Libmeldy-treated arm have the modelled effect up until year 15 (scenario 2). In addition, a combination of scenario 1 and 2 is presented to illustrate the impact of the two main alterations combined. In addition, extensive scenario/sensitivity analysis where the main parameters of interest are altered will be presented.

Because of the differences in the treated and untreated population (discussed further in chapter 3), the treatment effect related to slower disease progression cannot be reliably determined. This limitation remains despite reclassification of patients or restraining the effect of the intervention in the FINOSE scenarios.

4.1.2 Health related quality of life

There were no health-related quality of life (HRQoL) data collected in the clinical trials for Libmeldy. Instead, the company conducted a separate study to derive utility values for each health state in the model. The utility study was conducted in the UK using case vignettes specifically developed to comprehensively depict the impact of MLD in each progressive GMFC-MLD stage and cognitive impairment.

The aim of the vignette study was to elicit utility values for LI and juvenile MLD. Health states vignettes were developed through a literature review and qualitative interviews with clinicians (N=6) and caregivers (N=21). Health states were defined by the Gross Motor Function Classification (GMFC-MLD 1 to 6) and by Development Quotient (DQ) scores. Health states were valued by members of the UK general public (N=100 for LI MLD; N=101 for EJ MLD) who completed a visual analogue scale (VAS) and time trade-off (TTO) assessment, using the composite method with lead-time for health states worse than death and conventional TTO for health states better than death. The resulting health state utilities are found in Table 17.

Table 17. HRQoL values used in the health economic model.

Health State	LI Utility Value	EJ Utility Value Normal Cognition (DQ ≥ 70)	EJ Utility Value Cognitive Impairment (70 > DQ ≥ 55)	EJ Utility Value Severe Cognitive Impairment (DQ < 55)
[----------]	[----------]	[----------]	[-------]	[-------]
[----------]	[-------]	[-------]	[-------]	[-------]
[----------]	[-------]	[-------]	[-------]	[-------]
[----------]	[-------]	[-------]	[-------]	[-------]
[----------]	[-------]	[-------]	[-------]	[-------]
[----------]	[-------]	[-------]	[-------]	[-------]
[----------]	[-------]	[-------]	[-------]	[-------]

Whilst there were no adverse events directly linked to treatment with Libmeldy, adverse events expected with busulfan conditioning and hematological reconstitution were accounted for in the model as a disutility decrement associated with complications due to conditioning.

For Libmeldy-treated patients, a [----------] has been applied to patients for the first 3 months following treatment, i.e., model entry to model the impact of busulfan conditioning.

There is a considerable physical and psychological burden placed on caregivers of children with MLD. Therefore, an average caregiver disutility of -0.108 per caregiver has been applied to patients in GMFC-MLD 2 and above as per Table 18. The calculation is based on the mean

index utility value [------] for all respondents (n=21 total UK, US and German respondents) completing the EQ-5D in the MLD Caregiver Survey subtracted from UK General Population Utility at 40 years of age [--------]. The number of caregivers progress as the patients progress in MLD-stages. The caregiver´s disutility is assumed to last for 30 years, as adult MLD patients are less likely to be cared for at home and more likely to have residential care.

Table 18. Caregiver disutility applied in the model across different GMFC health states.

GMFC-MLD state	Number of caregivers	Total Caregiver Disutility
GMFC-MLD 0	0	0
GMFC-MLD 1	0	0
GMFC-MLD 2	0.5	-0.054
GMFC-MLD 3	1	-0.108
GMFC-MLD 4	1	-0.108
GMFC-MLD 5	2	-0.216
GMFC-MLD 6	2	-0.216

FINOSE discussion

The study design in the vignette study did not follow recommendations as reference case because it directly modelled public preferences with no explicit consideration of the patients' quality of life. This creates a methodological problem when the public considered cognitive impairment outside the context of a disease affecting children, in which many participants chose extreme values for cognitive impairment. This way of eliciting utility values will in addition lack face validity; more challenging health states were rated as better than less challenging health states. Also, the results lacked external validity compared with utility values used in other appraisals, for example utility values that were lower than the EQ-5D worst health state. It is challenging to assess the validity of EQ-5D-values below one, which is the case for several health state EQ-5D-values. If a value is below one, then the health state has been valued as "worse than death" e.g., that subjects have rated the health state as a state in which they would rather be dead, than experience. Furthermore, it lacks face validity in that there is a declining rate below one for a majority of health states, and already in GMFC-MLD 3 for patients in the late-infantile subgroup. In this health state children are still sitting without support and crawling/rolling is possible. This cannot be aligned with a state in which death is the preferred option. As an alternative, the company could have used clinical experts as proxies for patients to derive utilities for each health state, although this approach is not methodologically perfect, it is preferred compared to the company's approach. The company also submitted on the request of FINOSE additional analysis, using Danish EQ-5D set. FINOSE used this primarily as validation towards the values in the base case.

No available literature has been identified where MLD-patients value their own quality of life, which is expected given the early onset of disease and detrimental impact MLD has on both cognitive abilities and life expectancy.

The company argues that there is a considerable physical and psychological burden placed on caregivers of children with MLD. This is very probable given the detrimental impact this disease has on young children, and their respective parents, siblings and other potential caregivers. There is however limited evidence to quantify this in a plausible manner, both with regards to the limited number of caregivers (n=21) that were included in the analysis, the exact number of caregivers and the time horizon in which this might be applicable.

FINOSE conclusion: There is generally a high level of uncertainty when using vignette studies for the purpose of evaluating and eliciting health related quality of life-values. They are

often not standardized and are subjected to a number of different biases. The FINOSE evaluators also regard the specific values obtained by the vignette to be implausibly low for a number of the health states. To correct for the above-mentioned biases and lack of face validity, alternative values for utility values/QALY-weights are used in the FINOSE scenarios**.** FINOSE has recalculated the submitted QALY-weights to not allow for negative values, calculated as the mean percentage decline of the observed positive values. The table with the HRQoL-values used in the FINOSE scenario are presented in the Appendix 8.

The FINOSE scenarios do not include caregiver's disutility. This is also in alignment with the different guidelines within Norway, Finland and Sweden. Yet the FINOSE evaluators acknowledge the detrimental impact MLD has on family, siblings, and other caregivers. A scenario analysis in which the decrement limited to one (1) caregiver from GMFC-MLD 3 to GMFC-MLD 6 is presented, in addition to other sensitivity analysis which includes additional/more caregivers (up to two and a half).

4.2 Costs and resource utilization

4.2.1 Medicine costs (Libmeldy)

Libmeldy is a single treatment, given as an infusion into a vein, and the dose depends on the patient's weight. The price is not weight-based (Table 19). A few days before treatment with Libmeldy another medicine, busulfan, is given as a so-called conditioning treatment, to clear out existing bone marrow cells so they can be replaced with the modified cells in Libmeldy. The cost of busulfan is already accounted for in the pre-treatment cost input.

Table 19. Price of Libmeldy. Costs in NOK.

Item	Value	Source
Libmeldy	NOK 30 074 576	Orchard

Patients are also given other medicines prior to Libmeldy treatment to reduce the risk of reactions. Throughout the model, as some patients may progress, other medications may be necessary. These are primary target towards pain relief and symptoms. These are listed in the Appendix.

4.2.2 Administration costs

According to the SmPC, Libmeldy is to be administered at a qualified specialist treatment centre with experience in delivering HSCT for neurometabolic patients. Currently, there are five treatment centres in Europe that are certified or in the process to be certified for administration of Libmeldy. In the model base case, it is assumed that patients will be transferred to the qualified treatment centre in Manchester, hence treatment related costs in the model are reflecting UK NHS costs applied in the recent NICE submission, converted to local currency by current exchange rates.

Libmeldy drug administration costs consisting of leukapheresis (cell harvest), conditioning, administration and hospitalization, and follow-up transplant costs were derived from literature and NHS National Reference costs (2018/2019). Leukapheresis (cell harvest), conditioning, and administration and hospitalization costs were all applied to patients immediately upon model entry. Follow-up transplant costs were evenly distributed to patients over the first 2 years of the model based on clinical expert feedback that the follow-up for autologous transplants costs is the same as for allogeneic stem cell transplants, and patients will be discharged to metabolic care after 2 years.

Table 20. Transplant related costs associated with Libmeldy. Costs in NOK.

Items	Value	Source
Leukapheresis (cell harvest)	NOK 49 996	NHS 2018/19 National Cost Collection data
Conditioning	NOK 92 443	Hospitalisation cost: NHS 2018/19 National Cost Collection data. Busulfan cost: eMIT 2019 database Busulfan 60 mg vial – 8 pack = GBP 367.81
Administration and hospitalization	NOK 283 076	Average cost per patient = GBP 24,188 NHS 2018/19 National Cost Collection data. The SmPC states patient would stay about 4 – 12 weeks (average of 7.5 weeks) in the hospital.
Follow-up transplant costs	NOK 725 187	Hettle et al – NICE Regenerative Medicines report. 2017. Follow-up costs for allogeneic stem cell transplants (2 years).

4.2.3 Health care resources costs

The monthly costs for management of MLD patients aged 0-5, 6-18 and 19+ are summarized in Table 21, reported as average monthly per patient costs for each GMFC-MLD stage by cost category. Weighted means of proportions of patients using specific resources, frequency and where relevant, duration, of each type of resource used were calculated. What is included in each of the groups above, with consideration to specific parameter inputs, is summarized in Appendix 9. Clinical experts were asked to provide information on the frequency and proportion of HCRU for MLD patients in each GMFC-MLD stage. Average monthly costs were stratified into 3 age cohorts (0-5 years, 6-18 years, and 19+ years of age) to account for differences in treatment practice based on age. Every cost category is divided as a monthly cost on the background of an estimated yearly cost. It is also divided by the proportion of patients expected to utilize the resource.

Table 21. Management costs for MLD patients, divided by GMFC-MLD-state and age-group. Monthly costs (bottom - total). Costs in NOK.

Health care resource	GMFC-MLD-state (1 to 6)							Age group
	0	1	2	3	4	5	6*	
Drugs	-	972	1 049	1 057	1 080	1 281	1 393	0-5
	-	972	1 049	1 057	1 080	1 281	1 393	5-18
	-	972	1 049	1 057	1 080	1 281	1 393	18+
Medical tests	-	1 281	532	529	529	549	520	0-5
	-	1 281	532	529	529	549	520	5-18
	-	1 281	532	529	529	549	520	18+
Medical visits	-	4 558	4 091	5 261	5 488	5 760	5 776	0-5
	-	4 558	4 091	5 261	5 488	5 760	5 776	5-18

	-	4 558	4 091	5 261	5 488	5 760	5 776	18+
Hospitalisations	2 863	4 581	13 742	20 614	32 466	37 792	137 539	0-5
	2 863	4 581	13 742	20 614	32 466	37 792	137 539	5-18
	-	-	9 162	15 460	26 740	31 493	130 553	18+
GP & Emergency	-	748	1 059	1 246	1 645	1 869	2 180	0-5
	-	748	1 059	1 246	1 645	1 869	2 180	5-18
	-	748	1 059	1 246	1 645	1 869	2 180	18+
Healthcare equipment	-	410	709	996	996	1 035	1 035	0-5
	-	410	709	996	996	1 035	1 035	5-18
	-	410	709	996	996	1 035	1 035	18+
Social services	-	-	-	-	-	-	15 355	0-5
	-	-	-	-	-	-	15 355	5-18
	-	-	140	560	1 121	1 681	17 036	18+
Total	**2 863**	**12 550**	**21 182**	**29 703**	**42 205**	**48 285**	**163 789**	**0-5**
	2 863	**12 550**	**21 182**	**29 703**	**42 205**	**48 285**	**163 789**	**5-18**
		7 969	**16 741**	**25 110**	**37 600**	**43 667**	**158 493**	**18+**

*(10% of patients in hospital, 90% of patients at home)

4.2.4 Indirect costs

Out of pocket costs

The company has included out of pocket costs incurred due to health-related expenses. Respondents from the UK, Germany and the USA recorded how much out of pocket cost they had incurred as a result of having a child with MLD with a caregiver survey. The costs were summed and then averaged equating to EUR 3 476 across all health states. These costs have then been recalibrated across the health states intuitively, such that the less severe health states would have a lower out of pocket cost as compared to the most severe health states. The resulting value was converted to local value by PPP index versus the 19 euro countries in 2019. Table 22 details the predicted annual and monthly out of pocket costs per health state, as used in the model.

Table 22. Predicted out of pocket costs used in the model. Costs in NOK.

GMFC-MLD-stage	Annual out of pocket costs, NOK	Monthly out of pocket costs, NOK
0	0	0
1	23 966	1 997
2	23 966	1 997
3	47 931	3 994
4	47 931	3 994
5	71 897	5 991
6	71 897	5 991

Lost family income due to caregiver responsibilities

An analysis of the MLD caregiver survey was performed to calculate lost family income due to caring for patients with MLD. This has been included regardless of whether the caregiver was

or would otherwise be employed and could function as a proxy for less government expenditure on health care/social worker with at-home services. Time spent caring for patients were multiplied with the average annual income/salary in the Netherlands. Table 23 details the monthly caregiver cost by health state and age band, respectively.

Table 23. Monthly lost family income by health stage and age band. Costs in NOK.

Age band	GMFC-MLD-0	GMFC-MLD-1	GMFC-MLD-2	GMFC-MLD-3	GMFC-MLD-4	GMFC-MLD-5	GMFC-MLD-6
0-18 years	-	706	706	16 182	16 182	34 199	34 199
19+ years	-	-	-	-	-	-	-

FINOSE discussion

There are currently no national guidelines for the treatment and management of MLD in Norway, Finland or Sweden. According to the clinical experts in each country, LI and EJ forms of MLD is mainly treated with supportive care. Supportive care consists of paediatric neurologist, physiotherapist, neuropsychologist, occupational therapist, speech therapist, assistive device, symptomatic medicines (baclofen, pain killers etc.), patient and family psychosocial support, dietician, genetic counselling etc. In addition, there is an extensive use of healthcare equipment used at home, such as electrical wheelchair, beds, and other aids. The use of at-home visits from specialist aid/nurse is great and expands over time and in magnitude, depending on whether home care or specialized care-home is needed. Whether or not this fully captures the full extent of resources needed to care for an MLD-patient is unknown, but in general MLD-patients, especially in GMFC-MLD4-6 are very resource demanding and require extensive attention from both the government/municipality side and family/caregivers. Family/caregiver expenses due to having a child with MLD is included in the analyses, but also in this regard it is hard to estimate an exact value on out-of-pocket costs, and when they are functioning on behalf of/instead of a health care/social worker. The average annual income in the Netherlands is a little lower than in the Nordic countries, but overall comparable.

FINOSE conclusion: The transplant and drug costs of Libmeldy is the key cost driver affecting the results of the economic evaluation. Adverse events associated with Libmeldy were not included in the model. These were instead handled as quality-of-life impairments. Out-of-pocket costs and caregiver responsibilities by parents have been included in the analyses, and FINOSE will explore the extent of this in sensitivity analysis.

5 Results of the cost-effectiveness analysis

Libmeldy is associated with a one-time upfront cost and the health benefits are expected to be gained over a lifetime.

5.1 The company's base case

The company assumes that treatment with Libmeldy improves both survival and health-related quality of life.

In the company base case, the results of the cost-effectiveness analysis are presented for the combined early-onset MLD cohort based on the combined patient population of the subtypes of disease that make up the full eligible population in the base case model, i.e. PS-LI, PS-EJ, ES-EJ.

Subgroup analyses of each of the eligible MLD disease cohorts were also undertaken. Each of the disease cohorts within the combined cohort are analysed in the subgroup analysis.

5.1.1 Key assumptions in the company base case scenario

- Pre-symptomatic Libmeldy treated patients who are full responders will not develop clinical manifestations of MLD throughout their life.
- A proportion of pre-symptomatic or early symptomatic Libmeldy treated patients who are partial responders will stabilize and halt disease progression at GMFC-MLD 1, 2, 3, and 4.
- Pre-symptomatic or early-symptomatic Libmeldy treated patients who are classified as unstable[5] partial responders will have slower disease progression compared to natural history patients.
- In early-symptomatic EJ patients there will be a delay for the clinical effects of Libmeldy to become apparent.
- Treatment with Libmeldy will delay cognitive decline in Early Juvenile patients.
- Mortality in line with the general population for pre-symptomatic Libmeldy treated patients who are full responders.
- No adverse events related to Libmeldy over the time horizon.
- Utility weights derived from Vignette methodology (UK population)
- Lifelong time horizon (100 years)

5.1.2 Results in the company base case scenario

According to the company base case results for Libmeldy versus best supportive care the patient gains more quality adjusted life years, QALYs (18.8) at a higher cost (23 408 000 NOK) (Table 24). The cost per QALY gained was estimated at 1 246 000 NOK (no specific payment

[5] Unstable partial responders are classified as those patients who continue to have disease progression despite treatment, but at a slower rate than natural history.

model). This result applies to the combined patient population (derived from the study population) of the three populations. All costs and effects are discounted according to the rates described in Chapter 4.1.

The subgroup specific results are as follows:

- PS-LI: According to the company base case results for Libmeldy versus best supportive care the patient gains more quality adjusted life years, QALYs (19.9) at a higher cost (22 562 000 NOK) (Table 25). The cost per QALY gained was estimated at 1 132 700 NOK.
- PS-EJ: According to the company base case results for Libmeldy versus best supportive care the patient gains more quality adjusted life years, QALYs (22.7) at a higher cost (22 580 000 NOK) (Table 26). The cost per QALY gained was estimated at 997 000 NOK.
- ES-EJ: According to the company base case results for Libmeldy versus best supportive care the patient gains more quality adjusted life years, QALYs (7.7) at a higher cost (29 840 000 NOK) (Table 27). The cost per QALY gained was estimated at 3 885 000 NOK.

Table 24: Company base case results for the combined patient population, NOK. Costs and effect discounted (updated company base case).

	Libmeldy	BSC	Diff.
Total costs (drug, administration, care)	35 809 321	12 349 750	23 407 869
Life years (LY)	[---]	[---}	[---]
QALYs	14.3	-4.5	18.8
Cost per LY gained			[----------]
Cost per QALY gained			**1 246 062 NOK**

Table 25: Company base case results for the PS-LI population, NOK. Costs and effect discounted (updated company base case).

	Libmeldy	BSC	Diff.
Total costs (drug, administration, care)	35 048 724	12 487 205	22 561 519
Life years (LY)	[---]	[---}	[---]
QALYs	15.6	-4.3	19.9
Cost per LY gained			[----------]
Cost per QALY gained			**1 132 706 NOK**

Table 26: Company base case results for the PS-EJ population, NOK. Costs and effect discounted (updated company base case).

	Libmeldy (LIB-MELDY)	BSC	Diff.
Total costs (drug, administration, care)	34 487 261	11 907 074	22 580 187
Life years (LY)	[---]	[---}	[---]
QALYs	17.8	-4.9	22.7
Cost per LY gained			[----------]
Cost per QALY gained			**996 517 NOK**

Table 27: Company base case results for the ES-EJ population, NOK. Costs and effect discounted (updated company base case).

	Libmeldy (LIB-MELDY)	BSC	Diff.
Total costs (drug, administration, care)	41 921 716	12 081 876	29 839 840
Life years (LY)	[---]	[---}	[---]
QALYs	2.3	-5.4	7.7
Cost per LY gained			[----------]
Cost per QALY gained			**3 884 792 NOK**

The key cost driver affecting the results of the economic evaluation is the effect parameters combined with the direct drug expense of Libmeldy. This should be compared to extensive at-home/care costs and hospitalizations for untreated patients over a lifetime with a discount rate according to the rates described in Chapter 4.1.

5.1.3 Company's sensitivity analyses

The company has performed several one-way sensitivity analyses to explore the sensitivity of individual parameters/ input variables in the deterministic base-case model results. The company notes that the discount rate and time horizon have a greater impact on the results than the performed one-way sensitivity analyses.

The company has also presented the results as a tornado diagram indicating that the percentage of patients classified as responders, and at what health state partial responders stabilize at, as these parameters have the greatest impact on the results according to the company. The company notes that the discount rate and time horizon have a greater impact on the results than the performed one-way sensitivity analyses.

5.2 FINOSE scenarios

Based on FINOSEs assessments throughout the report, one conclusive ICER cannot be calculated. FINOSE has therefor calculated two scenarios, one combined scenario, and several additional analyses with the aim of highlighting the main uncertainties in the health economic model. FINOSE emphasize that the company's chosen modelling approach and corresponding structure, while it might capture the natural history of the disease, lead to an unreasonable estimation of benefit for patients treated with Libmeldy. The build of the model relies on "either/or" classifications of lifelong response. As a consequence, small adjustments or alterations in the modelled responder's status have a large impact on the cost-effectiveness results.

This is due to a model with many health states, and relatively few patients to inform each health state, in conjunction with the assumption that patients who had not progressed during the follow-up time will remain in the same health state for the rest of the modelled time horizon.

FINOSE presents two scenarios:
- One (scenario 1) in which FINOSE addresses the uncertainty in responder status categorization. In this scenario, patients with too short follow-up to conclude on responder-status as full responders are instead modelled as partial responders.
- Scenario 2, in which FINOSE addresses the uncertainty of long-term efficacy of Libmeldy. In this scenario, the responder-status and Libmeldy treatment effect are modelled as in the company's base case until year 15, after which the patients in the Libmeldy-arm follow natural disease progression as in the NHx-study.

In addition, a combined scenario of the two mentioned scenarios will be presented. Several other assumptions were adjusted compared to the company base case. These changes are listed below, in addition to be explained throughout the report in the corresponding conclusion boxes.

5.2.1 Key assumptions in the FINOSE scenarios

- No utility decrement for caregivers, instead of including caregiver's utility of up to two caregivers for the first thirty years.
- Utility values recalculated to not allow for negative values, calculated as the mean percentage decline of the observed positive values.
- Regrouping of the responders of Libmeldy treatment, between the company's assumption depicted in
-
-

- Figure 22, Figure 23 and Figure 24, and the FINOSE reclassification depicted in Figure 25 and Figure 26 (Scenario 1).

- Patients in the Libmeldy-treated arm have the modelled effect up until year 15 (modelled year, not patient year), after which the patients in the Libmeldy-arm follow natural disease progression as in the NHx-study. (Scenario 2).
- In addition, a combined scenario of the two mentioned above is presented.

Scenario 1:

FINOSE evaluators mostly agree with the company's classification of patients into different responder categories. The FINOSE evaluators do not agree with the company's classification of some of the patients as the observation period is too short to conclude on which group of response they might belong to. FINOSE presents a scenario where these patients are reclassified according to FINOSEs criteria of necessary follow-up time. The numbers used for grouping of the patients in scenario 1 are presented in Appendix 11.2.

Table 28: FINOSE results for the combined patient population (scenario 1), NOK. Costs and effect discounted.

	Libmeldy (LIBMELDY)	BSC	Incremental
Total costs (drug, administration, care)	41 498 227	15 616 085	25 882 142
Life years (LY)	19.2	8.8	10.4
QALYs	9.3	1.2	8.0
Cost per LY gained			NOK 2 489 214
Cost per QALY gained			**NOK 3 225 418**

Table 29: FINOSE results for the PS-LI population (scenario 1), NOK. Costs and effect discounted.

	Libmeldy (LIBMELDY)	BSC	Incremental
Total costs (drug, administration, care)	40 689 011	15 784 174	24 904 837
Life years (LY)	20.2	8.2	12.0
QALYs	9.8	0.9	8.9
Cost per LY gained			NOK 2 080 971
Cost per QALY gained			**NOK 2 799 556**

Table 30: FINOSE results for the PS-EJ population (scenario 1), NOK. Costs and effect discounted.

	Libmeldy (LIBMELDY)	BSC	Incremental
Total costs (drug, administration, care)	43 587 549	15 177 700	28 409 849
Life years (LY)	17.2	10.4	6.8
QALYs	7.8	2.2	5.6
Cost per LY gained			NOK 4 179 762
Cost per QALY gained			**NOK 5 059 120**

Table 31: FINOSE results for the ES-EJ population (scenario 1), NOK. Costs and effect discounted.

	Libmeldy (LIBMELDY)	BSC	Incremental

Total costs (drug, administration, care)	43 709 636	15 162 130	28 547 506
Life years (LY)	15.7	10.1	5.6
QALYs	7.6	1.8	5.8
Cost per LY gained			NOK 5 143 467
Cost per QALY gained			**NOK 5 050 752**

Scenario 2:

The overall follow-up time is too short to conclude on the long-term effect of Libmeldy, especially given the patients young age at the time of treatment and the lifelong time horizon in which the effect is supposed to take place. While a few patients have been followed for up to 8 years, other patients have a very short follow-up period and subsequently limited number of observations. To address the uncertainty related to long-term effects of Libmeldy, FINOSE presents a scenario where patients in the Libmeldy-treated arm have the modelled effect up until year 15 (scenario 2), after which the treated patients have the same rate of disease progression as untreated patients in the natural history cohort.

Table 32. FINOSE results scenario 2, separated by patient population, NOK. Costs and effect discounted.

Scenario 2	Δ Costs	Δ LY	Δ QALYs	Cost/ QALY
PS-LI	20 380 244	6.0	6.6	3 105 129
PS-EJ	20 185 991	4.1	7.6	2 662 553
ES-EJ	25 765 281	3.8	6.2	4 181 307
Combined patient population	21 013 271	5.4	6.7	3 151 472

Combination of scenario 1 and scenario 2:

Table 33. FINOSE results for a combination of scenario 1 (FINOSE classification) and scenario 2 (capped effect at 15 years), separated by patient population, NOK. Costs and effect discounted. Costs in NOK.

Combination of scenario 1 and scenario 2	Δ Costs	Δ LY	Δ QALYs	Cost/ QALY
PS-LI	24 904 837	5.2	4.3	5 857 541
PS-EJ	28 409 849	3.7	3.4	8 259 076
ES-EJ	28 547 506	3.2	3.8	7 575 177
Combined patient	25 882 142	4.7	4.1	6 359 681

There is still little evidence as to how long the effect and possible added benefit of Libmeldy might persist. In both scenarios, a lifelong time horizon is applied.

5.2.2 FINOSE sensitivity analyses

FINOSE has also performed sensitivity analyses to explore how different stabilization and sustained GMFC-MLD stages affect the results. The degree and sustainability of stabilization might be both higher and lower. Due to lack of data on long-term effect, FINOSE presents several analyses to illustrate how the results are affected by the uncertainty in the sustainability of effect over time. In the FINOSE sensitivity analysis, altering assumptions with regards to response categorization the cost per QALY gained rises to between 5.7 – 25.7 million NOK. The cost per QALY gained become even higher if a shorter time horizon is employed. FINOSE concludes that there is a substantial degree of uncertainty in this analysis.

Tables showing how different discount rates for scenario 1, scenario 2 and the combined scenario, on the acquisition cost of Libmeldy are presented in Table 35, Table 36 and Table 37.

Table 34. FINOSE sensitivity analysis based on either scenario 1*, scenario 2, or a combination of scenario 1 and 2***, NOK.**

	Sensitivity analysis/parameter	Δ Costs	Δ LYs	Δ QALYs	Cost/ QALY
1	**One caregiver included from GMFC-2 to GMFC-6*:**				
	PS-LI	24 904 837	12.0	9.0	2 761 341
	PS-EJ	28 409 849	6.8	5.5	5 150 413
	ES-EJ	28 574 506	5.6	5.5	5 145 688
	Combined patient population	25 558 142	10.4	8.1	3 209 917
2	**Include caregivers as in the company's base case (see section 4.1.2)***				
	PS-LI	24 904 837	12.0	9.5	2 631 443
	PS-EJ	28 409 849	6.8	5.6	5 067 290
	ES-EJ	28 574 506	5.6	6.0	4 737 795
	Combined	25 558 142	10.4	8.5	3 059 782

3	**Discount rate (only calculated for the combined patient population average)***				
	4% for the whole time horizon for both costs and effect	25 687 254	8.5	7.0	3 675 642
	3% for the whole time horizon for both costs and effect	25 761 887	11.2	8.6	2 985 694
	2% for the whole time horizon for both costs and effect	25 987 905	15.3	11.1	2 345 280
	1% for the whole time horizon for both costs and effect	25 278 087	25.6	16.8	1 502 068
	0% for the whole time horizon for both costs and effect	27 439 760	33.1	21.3	1 289 174
4	**Time horizon (combined patient population)***				
	10	24 837 972		2.5	9 784 387
	20	24 910 700		4.2	5 926 911
	30	25 327 397		5.3	4 797 453
	40	25 516 071		6.0	4 239 526
	50	25 643 690		6.7	3 831 723
	60	25 726 518		7.2	3 594 624
	70	25 783 653		7.5	3 444 378
	80	25 843 006		7.8	3 301 280
	90	25 876 991		8.0	3 235 113
5	**Time horizon (combined patient population) ****				
	10	21 921 295	1.3	4.2	5 270 076
	20	20 048 061	4.5	6.5	3 070 376
	30	20 200 453	5.4	6.7	3 033 674
	40	20 413 780	5.4	6.7	3 061 404
6	**Extrapolation of GMFC-MLD 6 to death for the PS-LI population* – BSC-arm**				
	Log-normal	25 341 572	10.1	8.0	3 158 762
	Log-logistic	25 207 890	10.1	8.0	3 141 136
	Exponential	25 515 101	10.2	8.0	3 181 198
	Gompertz	26 034 089	10.5	8.0	3 243 488
	Gamma	25 826 728	10.4	8.0	3 218 747
	Generalized Gamma	25 252 612	10.2	8.0	3 184 382
7	**Extrapolation of GMFC-MLD 6 to death for the EJ population* – BSC-arm**				
	Log-normal	25 793 450	10.3	8.0	3 214 077
	Log-logistic	25 766 018	10.3	8.0	3 210 347
	Exponential	25 832 992	10.4	8.0	3 219 525
	Gompertz	25 908 134	10.4	8.0	3 228 565
	Gamma	25 873 974	10.4	8.0	3 224 406
	Generalized Gamma	25 828 578	10.4	8.0	3 218 660
8	**Excluding non-direct costs (only calculated for the combined patient population average) ***				
	Combined patient population	25 867 750	10.4	8.0	3 223 624
9	**Excluding caregiver costs (only calculated for the combined patient population average) ***				
	Combined patient population	26 992 084	10.4	8.0	3 363 738
10	**Source of NHx-data (only calculated for the combined patient population average) ***				
	Eigun 2019	25 910 623	10.0	7.9	3 275 337
	Kehrer 2011	25 986 483	9.9	7.8	3 335 819
11	**Including neuro-disability related mortality in GMFC-MLD 2-5***				
	PS-LI	24 873 994	11.8	8.8	2 821 553
	PS-EJ	28 324 446	6.7	5.6	5 042 879
	ES-EJ	28 507 839	5.4	5.8	4 956 985
	Combined patient population	25 841 975	10.2	8.0	3 248 230
12	**PS-LI-population re-classification on responders (only calculated for the PS-LI-population) ***				
	Full responders 0%	29 729 113	11.6	3.8	7 887 227
	Stable at GMFC-MLD-1 10%				
	Stable at GMFC-MLD-2 10%				
	Stable at GMFC-MLD-3 10%				

	Stable at GMFC-MLD-4	10%				
	Stable at GMFC-MLD-5	10%				
	Partial responders	50%				
13	**PS-LI-population re-classification on responders (only calculated for the PS-LI-population) ***					
	Full responders	0%	28 080 006	7.5	4.9	5 738 705
	Stable at GMFC-MLD-1	10%				
	Stable at GMFC-MLD-2	10%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	80%				
14	**PS-EJ-population re-classification on responders (only calculated for PS-EJ-population) ***					
	Full responders	0%	31 400 342	3.8	1.2	25 721 760
	Stable at GMFC-MLD-1	0%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	100%				
15	**ES-EJ-population re-classification on responders (only calculated for ES-EJ-population) ***					
	Full responders	0%	29 938 618	2.2	2.1	14 211 690
	Stable at GMFC-MLD-1	0%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	100%				
16	**Result for the combined patient population when using the company's updated reclassification***					
	Full responders	NA	22 598 141	15.1	12.4	1 825 685
	Stable at GMFC-MLD-1					
	Stable at GMFC-MLD-2					
	Stable at GMFC-MLD-3					
	Stable at GMFC-MLD-4					
	Stable at GMFC-MLD-5					
	Partial responders					
17	**Result for the PS-LI- population when using the company's updated reclassification***					
	Full responders	40%	22 066 008	15.7	12.4	1 786 294
	Stable at GMFC-MLD-1	20%				
	Stable at GMFC-MLD-2	33.3%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	6.7%				
18	**Result for the PS-EJ- population when using the company's updated reclassification***					
	Full responders	75%	20 185 991	14.9	17.7	1 140 369
	Stable at GMFC-MLD-1	0%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	25%				
19	**Result for the ES-EJ- population when using the company's updated reclassification***					
	Full responders	0%	28 700 282	12.2	6.0	4 791 439
	Stable at GMFC-MLD-1	20%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	20%				

	Stable at GMFC-MLD-4	20%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	40%				
20	**Result for the combined patient population when using the company's updated reclassification*** **					
	Full responders	NA	22 608 067	5.2	5.7	3 947 572
	Stable at GMFC-MLD-1					
	Stable at GMFC-MLD-2					
	Stable at GMFC-MLD-3					
	Stable at GMFC-MLD-4					
	Stable at GMFC-MLD-5					
	Partial responders					
21	**Result for the PS-LI- population when using the company's updated reclassification*** **					
	Full responders	40%	22 081 963	5.7	5.7	3 905 646
	Stable at GMFC-MLD-1	20%				
	Stable at GMFC-MLD-2	33.3%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	6.7%				
22	**Result for the PS-EJ- population when using the company's updated reclassification*** **					
	Full responders	75%	20 177 255	4.2	7.6	2 657 437
	Stable at GMFC-MLD-1	0%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
23	Partial responders	25%				
	Result for the ES-EJ- population when using the company's updated reclassification* **					
	Full responders	0%	28 697 531	3.8	3.9	7 417 482
	Stable at GMFC-MLD-1	20%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	20%				
	Stable at GMFC-MLD-4	20%				
24	Stable at GMFC-MLD-5	0%				
	Partial responders	40%				
	PS-LI-population re-classification on responders (only calculated for the PS-LI-population)*					
	Full responders	100%	15 882 723	18.8	20.8	843 087
	Stable at GMFC-MLD-1	0%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
25	Partial responders	0%				
	PS-LI-population re-classification on responders (only calculated for the PS-LI-population)*					
	Full responders	0%	19 685 914	16.1	20.8	1 221 327
	Stable at GMFC-MLD-1	100%				
	Stable at GMFC-MLD-2	0%				
	Stable at GMFC-MLD-3	0%				
	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	0%				
26	**PS-LI-population re-classification on responders (only calculated for the PS-LI-population)***					
	Full responders	0%	22 639 407	13.8	20.8	1 638 518
	Stable at GMFC-MLD-1	0%				
	Stable at GMFC-MLD-2	100%				
	Stable at GMFC-MLD-3	0%				

	Stable at GMFC-MLD-4	0%				
	Stable at GMFC-MLD-5	0%				
	Partial responders	0%				
	Difference in progression parameter (PS-LI-population) *					
27	10 % longer time in each GMFC-MLD-level (from the company's calculation, for the partial responder)		24 893 055	12.1	8.9	2 778 619
	20 % longer time in each GMFC-MLD-level (from the company's calculation, for the partial responder)		24 877 735	12.3	9.0	2 757 903
	70 % longer time in each GMFC-MLD-level (from the company's calculation, for the partial responder)		24 756 265	13.0	9.3	2 657 210

The sensitivity analyses show that there is great variation in results when different assumptions are applied. The parameters that have the largest impact on the result is the duration and grouping of clinical effect, i.e., response. This has been discussed throughout the report and remains one of the main uncertainties. FINOSE concludes that there is a high degree of uncertainty in the analysis. FINOSE attempts to identify and highlight the uncertainty concerning sustained effect with different scenario- and sensitivity analysis. We see when comparing scenario 2 and sensitivity analysis 5, the time horizon does not impose such variation on the result. This is due do FINOSEs alteration of constraint the effect of Libmeldy to occur only the first 15 years. When viewing sensitivity analysis 4, we see that the majority of QALYs gained are achieved in the first 20 years. This is mostly due to the discounting of effect over time. In sensitivity analysis 4, with a 20-year time horizon, the ICER for the combined patient population is approximately 5.9 million NOK. The ICER for the PS-LI population with this time horizon is approximately 5.3 million NOK. We see that this sensitivity analysis aligned within the interval between scenario 2 and the combined scenario. This could suggest that a combination of scenario 1 and scenario 2 might also be plausible, or in the interval between the observed scenarios.

FINOSE has identified the following main uncertainties in the modelling of the cost-effectiveness analysis of Libmeldy: 1) the assumption that for certain patients who have not experienced a progression or onset of disease during the follow-up time, these will stabilize in a given GMFC-MLD stage, which is sustained over the lifelong time horizon, 2) the duration of a potential disease stabilization, 3) Relative efficacy of Libmeldy compared to untreated patients in a real world setting, and 4) the QALY values accrued in each health state.

5.2.3 Cost per QALY gained at different price levels

Table 35. Sensitivity analyses on discount rate on acquisition cost of Libmeldy based on FINOSE scenario 1, NOK.

Sensitivity analyses	Cost/ QALY	Cost/ QALY	Cost/ QALY	Cost/ QALY
	PS-LI	**PS-EJ**	**ES-EJ**	**Combined patient population**
FINOSE scenario 1 (full acquisition cost)	NOK 2 799 556	NOK 5 059 120	NOK 5 050 752	NOK 3 225 418
FINOSE scenario 1 (10% discount acquisition cost)	NOK 2 461 396	NOK 4 523 563	NOK 4 376 781	NOK 2 850 630
FINOSE scenario 1 (20% discount acquisition cost)	NOK 2 123 340	NOK 3 988 006	NOK 3 861 395	NOK 2 475 843
FINOSE scenario 1 (30% discount acquisition cost)	NOK 1 785 284	NOK 3 452 449	NOK 3 346 009	NOK 2 101 055

FINOSE scenario 1 (40% discount acquisition cost)	NOK 1 447 228	NOK 2 916 893	NOK 2 830 623	NOK 1 726 267
FINOSE scenario 1 (50% discount acquisition cost)	NOK 1 109 171	NOK 2 381 336	NOK 2 315 237	NOK 1 351 480
FINOSE scenario 1 (60% discount acquisition cost)	NOK 771 115	NOK 1 845 779	NOK 1 799 851	NOK 976 692
FINOSE scenario 1 (70% discount acquisition cost)	NOK 433 059	NOK 1 310 222	NOK 1 284 465	NOK 601 904
FINOSE scenario 1 (80% discount acquisition cost)	NOK 95 003	NOK 774 665	NOK 769 079	NOK 227 117

Table 36. Sensitivity analyses on discount rate on acquisition cost of Libmeldy based on FINOSE scenario 2, NOK

Sensitivity analyses	Cost/ QALY	Cost/ QALY	Cost/ QALY	Cost/ QALY
	PS-LI	PS-EJ	ES-EJ	Combined patient population
FINOSE scenario 1 (full acquisition cost)	NOK 3 105 129	NOK 2 662 553	NOK 4 181 307	NOK 3 151 472
FINOSE scenario 1 (10% discount acquisition cost)	NOK 2 646 913	NOK 2 265 867	NOK 3 693 243	NOK 2 700 428
FINOSE scenario 1 (20% discount acquisition cost)	NOK 2 188 698	NOK 1 869 180	NOK 3 205 179	NOK 2 249 383
FINOSE scenario 1 (30% discount acquisition cost)	NOK 1 730 482	NOK 1 472 493	NOK 2 717 115	NOK 1 798 339
FINOSE scenario 1 (40% discount acquisition cost)	NOK 1 272 267	NOK 1 075 806	NOK 2 229 051	NOK 1 346 294
FINOSE scenario 1 (50% discount acquisition cost)	NOK 814 051	NOK 679 119	NOK 1 740 987	NOK 896 250
FINOSE scenario 1 (60% discount acquisition cost)	NOK 355 863	NOK 282 433	NOK 1 259 924	NOK 445 206
FINOSE scenario 1 (70% discount acquisition cost)	dominant	dominant	NOK 764 860	dominant
FINOSE scenario 1 (80% discount acquisition cost)	dominant	dominant	NOK 276 796	dominant
FINOSE scenario 1 (90% discount acquisition cost)	dominant	dominant	dominant	dominant

Table 37. Sensitivity analyses on discount rate on acquisition cost of Libmeldy based on the combination of FINOSE scenario 1 and scenario 2, NOK.

Sensitivity analyses	Cost/ QALY	Cost/ QALY	Cost/ QALY	Cost/ QALY
	PS-LI	PS-EJ	ES-EJ	Combined patient population
FINOSE scenario 1 (full acquisition cost)	NOK 5 857 541	NOK 8 259 076	NOK 7 575 177	NOK 6 359 681
FINOSE scenario 1 (10% discount acquisition cost)	NOK 5 150 196	NOK 7 384 773	NOK 6 777 138	NOK 5 620 698
FINOSE scenario 1 (20% discount acquisition cost)	NOK 4 442 851	NOK 6 510 469	NOK 5 979 099	NOK 4 881 715
FINOSE scenario 1 (30% discount acquisition cost)	NOK 3 735 506	NOK 5 636 166	NOK 5 181 060	NOK 4 142 731
FINOSE scenario 1 (40% discount acquisition cost)	NOK 3 028 162	NOK 4 761 863	NOK 4 383 021	NOK 3 403 748
FINOSE scenario 1 (50% discount acquisition cost)	NOK 2 320 817	NOK 3 887 560	NOK 3 584 982	NOK 2 664 756
FINOSE scenario 1 (60% discount acquisition cost)	NOK 1 613 472	NOK 3 013 257	NOK 2 786 943	NOK 1 925 781

FINOSE scenario 1 (70% discount acquisition cost)	NOK 906 128	NOK 2 138 954	NOK 1 988 904	NOK 1 186 798
FINOSE scenario 1 (80% discount acquisition cost)	NOK 198 783	NOK 1 264 651	NOK 1 190 865	NOK 447 815
FINOSE scenario 1 (90% discount acquisition cost)	dominant	NOK 390 347	NOK 392 826	dominant

5.3 Budget impact

According to the company the estimated number of patients eligible for treatment with Libmeldy is one every 2 to 3 years in Norway. The company has not estimated the number of patients for Sweden and Finland. The budget impact analysis presented is done from the Norwegian perspective, by applying estimated number of patients in Norway as well as Norwegian costs used in the CE model.

The patient population considered in the budget impact analysis is in line with the EMA marketing authorization for Libmeldy, which is limited to asymptomatic and early symptomatic MLD patients (PS-LI, PS-EJ, or ES-EJ MLD). In the absence of newborn screening, it is likely that the vast majority of prevalent MLD patients would be ineligible for Libmeldy treatment, on the basis that they would have already progressed beyond the narrow treatment window. In addition, if there were prevalent patients currently eligible for treatment with Libmeldy, they would likely lose eligibility by the time that Libmeldy effectively becomes available, due to the rapid disease progression seen in early-onset MLD. Hence, there is an absence of a prevalent pool of MLD patients eligible for treatment, and only incident patients are relevant to the budget impact analysis.

The estimated number of patients assumed in the budget impact analysis is that in Norway, one Libmeldy eligible patient will be diagnosed every third year, in line with the estimates discussed in the FINOSE clinical report and clinical expert input.

Table 38. FINOSE regarding number of eligible patient (separated into Sweden, Finland, and Norway) the first five years if Libmeldy is introduced.

		2022	2023	2024	2025	2026
Norway	Number of patients eligible for Libmeldy treatment	1	0	1	0	1
Sweden	Number of patients eligible for Libmeldy treatment	1	1	1	1	1
Finland	Number of patients eligible for Libmeldy treatment	1	0	1	1	1

Only Libmeldy eligible early-onset MLD patients are considered, as within the market authorization. As there are currently no treatment options for MLD that address the underlying disease/gene. If all eligible patients are treated with Libmeldy at once, this would imply that the one-time upfront transplant cost of Libmeldy would be 30 million NOK in Finland, Sweden, and Norway. If the patients are treated over the course of five years, it is assumed an annual budget impact of 150 million NOK in Sweden, 90 million NOK in Norway and 120 million NOK in Finland. The budget impact analysis from the company only includes the direct medical costs associated with Libmeldy (drug and transplant related costs)

FINOSE discussion

It is very challenging to estimate how many patients would be eligible for treatment with Libmeldy, especially in the absence of new-born screening. In the absence of new-born screening or known family history, most children with MLD are diagnosed because they have symptoms.

So, most patients would not be eligible for Libmeldy unless an older sibling was diagnosed before onset of their symptoms.

FINOSE conclusion: MLD is an extremely rare disease, with one new case for every 100 000 live births. Libmeldy is expected only to be given pre-symptomatically (or very early symptomatically), as stated in the market authorized indication. Therefore, it is not expected that any patients currently diagnosed with MLD will be eligible for treatment with Libmeldy if introduced. Hence, only incident patients are relevant to the budget impact analysis. FINOSE agrees with the company's estimated incidence number for Norway and have extrapolated this to Sweden and Finland.

5.4 Overall summary and conclusion

Libmeldy is indicated for the treatment of the rare inherited disease, metachromatic leukodystrophy (MLD). MLD is caused by mutations in the arylsulfatase A (ARSA) gene and leads to a reduction of ARSA enzymatic activity, and thereby build-up of harmful sulfatides. In Libmeldy treatment, autologous hematopoietic stem cells (CD34+), transduced with a functional copy of an ARSA gene, are administered to patients. The genetically modified cells secrete a functional ARSA enzyme, which breaks down and prevents the build-up of harmful sulfatides. The clinical evidence base of Libmeldy consists of single arm trials; the registrational study 201222, compassionate use programs and hospital exemptions.

The company performed a comparison with a natural history cohort of 31 patients with untreated MLD enrolled since 2004 and, when possible, a comparison with a matched sibling. The size of the treatment effects cannot be concluded based on this comparison because of differences in treated and untreated populations. This bias remains despite the age adjustment because of a large variation in the age of onset of the disease, also between siblings. These issues are most evident in the EJ group of patients. However, the natural history cohort evidence showed that patients had very poor outcomes. Most patients had complete loss of movement and loss of head and limb control (GMFC-MLD 6) and no remaining cognitive function (DQ) within a few years of diagnosis. On the contrary, for patients who were treated with Libmeldy, almost all patients had much better clinical outcomes. Based on the results, it seems clear that the treated patients mostly stay alive and do not develop severe symptoms of MLD during the follow-up. These effects are not typically seen in the comparator population in TIGET NHx study or in the natural course of the disease.

Libmeldy is given as a single (onetime) treatment with a drug cost of approximately 30 million NOK. This should be compared to extensive at-home/care costs and hospitalizations for untreated patients over a lifetime. However, it is uncertain to what degree patients treated with Libmeldy also would require supportive care in the long term.

In conclusion, given the reasons stated throughout the report, one conclusive ICER cannot be calculated. This is primarily a consequence of the limited number of patients observed in the clinical trial and the early access programs, limited follow-up time, and non-randomized studies without a control arm. However, there are several reasons to present different scenarios, with a variety of underlying assumptions on several parameters in the model. First, there is reason to believe that a randomized controlled trial with an active comparator/placebo-arm will not be performed in the foreseeable future. The historical control-arm constructed with the intent to inform any measurement of relative efficacy, although flawed with consideration to matching, is as good as can be expected at this time.

According to EMA, because MLD is a rare disease, the studies are necessarily small and the amount of data available on side effects is limited and will also need long-term follow-up. Furthermore, EMA considered the duration of follow-up limited for this type of gene therapy and this precludes to draw definite conclusions on the long-term efficacy in terms of persistence of engraftment levels of transduced cells, other parameters (namely, central and peripheral ARSA activity levels), and of treatment effects on clinical outcome measures. However, the benefits of Libmeldy in patients with MLD who had not yet developed symptoms were clear, and during the study period patients maintained a similar development as healthy subjects. Benefit was less marked and more variable in those with early juvenile MLD who already experienced symptoms. Although benefits with Libmeldy lasted several years in some patients, it is not yet clear whether the clinical effects of the treatment are sustained, and extended follow-up is needed. EMA has highlighted in their assessment of Libmeldy that although the quality of life was not directly assessed, data in the treated pre-symptomatic subject from both school performance and parent reported outcomes indicate that these subjects perform as healthy peers and go about their daily activities without special assistance. This is not the case for untreated patients.

6 Assessments in other countries

The National Institute for Health and Care Excellence (NICE) in the UK is currently in development of an assessment to evaluate the benefits and costs of OTL-200 (Libmeldy) within its marketing authorization for treating metachromatic leukodystrophy for national commissioning by NHS England. An ERG-assessment has been delivered to NICE, and according to the published committee paper it is stated that the results from the cost-effectiveness analysis are substantially lower than the HST (Highly Specialized Technology) cost per QALY thresholds, indicating that OTL-200 would be a cost-effective therapy in England and Wales. The latest notes in the timeline are there are currently conducting committee meetings. (27)

According to the Federal Joint Committee (G-BA) of Germany, there is a hint of considerable added benefit for children with MLD who are still symptom-free. Available data does not allow quantification of the added benefit for early symptomatic patients. (28)

There are currently no indications that Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC) or Institute for Clinical and Economic Review (ICER) in the US would be currently undertaking an assessment of Libmeldy.

7 Post launch evidence generation

7.1 Regulatory perspective

Libmeldy has been granted marketing authorization, according to normal procedure. However, as part of its recommendation for marketing authorisation, the committees requested that the company uses a registry of patients to learn more about the long-term efficacy and safety of the medicine. Results from this registry study will be submitted periodically for evaluation to EMA.

7.2 HTA perspective

The results of the cost-effectiveness analysis (section 5) show that changes in the following parameters have the biggest impact on the model's results:

- Treatment response and effect, i.e., preventing or slowing the clinical manifestation of the disease.
- Health Related Quality of Life
- Drug cost of Libmeldy

There is a significant uncertainty related to the long-term effects of Libmeldy treatment. This uncertainty could be mitigated by collecting real world data on actual survival and motor and cognitive performance of patients treated with Libmeldy. Because the age of onset of symptoms can vary especially in patients with EJ-MLD, the conclusions on treatment effect should be made only after several years of the predicted onset of symptoms.

8 References

1. EMA. Libmeldy, EPAR. 2020;
2. Orchard Therapeutics. Libmeldy (atidarsagene autotemcel) for the treatment of metachromatic leukodystrophy (MLD). Medical background and clinical evidence. Unpubl Work. 2021;
3. Gieselmann V, Krageloh-Mann I. Metachromatic leukodystrophy--an update. Neuropediatrics. 2010/06/24. 2010;41(1):1–6.
4. van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. Best Pr Res Clin Endocrinol Metab [Internet]. 2015/05/20. 2015;29(2):261–73. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1521690X14001237?via%3Dihub
5. Gomez-Ospina N. Arylsulfatase A Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews((R)). Seattle (WA): University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 2017.
6. Wang RY, Bodamer OA, Watson MS, Wilcox WR. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011/04/20. 2011;13(5):457–84.
7. Mahmood A, Berry J, Wenger DA, Escolar M, Sobeih M, Raymond G, et al. Metachromatic leukodystrophy: a case of triplets with the late infantile variant and a systematic review of the literature. J Child Neurol. 2009/12/30. 2010;25(5):572–80.
8. Fumagalli F, Zambon AA, Rancoita PM V, Baldoli C, Canale S, Spiga I, et al. Metachromatic Leukodystrophy: A Single-Centre Longitudinal Study Of 45 Patients. J Inherit Metab Dis [Internet]. 2021/04/16. 2021; Available from: https://www.ncbi.nlm.nih.gov/pubmed/33855715
9. Kehrer C, Blumenstock G, Gieselmann V, Krägeloh-Mann I. The natural course of gross motor deterioration in metachromatic leukodystrophy. Dev Med Child Neurol. 2011/06/29. 2011;53(9):850–5.
10. Biffi A, Cesani M, Fumagalli F, Del Carro U, Baldoli C, Canale S, et al. Metachromatic leukodystrophy - mutation analysis provides further evidence of genotype-phenotype correlation. Clin Genet. 2008/09/13. 2008;74(4):349–57.
11. Kehrer C, Elgun S, Raabe C, Bohringer J, Beck-Wodl S, Bevot A, et al. Association of Age at Onset and First Symptoms With Disease Progression in Patients With Metachromatic Leukodystrophy. Neurology [Internet]. 2020/10/14. 2021;96(2):e255–66. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33046606
12. Elgun S, Waibel J, Kehrer C, van Rappard D, Bohringer J, Beck-Wodl S, et al. Phenotypic variation between siblings with Metachromatic Leukodystrophy. Orphanet J Rare Dis. 2019/06/13. 2019;14(1):136.
13. EMA. Orphan Maintenance Assessment Report: Libmeldy (Autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA) Treatment of metachromatic leukodystrophy EU/3/07/446. Eur Med Agency [Internet]. 2020; Available from: https://www.ema.europa.eu/en/documents/orphan-maintenance-report/libmeldy-orphan-maintenance-assessment-report_en.pdf
14. Welfare SNB of H and. Socialstyrelsens kunskapsdatabas om sällsynta hälsotillstånd – metakromatisk leukodystrofi. Latest revision 2017-10-03. Available at https://www.socialstyrelsen.se/stod-i-arbetet/sallsynta-halsotillstand/metakromatisk-leukodystrofi/. 2017;
15. Frambu kompetansesenter för sjeldne diagnoser. Medisinsk beskrivelse av metakromatisk leukodystrofi. Latest update May 2020. Available at https://frambu.no/diagnosebeskrivelse/medisinsk-beskrivelse-metakromatisk-leukodystrofi/. 2020;

16. Metoder N. Metodevarsel Libmeldy, Metodevarsel ID2020 041. Oppdatert versjon 22.05.2020. Available at https://nyemetoder.no/Documents/Forslag/ID2020_045_Genterapi%20til%20Metakromatisk%20leukodystrofi_oppdatert%2009.09.20%20(metodevarsel).pdf. 2020;
17. SmPC L. Libmeldy Summary of Product Characteristics. 2020;
18. Adang LA, Sherbini O, Ball L, Bloom M, Darbari A, Amartino H, et al. Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies. Mol Genet Metab. 2017/09/03. 2017;122(1–2):18–32.
19. Van Haren K, Bonkowsky JL, Bernard G, Murphy JL, Pizzino A, Helman G, et al. Consensus statement on preventive and symptomatic care of leukodystrophy patients. Mol Genet Metab. 2015/01/13. 2015;114(4):516–26.
20. Solders M, Martin DA, Andersson C, Remberger M, Andersson T, Ringdén O, et al. Hematopoietic SCT: a useful treatment for late metachromatic leukodystrophy. Bone Marrow Transpl. 2014/05/07. 2014;49(8):1046–51.
21. Biffi A, Montini E, Lorioli L, Cesani M, Fumagalli F, Plati T, et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science (80-). 2013/07/13. 2013;341(6148):1233158.
22. Sessa M, Lorioli L, Fumagalli F, Acquati S, Redaelli D, Baldoli C, et al. Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. Lancet. 2016/06/13. 2016;388(10043 LB-TIGET-MLD):476–87.
23. Kehrer C, Blumenstock G, Raabe C, Krägeloh-Mann I. Development and reliability of a classification system for gross motor function in children with metachromatic leucodystrophy. Dev Med Child Neurol. 2011;53(2):156–60.
24. Loes DJ, Hite S, Moser H, Stillman AE, Shapiro E, Lockman L, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. 1994;15(9):1761–6.
25. Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. Biol Blood Marrow Transpl. 2009/04/14. 2009;15(5):523–36.
26. SmPC B. Busilvex Summary of Product Characteristics [Internet]. 2017. Available from: https://www.medicines.org.uk/emc/product/2235/smpc
27. National institute for health and care excellence (NICE). OTL-200 for treating metachromatic leukodystrophy. Evaluation consultation document. [Internet]. 2021. Available from: https://www.nice.org.uk/guidance/gid-hst10028/documents/evaluation-consultation-document
28. Federal Joint Committee of Germany (G-BA). Beschluss: Atidarsagen autotemcel (Metachromatische Leukodystrophie mit biallelischer Mutation im ARSA-Gen) [Internet]. 2021. Available from: https://www.g-ba.de/downloads/39-261-5103/2021-11-04_AM-RL-XII_Atidarsagen-autotemcel_D-678.pdf

9 Appendices

Appendix 1. GLIA guidance

Table 39. GLIA guidance on the preventive and symptomatic care of patients with leukodystrophies.

Topic	Details
Musculoskeletal issues	
Spasticity	Baclofen or diazepam in combination with physical therapy and daily stretching routines Chemodenervation with botulinum toxin or intramuscular neural lysis with phenol More invasive treatments such as intrathecal baclofen, Surgical interventions to lengthen or sever tendons or nerve pathways
Dystonia	Trihexyphenidyl (Artane) Dopaminergic drugs, such as Levodopa, and tetrabenazine Oral baclofen and benzodiazepines More invasive treatments include intrathecal baclofen and, in rare cases, deep brain stimulation (DBS)
Low bone mass/density and fractures	Active monitoring of bone health and vitamin D levels (25-OH-D) Consultation with a bone specialist or endocrinologist
Hip dislocation	Physiatry and orthopaedics to discuss appropriate management options Surgery Adductor releases and tone management, in patients under five years of age. Reconstructive surgery, in patients after six years of age
Scoliosis	Braces and external frames Spinal orthoses Spinal surgery if the curve exceeds a Cobb angle of 40–50°
Ambulation	Age-appropriate devices (e.g. orthotics, braces, gait trainers, walkers, lifts, and standers). Outpatient physical therapy
Nutrition, bowel and urinary tract	
Hypersalivation	Oromotor or behavioural exercises, positioning, replacing medications that stimulate saliva secretion Optimization of constipation, scoliosis, and gastroesophageal reflux Anticholinergics, which include hyoscine (oral/transdermal Scopolamine) and trihexyphenidyl (Artane) Sublingual 1% atropine ophthalmic solution Glycopyrrolate (in children older than 3 years of age). More intense or invasive treatments (targeted botulinum toxin A injections and salivary gland surgery
Upper gastrointestinal complications	Nutritionally complete diet, consulted by dietician Proper positioning, adjustment of food consistency, pacing of feeding, and equipment An expedited consultation with gastroenterology or general surgery for consideration of gastrostomy (G-tube) or jejunostomy (J-tube) tube placement
Gastroesophageal reflux	Optimise position and food consistency during feeding Adjunctive medications, such as acid buffering agents, antisecretory agents, and prokinetic Ranitidine, lansoprazole, and omeprazole Surgical interventions such as nissen fundoplication is often offered in conjunction with a gastrostomy or gastrojejunal tube placement

Topic	Details
Bladder health	Prophylactic anti-microbial agents With bladder retention, urinary catheterisation as guided by urology
Gastrointestinal and urinary health	Laparoscopic cholecystectomy for polyps larger than 5 mm
Respiratory health, sleep and communication	
Progressive respiratory insufficiency	Infection prevention Key airway maintenance strategies Mechanical ventilation
Communication	A comprehensive augmentative and alternative communication (AAC) evaluation
Sleep	Optimisation of sleep hygiene, with a consistent sleep schedule, avoiding screen time 1–2 h prior to bedtime, and minimising unnecessary medical interventions at night Primary caregivers can record a sleep diary Off-label options include clonidine, tricyclic antidepressants, and benzodiazepines Melatonin is often used to help with sleep initiation
Neurologic issues	
Pain	Gabapentin Benzodiazepines and neuroleptics
Seizures	Rectal diazepam and buccal or intranasal midazolam
Autonomic nervous system dysfunction	Gabapentin, cyproheptadine, baclofen, beta-blockers, and clonidine For acute attacks, diphenhydramine, acetaminophen, or ibuprofen
Additional neurologic consideration	Gabapentin, start at 15–20 mg/kg/d divided 2–3 times daily and to escalate as needed to 60 mg/kg/d. Non-validated alternatives include pregabalin, topiramate, tricyclic antidepressants, and valproic acid In refractory cases, benzodiazepines can be used with caution Risperidone and valproic acid may be helpful mood and behaviour stabilisers

Appendix 2. Details of relevant trials

Table 40. Details of study 201222 (1,2).

Study name, NCT number	Study 201222, NCT01560182
Study type and design	Phase I/II trial Non-randomised, open-label, prospective, comparative (non-concurrent control), single-centre study.
Purpose	To evaluate the safety and efficacy of Libmeldy in patients with pre-symptomatic LI or pre- or early-symptomatic EJ MLD.
Sample size	A total of 22 early-onset MLD subjects were screened and enrolled into Study 201222, with two subjects withdrawn prior to treatment. Among the 20 subjects treated with gene therapy were: • Nine subjects in the LI MLD subgroup. • 11 subjects in the EJ MLD subgroup (including one subject who was classified as having an 'Intermediate LI/EJ-variant' but was grouped with the EJ variant for analysis purpose).
Population	Children up to 6 years of age with early-onset MLD (LI or EJ variants).

Study name, NCT number	Study 201222, NCT01560182
	The LI variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms in the older sibling(s) ≤ 30 months and/or two null (0) mutant ARSA alleles and /or peripheral neuropathy at electroneurographic (ENG) study. The EJ variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms (in the patient or in the older sibling) between 30 months and 6 years (had not celebrated their 7th birthday), and/or one null (0) and one R mutant ARSA allele(s) and/or peripheral neuropathy at ENG study. Pre-symptomatic clinical status was defined as subjects without neurological impairment (disease- related symptoms), with or without signs of the disease revealed by instrumental evaluations (ENG and brain MRI). Early-symptomatic clinical status (for the EJ variant) was initially defined as subjects identified within 6 months from the first reported symptoms (two EJ subjects were enrolled using this definition: MLD04 under Protocol 2.0, 26Jan2010 and MLD08 under Protocol 3.0, 04Apr2012). Subsequently (Amendment 7, dated 10Dec2013), early-symptomatic EJ subjects were defined as subjects meeting the following two criteria: IQ ≥70 and the ability to walk independently for ≥10 steps. The rationale for this change was to prevent enrolment of subjects who had a rapidly progressive form of the disease as identified at the time of treatment. All LI subjects and some pre-symptomatic EJ subjects were identified after an older sibling had developed symptoms and received an MLD diagnosis, prompting testing in other family members.
Inclusion criteria	Documented biochemical and molecular diagnosis of MLD, based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles, either known or novel mutations. Novel mutations will be analysed with in silico prediction tools and excluded from being known common polymorphisms. In the case of a novel mutation(s), a 24-hour urine collection must show elevated sulfatide levels. Eligible subjects must have EITHER: 1. An older sibling affected by MLD (index case), whose age of symptom onset was ≤ 6 years of age (i.e. had not celebrated 7th birthday). Subjects will be classified as LI, EJ or intermediate LI/EJ based on age of symptom onset in the index case and their ARSA genotype; LI: symptom onset in index case ≤30 months of age and genotype typically 0/0; EJ: symptom onset in index case > 30 months and ≤ 6 years of age with genotype typically 0/R; Intermediate LI/EJ: symptom onset in index case ≤6 years of age but unable to unambiguously characterize index case as LI or EJ OR 2. If MLD is diagnosed in a pre-symptomatic child without an older affected sibling, (e.g. incidentally or via newborn screening) and the totality of the data available to the investigator strongly suggest that the subject has an early-onset variant of MLD likely to benefit from gene therapy, and the subject is ≤ 6 years of age (i.e. has not celebrated 7th birthday), the subject may be considered eligible after discussion and approval by the Orchard Therapeutics medical monitor. Parental/guardian signed and dated informed consent.

Study name, NCT number	Study 201222, NCT01560182
Exclusion criteria	Documented HIV infection (positive HIV RNA and/or anti-p24 antibodies). Malignant neoplasia (except local skin cancer) or a documented history of hereditary cancer syndrome. Subjects with a prior successfully treated malignancy and a sufficient follow-up to exclude recurrence (based on oncologist opinion) can be included after discussion and approval by the Medical monitor. Myelodysplasia, cytogenetic alterations characteristic of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), or other serious haematological disorders. Subjects currently enrolled in other interventional trials. Has previously undergone allogeneic haematopoietic stem cell transplantation and has evidence of residual cells of donor origin. Previous gene therapy. Has symptomatic herpes zoster, not responsive to specific treatment. Subjects with a recent history of herpes zoster may be included in the study. In such cases, inclusion, additional monitoring and treatment of the condition must be discussed and approved by the medical monitor. Evidence of active tuberculosis (TB) based upon medical examination, chest imaging and TB testing, i.e. QuantiFERON-TB Gold test and microbiological evidence. Subjects with latent tuberculosis, as documented by medical history and/or TB testing may be included in the study if receiving antibiotic prophylaxis (e.g. isoniazid). Inclusion, monitoring and treatment of TB in such subjects must be discussed and approved by the medical monitor. Acute or chronic stable Hepatitis B as evidenced by positive Hepatitis B surface antigen (HBsAg) test result at screening or within 3 months prior to onset of conditioning and/or positive hepatitis B virus (HBV) DNA. Subjects with positive Hepatitis B core antibody due to prior resolved disease may be enrolled, only if a confirmatory negative Hepatitis B surface antigen and negative Hepatitis B DNA test are obtained. Inclusion, monitoring and treatment of hepatitis in such subjects must be discussed and approved by the medical monitor. Presence of positive Hepatitis C RNA test result at screening; subjects who have previously tested positive for antibodies against hepatitis C can be treated, provided they demonstrate absence of ongoing infection using a nucleic acid test with a limit of quantification of ≤ 15 international units/millilitre (IU/mL). Negative test results are required on at least three sequential occasions over a period of at least 4 weeks, after completion of treatment for hepatitis C, with the final test conducted no more than 3 days prior to cell harvest. Inclusion, monitoring and treatment of hepatitis in such subjects must be discussed and approved by the medical monitor. End-organ dysfunction, severe active infection not responsive to treatment, or other severe disease or clinical condition which, in the judgment of the investigator, would make the subject inappropriate for entry into this study. In addition to the potential infections the PI should consider testing for other transmissible infectious agents listed in the European Union (EU) Cell and Tissue Directive as clinically appropriate and results discussed with the medical monitor prior to cell harvest. Subjects with alanine transferase (ALT) > 2x upper limit of normal (ULN) or total bilirubin > 1.5xULN may be included only after discussed and agreed with the

Study name, NCT number	Study 201222, NCT01560182
	medical monitor and considered in the context of the criterion for excluding subjects with other severe disease. Isolated elevation of total bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin < 35 percent of total.
Intervention including dose and dosing interval and number of patients	Fresh formulation of Libmeldy (n=20). Dose 2-20 × 10^6 cells/kg. Actual doses: • LI-MLD: Min 4.2 × 10^6 cells/kg; Max 19.5 × 10^6 cells/kg. (n=9) • PS EJ-MLD: Min 6.7 × 10^6 cells/kg; Max 16.3 × 10^6 cells/kg. (n=4) • ES EJ-MLD: Min 6 × 10^6 cells/kg; Max 11.1 × 10^6 cells/kg. (n=7)
Primary outcomes (including scoring methods and timings of assessments)	Co-primary efficacy endpoints: Improvement 10% in total GMFM score compared to historical control MLD population Significant (≥2 SD) increase in residual ARSA activity as compared to pre-treatment values, measured in peripheral blood mononuclear cells (PBMCs) at Year 2 after treatment Primary safety endpoints: Conditioning regimen-related safety: ○ Absence of engraftment failure or delayed haematopoietic reconstitution (prolonged aplasia), defined as ANC < 500/µL at +60 days after transplantation, with no evidence of BM recovery, requiring cellular back-up administration. ○ Absence of conditioning regimen-related toxicity, as determined by a surveillance of clinical (NCI grade ≥ 2) and laboratory (NCI grade ≥ 3) parameters applied in the short- and long-term follow-up of the treated subjects in order to assess the degree of morbidity associated with the conditioning regimen. Safety of LV-transduced cell infusion: ○ Short-term safety and tolerability of LV-transduced cell infusion, evaluated on the basis of adverse event (AE) reporting and monitoring of the systemic reactions to cell infusion. The short-term safety of LV-transduced cell infusion consists of the absence of serious adverse events (SAEs) within 48 hours of infusion. The long-term safety of LV-transduced cell infusion, which was evaluated as the absence of replication competent lentivirus (RCL) and the absence of Abnormal Clonal Proliferation (ACP).
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy outcomes: GMFC-MLD levels at different ages in treated subjects compared to the historical control MLD population. Nerve conduction velocity (NCV) Index at Year 2 after treatment significantly higher than scores observed in age-matched historical control MLD subjects Total brain magnetic resonance imaging (MRI) score at Year 2 after treatment significantly lower than in age-matched historical control MLD subjects. IQ > 55 (threshold for severe disability) at neuropsychological testing performed at 24-, 30-, and 36-month follow-ups.

Study name, NCT number	Study 201222, NCT01560182
	Transduced cell engraftment > 4% in PBMC and CD34+ progenitors in bone marrow (BM) (determined as vector copy number (VCN)/cell ≥ 0.04 at quantitative polymerase chain reaction [qPCR], equivalent to 4% assuming a VCN of 1) at Year 1 after transplant. Correlations between transduced cell engraftment parameters and busulfan exposure: Evaluations of percent lentiviral vector (LV), VCN in total PBMC and VCN in total BM at Month 12 and busulfan exposure (i.e. total area under the curve [AUC]) during the conditioning phase. Age at death in the treated subjects compared with the natural history subjects. Significant (≥ 2 SD) increase of residual ARSA activity compared to pre-treatment values, measured in BM mononuclear cells (MNCs), and peripheral blood (PB) and BM subpopulations at Year 2 after treatment. ARSA activity was also measured in cerebrospinal fluid (CSF) at multiple visits. Secondary safety outcomes: Absence of immune responses against the transgene (evaluated via immunoassay). Monitoring of AEs and SAEs, routine laboratory tests, vital signs, physical examinations, specialist examinations, and diagnostic imaging and instrumental tests (including chest x-ray, electrocardiogram and echocardiogram, and echo scan of abdomen and thyroid).
Follow-up time	Subjects will be followed up for at least 8 years post-treatment. At the time of the latest data cut-off for interim data analysis (30 March 2018), among all treated subjects (n=20), the median duration of post-treatment follow-up was 4.0 years (range: 0.6 to 7.5 years), and all surviving subjects (n=18) had at least 3 years of post-treatment follow-up as of their last study visit.

Table 41. Details of Early Access Programmes

Study name	CUP207394	HE 205029	CUP 206258
Study type and design	Compassionate use programme. In June 2013, one early-symptomatic EJ patient was treated under a compassionate use scheme as enrolment in Study 201222 was closed to EJ patients. The CUP was conducted at the same clinical site and by the same study site staff as Study 201222 and followed the design of Study 201222 where feasible and appropriate.	Hospital Exemption. Three patients treated with Libmeldy in 2016. Because Study 201222 was closed for enrolment and no other clinical trials with Libmeldy were open for recruitment, three pre-symptomatic patients were treated under a Hospital Exemption (HE) programme. The study design was similar to that defined for Study 201222.	Compassionate use programme. Five patients treated Libmeldy in 2016. Following HE 205029, a new CUP was initiated and five pre-symptomatic patients were treated. The study design was similar to that defined for Study 201222.
Purpose	To evaluate the safety and efficacy of Libmeldy in patients with pre-symptomatic LI or pre- or early-symptomatic EJ MLD.		
Sample size	N=1	N=3	N=5
Population	Symptomatic EJ variant of MLD (n=1).	Early-onset MLD patients (all pre-symptomatic LI variant) (n=3).	Early-onset MLD patients (four LI, one EJ variant), all pre-symptomatic at the time of treatment (LI n=4, EJ n=1).
Inclusion criteria	No formal inclusion or exclusion criteria were established for this CUP; however, the patient m*et* all eligibility criteria defined for Study 201222 except the inclusion criterion of ≤ 6 months from onset of symptoms.	The enrolment criteria were similar to those defined for study 201222.	
Exclusion criteria	The enrolment criteria were similar to those defined for study 201222.		
Intervention including dose and dosing interval and number of patients	Fresh formulation of Libmeldy (n=1) Dose 2-25 × 10^6 cells/kg.	Fresh formulation of Libmeldy (n=3) Dose 2-20 × 10^6 cells/kg.	Fresh formulation of Libmeldy (n=5) Dose 2-30 × 10^6 cells/kg. (The maximum dose was increased from the level specified in the Study 201222 and HE protocols)
Primary outcomes	The efficacy endpoints were similar to those defined for Study 201222.		
Secondary outcomes	The efficacy endpoints were similar to those defined for Study 201222.		
Follow-up time	Follow-up ongoing. Current time of follow up is between 1 year and 5 years (mean = 2 years, median 1.50 years).		

Table 42. Details of study 205756.

Study name, NCT number	Study 205756, NCT03392987
Study type and design	Phase II trial. Non-randomised, open-label, prospective, comparative (non-concurrent control), single-centre study.
Purpose	To evaluate the efficacy and safety of the cryopreserved formulation of Libmeldy in up to 10 patients with pre-symptomatic LI or EJ MLD.
Sample size	N=6 (as of the last data cut); planned total n=10.
Population	Pre- or early-symptomatic early-onset MLD patients (LI, EJ variants or intermediate variant between LI/EJ) (n=10). Children up to 6 years of age with early-onset MLD (LI or EJ variants). The LI variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms in the older sibling(s) ≤ 30 months and/or two null (0) mutant ARSA alleles and /or peripheral neuropathy at electroneurographic (ENG) study. The EJ variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms (in the patient or in the older sibling) between 30 months and 6 years (had not celebrated their 7th birthday), and/or one null (0) and one R mutant ARSA allele(s) and/or peripheral neuropathy at ENG study. Pre-symptomatic clinical status was defined as subjects without neurological impairment (disease- related symptoms), with or without signs of the disease revealed by instrumental evaluations (ENG and brain MRI).

Inclusion criteria	Pre-symptomatic MLD subjects with the LI variant or the EJ variant.
	
	Parental/guardian signed and dated informed consent.
	
	The MLD diagnosis was based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles, either known or novel mutations. Novel mutations were analysed with in silico prediction tools and excluded from being known common polymorphisms. In the case of a novel mutation(s), a 24-hour urine collection was required to show elevated sulfatide levels.
	
	Eligible participants must have had EITHER:
	
	• An older sibling affected by MLD (index case), whose age of symptom onset was ≤ 6 years of age (i.e. had not celebrated 7th birthday). Participants were classified as LI, EJ, or intermediate LI/EJ based on age of symptom onset in the index case and their ARSA genotype.
	  ○ LI: symptom onset in the index case ≤ 30 months of age, genotype typically 0/0
	  ○ EJ: symptom onset in index case > 30 months and ≤6 years of age, genotype typically 0/R
	  ○ Intermediate LI/EJ: symptom onset in index case ≤6 years of age but unable to unambiguously characterize index case as LI or EJ
	
	OR
	
	If MLD was diagnosed in a pre-symptomatic child without an older affected sibling (e.g. incidentally or via newborn screening) and the totality of the available data to the investigator strongly suggested that the subject had an early-onset variant of MLD likely to benefit from GT and the subject was ≤6 years of age (i e, had not celebrated 7th birthday), the subject was considered eligible after discussion and approval of the Orchard Therapeutics (Europe) Ltd Medical Monitor (OTL-MM).

Study name, NCT number	Study 205756, NCT03392987
Exclusion criteria	Subjects who had symptoms of MLD, defined as EITHER of the following were excluded from study admission: a. Delay in expected achievement of independent standing or independent walking, together with abnormal signs at neurological evaluation b. Documented neurological signs and symptoms of MLD associated with cognitive, motor, or behavioural functional impairment or regression (substantiated by neurological examination and/or neuropsychological tests appropriate for age). Note that seizures and signs of disease revealed at instrumental evaluations (electroneurographic recordings and brain MRI) were not exclusionary if present alone. The appearance of symptoms was reassessed by the responsible physician at or immediately before hospitalisation for therapeutic stem cell harvest and again immediately before commencement of the conditioning regimen in order to confirm treatment eligibility based on absence of disease-related symptoms. In particular, treatment was no longer indicated if the subject had developed the onset of neurological symptoms attributable to disease progression.
Intervention including dose and dosing interval and number of patients	Cryopreserved formulation of Libmeldy (n=6). Dose 3-30 × 10^6 cells/kg. All treated parents have been pre-symptomatic; PS LI-MLD (n=5), PS EJ-MLD (n=1)
Primary outcomes (including scoring methods and timings of assessments)	Primary efficacy endpoint: GMFM score at 24 months post-gene therapy.
Secondary outcomes (including scoring methods and timings of assessments)	Clinical efficacy: • GMFM score post-gene therapy at multiple visits over time; • Clinical efficacy at 24 months post-gene therapy and multiple visits over time, as measured by: a) GMFC-MLD score b) Neurological examinations c) Assessment of nerve conduction velocity (NCV) d) Evaluation of brain MRI assessments/parameters (e.g. modified Loes score) e) Neurocognitive assessments Evaluation of engraftment: • %LV positive clonogenic progenitors in bone marrow (BM) at Day 30 post-gene therapy and at multiple visits over time • Vector copy number (VCN) in BM mononuclear cells at Day 30 post-gene therapy and at multiple visits over time • VCN in peripheral blood (PB) mononuclear cells at Day 60 post-gene therapy and at multiple visits over time Pharmacodynamic effect: • The following at Day 60 post-gene therapy and at multiple visits over time:

Study name, NCT number	Study 205756, NCT03392987
	a) ARSA activity in total peripheral blood mononuclear cells (PBMCs) b) ARSA activity in PB $CD15^+$ cells c) ARSA activity in PB $CD14^+$ cells • ARSA activity in cerebrospinal fluid (CSF) at Day 90 post-gene therapy and at multiple visits over time Safety and tolerability: Safety and tolerability as measured by adverse events (AEs) reporting including: o Conditioning regimen related toxicity and AEs o Non-conditioning related AEs Haematological recovery, defined as reconstitution of absolute neutrophil count (ANC) > 500 neutrophils/µL, associated with evidence of BM recovery (i.e. no hypocellular marrow) by Day +60 Incidence and titres of antibodies against ARSA Absence of malignancy or abnormal clonal proliferation due to insertional oncogenesis Absence of RCL
Follow-up time	Subjects will be followed up for at least 8 years post-treatment. At the time of the latest data cut-off (end of 2019), among all subjects (n=6), the median duration of follow-up was 0.7 years (range: 0 to 1.5 years).

Appendix 3. Brain MRI and NCV index

Table 45. Reconstitution of ARSA activity — total PBMC (adjusted mean; nmol/mg/h)

Tabellen omfattas av sekretess

* Values below the lower limit of quantification (LLQ, 25.79 nmol/mg/h) are imputed with LLQ.

Table 6. Brain MRI (total score) for treated and untreated patients.

Tabellen omfattas av sekretess

Table 7. NCV Index compared to NHx data (adjusted mean).

Tabellen omfattas av sekretess

Appendix 4. Cost-effectiveness analysis – Original documentation and Clinical effectiveness

Based in the original documentation sent in by the company. The patients could be classified into four different groups. Cost-effectiveness results and grouping of patients according to their assumed response status – The company's base case (original version):

Table 43: Company base case results for the combined patient population, NOK. Costs and effect discounted (original documentation June 2021).

	Libmeldy	BSC	Diff.
Libmeldy (LIBMELDY)	30 074 576	0	30 074 576
Administration costs	1 150 548	0	1 150 548
Mean treatment cost for MLD (all care cost)	4 809 920	13 262 521	-8 452 601
Total costs	*36 038 428*	*13 262 607*	*22 775 908*
Life years (LY)	[---]	[---]	[---]
QALYs	15.8	-4.9	20.7
Cost per LY gained			[----------]
Cost per QALY gained			**1 101 495 NOK**

Table 44: Company base case results for the PS-LI population, NOK. Costs and effect discounted (original documentation June 2021).

	Libmeldy	BSC	Diff.
Libmeldy (LIBMELDY)	30 074 576	0	30 074 576
Administration costs	1 153 919	0	1 153 919
Mean treatment cost for MLD (all care cost)	4 342 450	13 323 764	-8 981 314
Total costs	*35 570 945*	*13 323 764*	*22 247 181*
Life years (LY)	28.3	8.6	19.7
QALYs	15.7	-4.6	20.3
Cost per LY gained			[----------]
Cost per QALY gained			**1 095 929 NOK**

Table 45: Company base case results for the PS-EJ population, NOK. Costs and effect discounted (original documentation June 2021).

	Libmeldy (LIB-MELDY)	BSC	Diff.
Libmeldy (LIBMELDY)	30 074 576	0	30 074 576
Administration costs	1 153 988	0	1 153 988
Mean treatment cost for MLD (all care cost)	3 682 478	13 043 710	-9 361 232
Total costs	*34 911 042*	*13 043 710*	*21 867 332*
Life years (LY)	[---]	[---]	[---]
QALYs	18.8	-5.4	24.2
Cost per LY gained			[----------]
Cost per QALY gained			**902 039 NOK**

Table 46: Company base case results for the ES-EJ population, NOK. Costs and effect discounted (original documentation June 2021).

	Libmeldy (LIB-MELDY)	BSC	Diff.
Libmeldy (LIBMELDY)	30 074 576	0	30 074 576
Administration costs	1 153 941	0	1 153 941
Mean treatment cost for MLD (all care cost)	8 953 231	13 169 661	-4 216 429
Total costs	*40 181 749*	*13 169 661*	*27 012 088*
Life years (LY)	[---]	[---]	[---]
QALYs	12.5	-6.0	18.5
Cost per LY gained			[----------]
Cost per QALY gained			**1 457 847 NOK**

The key cost driver affecting the results of the economic evaluation is the effect parameters combined with the direct drug expense of Libmeldy. This should be compared to extensive at-home/care costs and hospitalizations for untreated patients over a lifetime with a discount rate according to the rates described in Chapter 4.1.

The undiscounted life years gained according to the company for the weighted patient population is [----------]

The subgroup specific undiscounted life years gained according to the company are as follows:

- PS-LI: [----------] in the comparator arm.
- PS-EJ: [----------] in the comparator arm.
- ES-EJ: [----------] in the comparator arm.

Company's sensitivity analyses (original documentation June 2021)

The company has performed several one-way sensitivity analyses to explore the sensitivity of individual parameters/ input variables in the deterministic base-case model results. These are presented below. The company notes that the discount rate and time horizon have a greater impact on the results than the performed one-way sensitivity analyses.

Table 47: The company's scenario analysis, based on the combined patient population, NOK (original documentation June 2021).

Sensitivity analyses	+/- Δ Costs	+/- Δ QALYs	Cost/ QALY
Alternative discount rates:			
0%	23 231 204	46.39	**507 294**
3%	22 775 908	20.68	**1 101 495**
5%	23 332 600	14.76	**1 580 820**
Time horizon:			
30 years	22 593 365	13.85	1 630 941
50 years	22 949 035	16.66	1 377 523
Utility set applied to LI patients at ages >48 months	23 301 712	20.78	1 121 172
Responders' status proportions	23 792 940	18.18	1 309 059

The company has also presented the results as a tornado diagram indicating that the percentage of patients classified as responders, and at what health state partial responders stabilize at, as these parameters have the greatest impact on the results according to the company. The company notes that the discount rate and time horizon have a greater impact on the results than the performed one-way sensitivity analyses.

The company's original classification of responders

Figuren omfattas av sekretess

Figure 22. The company's classification of patients into response-groups, late-infantile population.

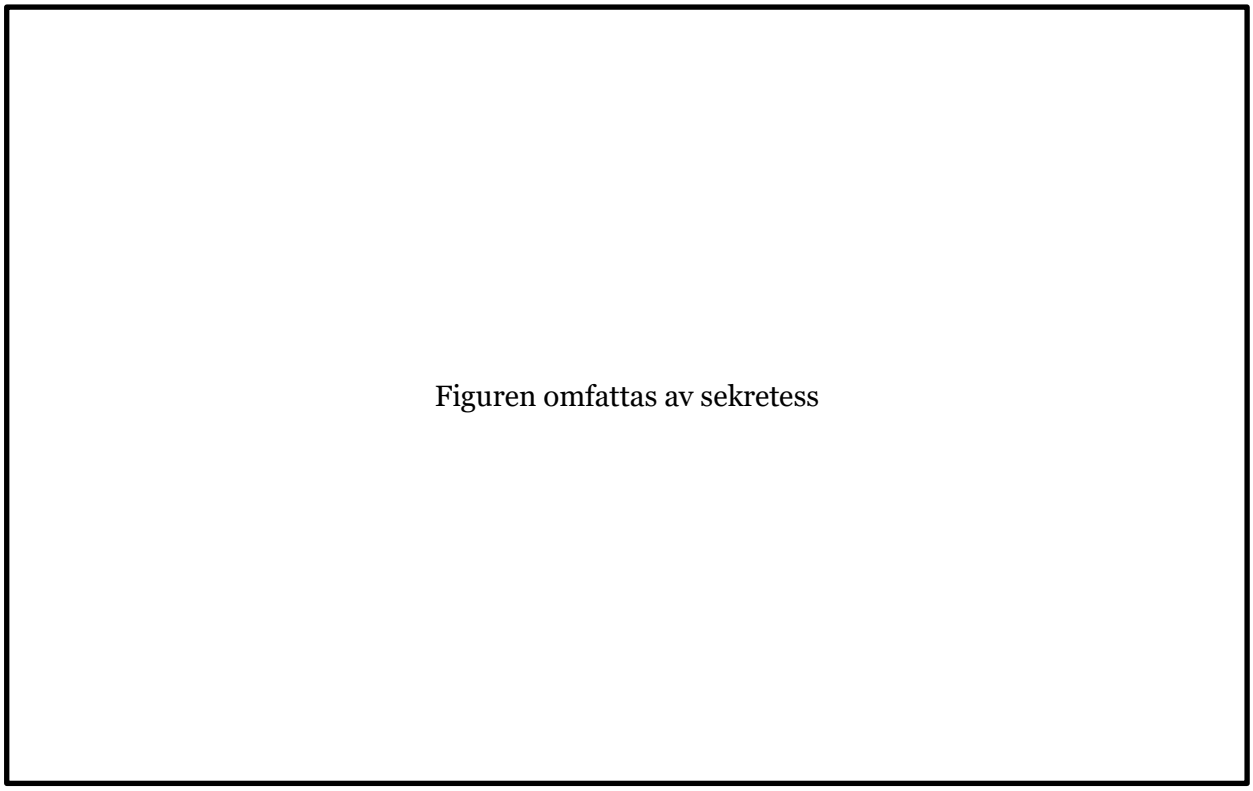


Figure 23. The company's classification of patients into response-groups, early juvenile pre-symptomatic population.

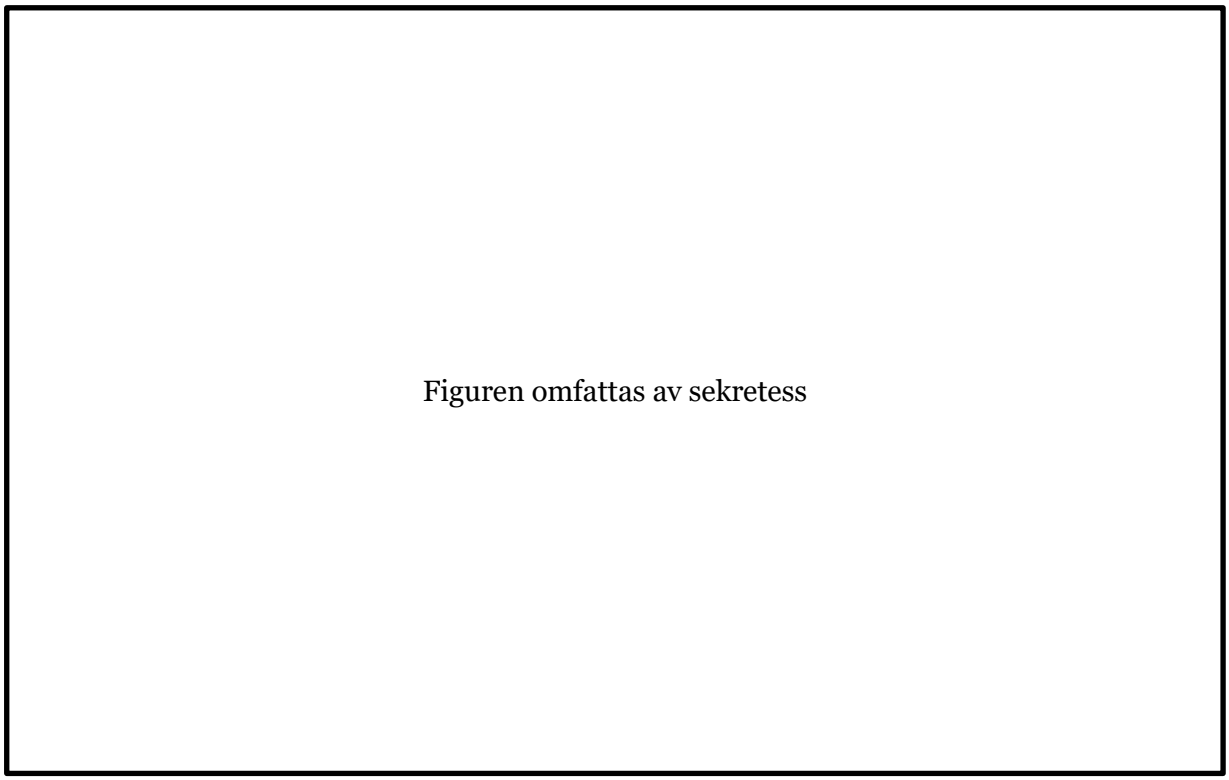


Figure 24. The company's classification of patients into response-groups, early juvenile symptomatic population.

Table 8. Libmeldy indicated population dataset, with responder-status classification as assumed in the original documentation. The patients marke with blue, additional data was made available during this assessment and reclassified in the company's new base case.

Tabellen omfattas av sekretess

Table 48. Updated responders status classification in the new company base case.

Tabellen omfattas av sekretess

In August 2021 and January 2022, the company sent updated data for selected patients in the different clinical trials (Pivotal study (201222) and CO2 (CUP 207394)), as referenced in Chapter 3.6. The updated GMFC-MLD data which altered the reclassifications compared to the companys basecase from the original submitted, is depicted in in Appendix 10.

Appendix 5. Grouping of patients according to their assumed response status – FINOSE

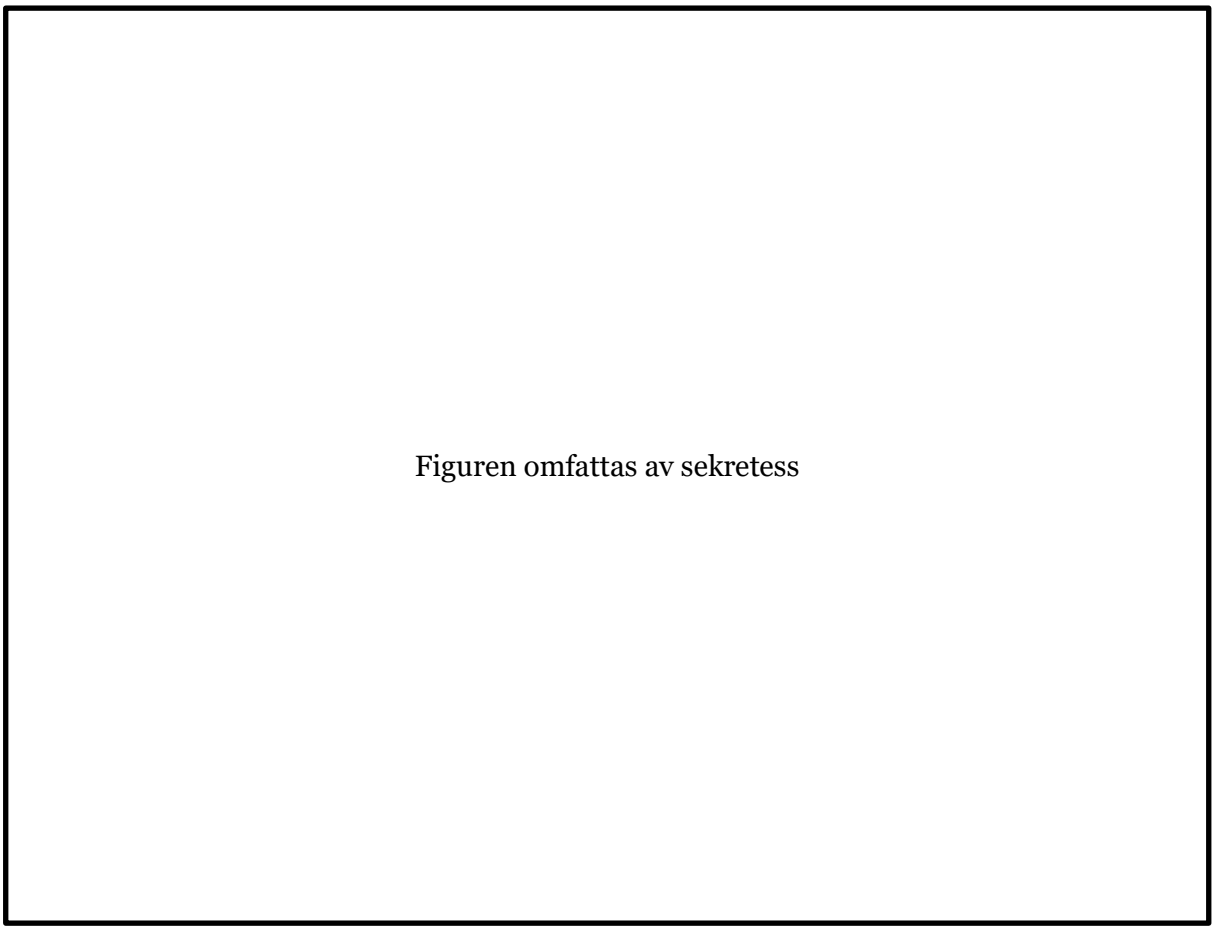


Figure 25. FINOSE sensitivity-analysis classification of patients into response-groups, late-infantile population.

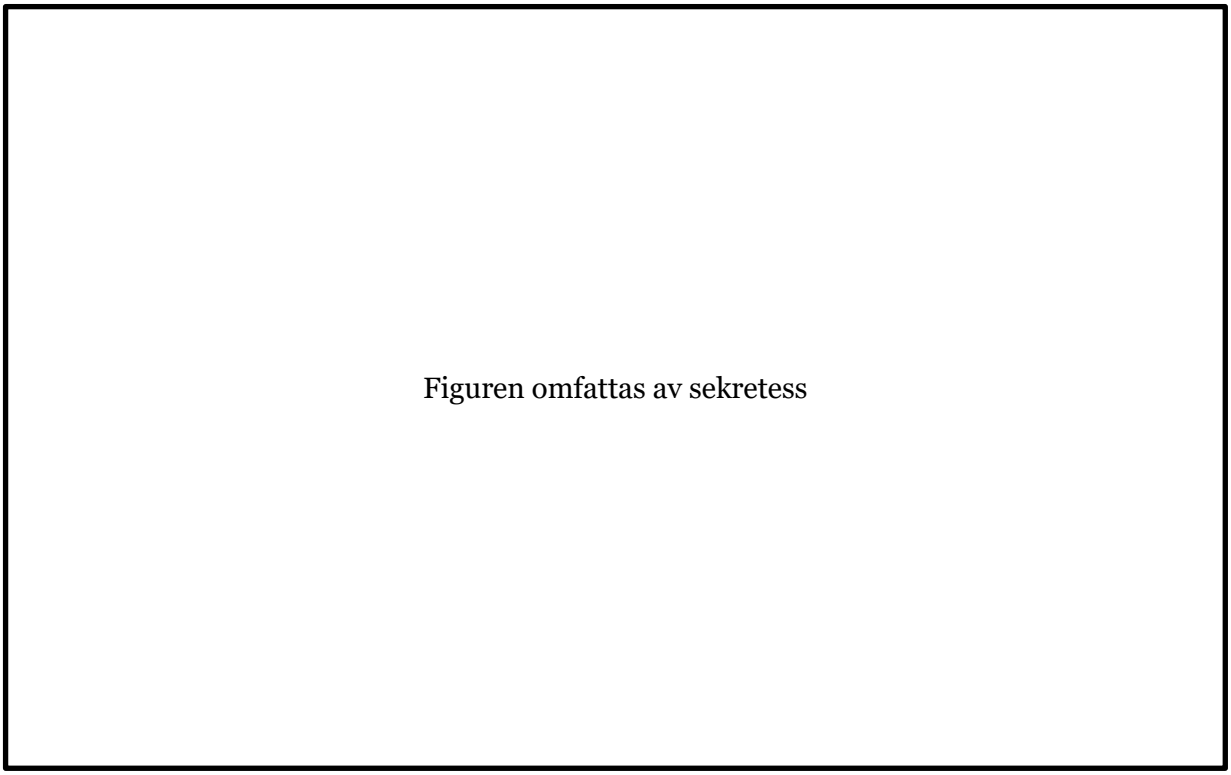


Figure 26. FINOSE sensitivity-analysis classification of patients into response-groups, early juvenile population (pre-symptomatic and symptomatic).

LI patients

- [----------] progresses after being stable for 30 months after the expected onset of the disease
- Based on this, all patients less than 30 months stable are assumed to be progressing
- This would mean the following distribution for LI:
    - Full responders: [------]
    - Partial stable, level 1: [------]
    - Partial stable, level 2: [------]
    - Unstable: [------]
- Also, patients that are improving [----------] are considered to be stable at level where they are at the end of the follow up

EJ patients

- [----------] progresses after being stable for more than 3 years after treatment
- All patients that are stable for less than 3 years are considered unstable
- The distribution for pre-Symptomatic EJ
    - Full responders: [-----]
    - Unstable: [-----]
- The distribution for ES-EJ:
    - Partial stable, level 2: [-----]
    - Unstable: [-----]

Appendix 6. Validation of the BSC-arm, from the NHx-study vs. Published literature

Table 50. Best supportive care (BSC) modelled late-infantile inputs for mean time to transition. From the natural history control arm in the second column, and from two published articles in the two-last column on the right.

Tabellen omfattas av sekretess

Note: GMFC-MLD 2 to 3, GMFC-MLD 3 to 4 and GMFC-MLD 4 to 5 calculated by evenly distributing the months from GMFC-MLD 2 to 5.
*Calculation based on difference between patient age at model entry (18 months) and average age at entry into GMFC-MLD 1 in the TIGET NHx study for LI patients
**Not reported in publication, used value from Orchard Therapeutics clinical trial as proxy

Table 51. Best supportive care (BSC) modelled early-juvenile inputs for mean time to transition. From the natural history control arm in the second column, and from two published articles in the two last column on the right.

Tabellen omfattas av sekretess

Note: GMFC-MLD 2 to 3, GMFC-MLD 3 to 4 and GMFC-MLD 4 to 5 calculated by evenly distributing the months from GMFC-MLD 2 to 5.
*Calculation based on difference between patient age at model entry (45 months) and average age at entry into GMFC-MLD 1 in the TIGET NHx study for EJ patients
**Not reported in publication, used value from Orchard Therapeutics clinical trial as proxy

Appendix 7. HRQoL values used in the FINOSE scenario

Table 52. EQ-5D utility values applied in the FINOSE scenario

Health State	LI Utility Value	EJ Utility Value Normal Cognition (DQ ≥ 70)	EJ Utility Value Cognitive Impairment (70 > DQ ≥ 55)	EJ Utility Value Severe Cognitive Impairment (DQ < 55)
GMFC-MLD 0	General Population	General Population	0.75	0.46
GMFC-MLD 1	0.71	0.91	0.63	0.34
GMFC-MLD 2	0.44	0.84	0.56	0.27
GMFC-MLD 3	0.13	0.38	0.10	0.08
GMFC-MLD 4	0.04	0.17	0.01	0.03
GMFC-MLD 5	0.01	0.07	0.00	0.01
GMFC-MLD 6	0.00	0.03	0.00	0.00

Appendix 8. Additional drugs included in the analysis

Table 53. Additional drugs included in the analysis.

Cost Category	Item
Drugs	Amoxicillin
Drugs	Lansoprazole
Drugs	Ranitidine
Drugs	Paracetamol
Drugs	Oramorph syrup
Drugs	Bicarbonates
Drugs	Baclofen
Drugs	Botox
Drugs	Tizanidine
Drugs	Clonazepam or other benzodiazepine
Drugs	Carbamazepine
Drugs	Sodium valproate
Drugs	Phenobarbital
Drugs	Levetiracetam
Drugs	Phenytoin
Drugs	Gabapentin
Drugs	Lacosamide
Drugs	Scopolamine Patch

Appendix 9. Unit costs applied in the cost-effectiveness analysis, with regards to the resource use.

Table 4. Unit costs, inpatient hospitalization (with regards to Table 20 in Chapter 4.3.3).

Resource	Cost per Episode/ Day	Reference/Source	Assumption
MLD related hospitalization (1. Pediatric Metabolic Disorders – non-elective inpatient HRGs)	NOK 18,080	SLV Enhetskostnadsdatabase 2020 [29] [Sykehus Liggedøgn – Generelt]	Cost per day, hospitalization (general)
MLD related hospitalization (2. Pediatric Metabolic Disorders – elective inpatient HRGs)	NOK 50,632	SLV Enhetskostnadsdatabase 2020 [29] [Sykehus Liggedøgn – Intensivdøgn]	Cost per day, hospitalization (intensive care)

Table 55. Unit costs, medical visits (with regards to Table 20 in Chapter 4.2.3).

Resource	Cost per Visit	Reference/Source
Pediatrician visits	NOK 2,289	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG;910O -Polikliniske konsultasjoner]
Neurologist visits	NOK 3,597	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; 901O - Disease of nervous system, short therapy w / o significant procedure]

Neuropsychologist	NOK 13,455	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG code: XD90B - Polikliniske konsultasjoner - Andre problemstillinger - Barn og unge]
Physiotherapist	NOK 1,168	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; 908O Disease or disorder of the musculosceletal system, short therapy w/o significant procedure]
Psychiatrist	NOK 5,046	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; 919O -Mental disease or disorder, short therapy w/o significant procedure]
Speech therapist	NOK 1,759	Södra regionvårdsnämnden, prislista 2021 [31] [Öron-näsa-halssjukvård, Logopedbehandling; BSVBL1; p.69; SEK 1,777]
Surgical visit (for PEG and cholecystectomy) <=18	NOK 9,951	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG;156O -Stomach, esophageal & duodenal procedures, short therapy]
Pneumological visit (for respiratory complications)	NOK 2,336	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; 904O -Disease and disorder of the respiratory system, short therapy w/o significant procedure]
Orthopedic visit (for tendon retractions / scoliosis)	NOK 2,009	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; 908A - Poliklinisk konsultasjon vedr brudd, dislokasjon eller bløtdelsskade i armer, ben eller bekken/

Table 56. Unit costs, emergency room visit (with regards to Table 20 in Chapter 4.2.3).

Resource	Cost per Episode/Day	Reference/Source
MLD-related acute event	NOK 13,455	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; XD90B -Polikliniske konsultasjoner - Andre problemstillinger - Barn og unge]

Table 57. Unit costs, medical procedures (with regards to Table 20 in Chapter 4.2.3).

Resource	Cost per Procedure	Reference/Source
Salivary gland botox	NOK 4,578	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG; 801W - Poliklinisk behandling av tilstander i nervesystemet med lokal injeksjon av botulinumtoksin]
Baclofen pump implantation	NOK 13,876	Innsatsstyrt finansiering (ISF) – regelverk 2021 - Helsedirektoratet. [30] [DRG 477O; Non-extensive o. r. procedure unrelated to principal diagnosis, short therapy]

Table 58. Unit costs, lab tests (with regards to Table 20 in Chapter 4.2.3).

Resource	Cost per Medical Test	Reference/Source
Routine Lab tests	NOK 122	SLV Enhetskostnadsdatabase 2020 [29] [Tester og undersøkelser; Blodprøve]
Abdominal Ultrasound	NOK 280	Fastlegetariffen 2020-2021 [32] [Normaltariffen Takst 108a-f: Diagnostisk ultralyd hos allmennlege ved vurdering av hudnære sykelige prosesser (abscesser, cyster mv); Adjusted according to NoMA guidelines as the total of the tariff per investigation /consultation and the patient's contribution, multiplied by two]

ENG Electromyography <= 18	NOK 4,671	Södra regionvårdsnämnden, prislista 2021 [31] [DRG A820; Elektromyo- och neurografier O; p.28; SEK 3,721]
MRI Brain sedation (every 2 years)	NOK 1,397	Lovdata, Forskrift om stønad til dekning av utgifter til undersøkelse og behandling i private medisinske laboratorie- og røntgenvirksomheter [MR5, Hode] https://lovdata.no/dokument/SF/forskrift/2003-06-27-959
EEG <=18	NOK 2,368	Södra regionvårdsnämnden, prislista 2021 [31] [DRG A810; Elektroencefaliografier O; p.28; SEK 2,392]
PEV (Visual evoked potential) <= 18	NOK 6,756	NHS 2018/19 National Cost Collection data [23] [CA38B; Visual Evoked Potential (PEV) or Brainstem auditory evoked potential (PEA)l - Evoked Potential Recording, 18 years and under; GBP 574]
PEA (Brainstem auditory evoked potentials) <=18	NOK 6,756	NHS 2018/19 National Cost Collection data [23] [CA38B; Visual Evoked Potential (PEV) or Brainstem auditory evoked potential (PEA)l - Evoked Potential Recording, 18 years and under; GBP 574]

Table 59. Unit costs, medical equipment (with regards to Table 20 in Chapter 4.2.3).

Resource	Cost of Equipment	Reference/Source
Orthosis (Ankle-foot-orthosis)	NOK 1,187	Rehaboteket.se [Dorsalskena; SEK 1,199] https://www.rehaboteket.se/ortos/fotled/dorsalskena-malleum-afo
Pram / Stroller	NOK 2,828	Nettomedical.no [Liten Rullator Dietz rullator Taima S GT til utendørs bruk] https://nettomedical.no/nettbutikk/91-rullator/2008-dietz-rullator-taima-s-gt/
Walker	NOK 859	Nettomedical.no [Dietz Gangstativ Starr G-104] https://nettomedical.no/nettbutikk/92-gaastoler/386-dietz-gangstativ-starr-g-104/
Normal High chair	NOK 795	IKEA [Junior/Barnstol] https://www.ikea.com/no/no/p/langur-junior-hoystol-hvit-s09252593
Adaptable bed with anti-decubitus mattress	NOK 3,131	National Schedule of NHS Costs (NHS trusts and NHS foundation trusts) for 2018-2019 [23] [IC02; Intermediate Care Bed Based Services - National Schedule of NHS Costs - Year 2018-19 - NHS trusts and NHS foundation trusts - Other Currencies Data; GBP 266.05]
Bath tub aids	NOK 2,697	Nettomedical.no [Badkaresete Dietz Aquaswift] https://nettomedical.no/nettbutikk/84-badeheiser-og-seter/1249-badkaresete-dietz-aquaswift/
Car for transporting wheelchairs	N/A	No relevant unit cost identified
Enteral feeding pump	N/A	No relevant unit cost identified
Pulse oximeter / aspirator / cough machine	NOK 920	Nettomedical.no [Fingerpulsoximeter MS 20] https://nettomedical.no/nettbutikk/74-pulsoxymeter/545-fingerpulsoximeter-ms-20/

Table 60. Unit costs, social services (with regards to Table 20 in Chapter 4.2.3).

Resource	Cost per Hour	Reference/Source	Assumption
Enteral nutrition - days per year (age <=18)	NOK 442	SLV Enhetskostnadsdatabase 2020 [29] [Sykepleier Kr/time]	Nurse cost per hour

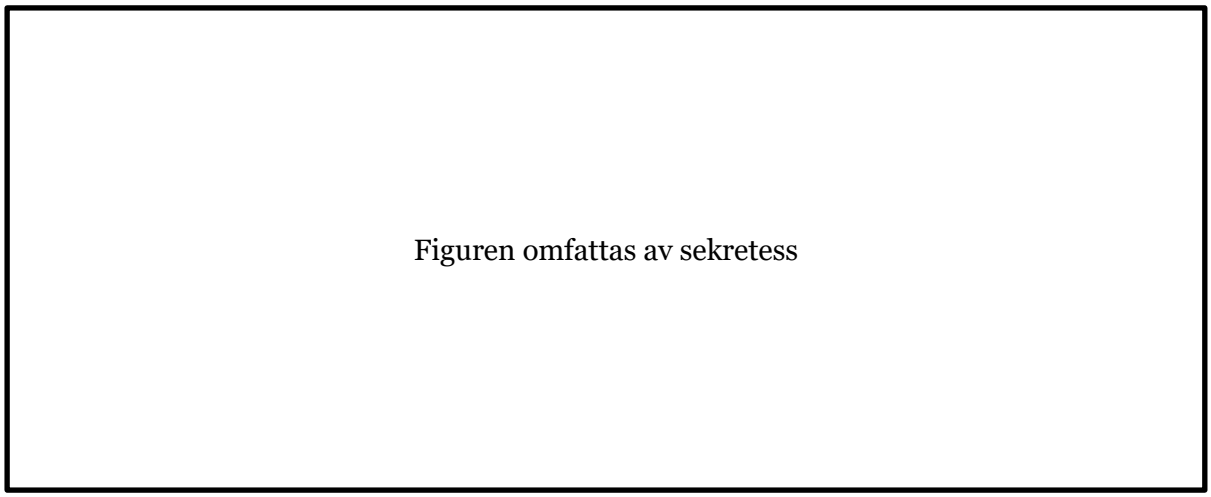
Social caregiver - days per year (age <=18)	NOK 239	Tariffavtale Uloba 2016 http://www.fagforbundet.no/shs/personlige-assistenter/	Minimum wage + 40% (National Insurance contributions + employer's contribution.)
Community Nurse	NOK 442	SLV Enhetskostnadsdatabase 2020 [29] [Sykepleier Kr/time]	Nurse cost per hour
Local provision care home for adults	NOK 600	PSSRU Unit Costs of Health and Social Care 2019 [Social worker (adult services) Unit costs available 2017/2018; GBP 51 per hour]	Cost per hour

Table 61. Respite/palliative care (with regards to Table 20 in Chapter 4.2.3).

Resource	Mean Cost per Episode	Reference/Source
Respite/Palliative Care	NOK 59,001	SLV Enhetskostnadsdatabase 2020 [29] [Kostnader Livets sluttfase]

Appendix 10. Additional data from pivotal study 201222 and CUP 207394 for selected patients.

In August 2021 and January 2022, the company sent updated data for selected patients in the different clinical trials (Pivotal study (201222) and CO2 (CUP 207394)), as referenced in Chapter 3.6. The updated GMFC-MLD individual level patient data which altered the reclassifications compared to the company's base case from the original submitted, is depicted in in this Appendix, which should be viewed in conjunction with Appendix 4 and 5.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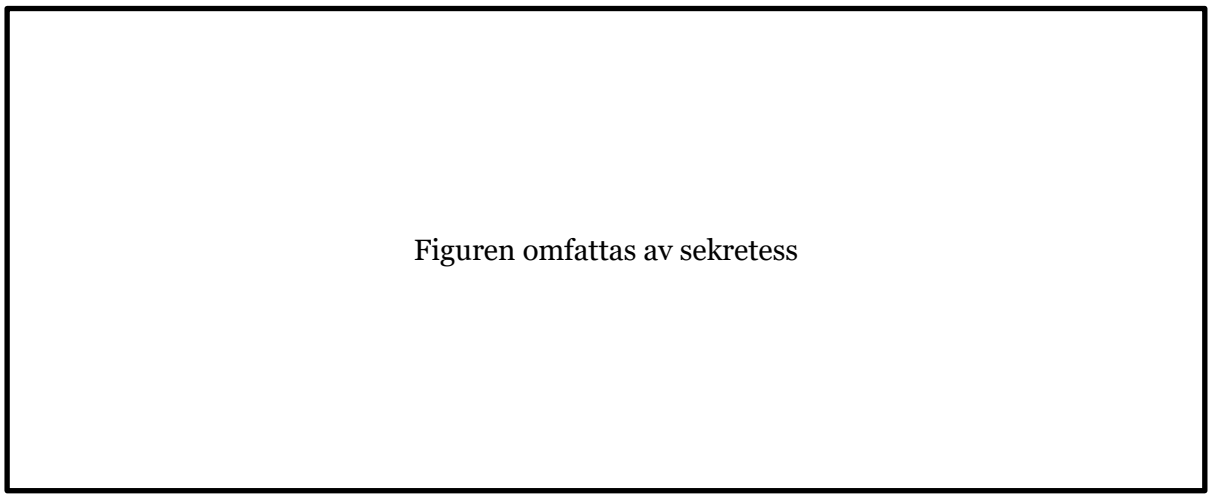
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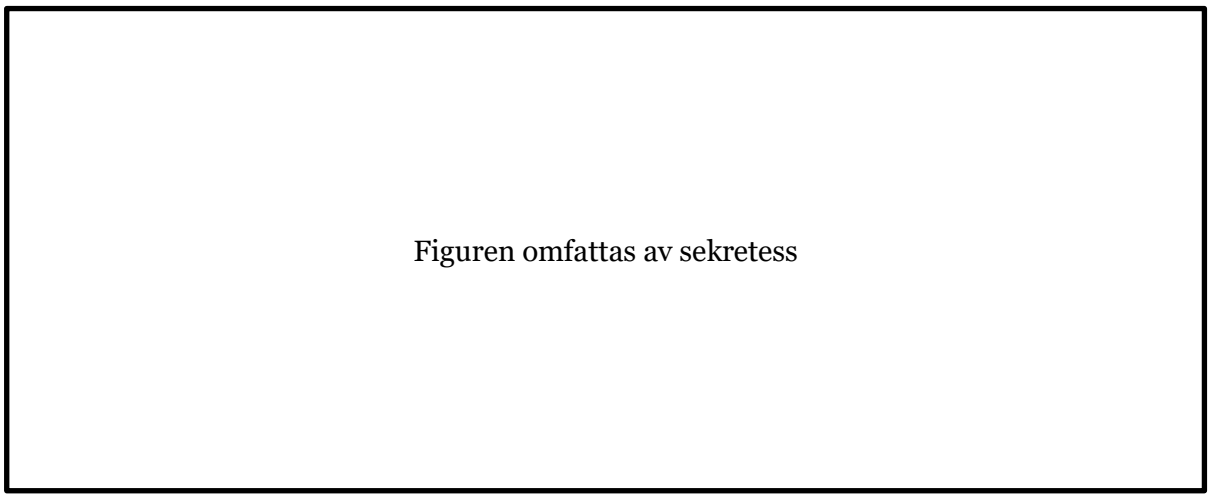
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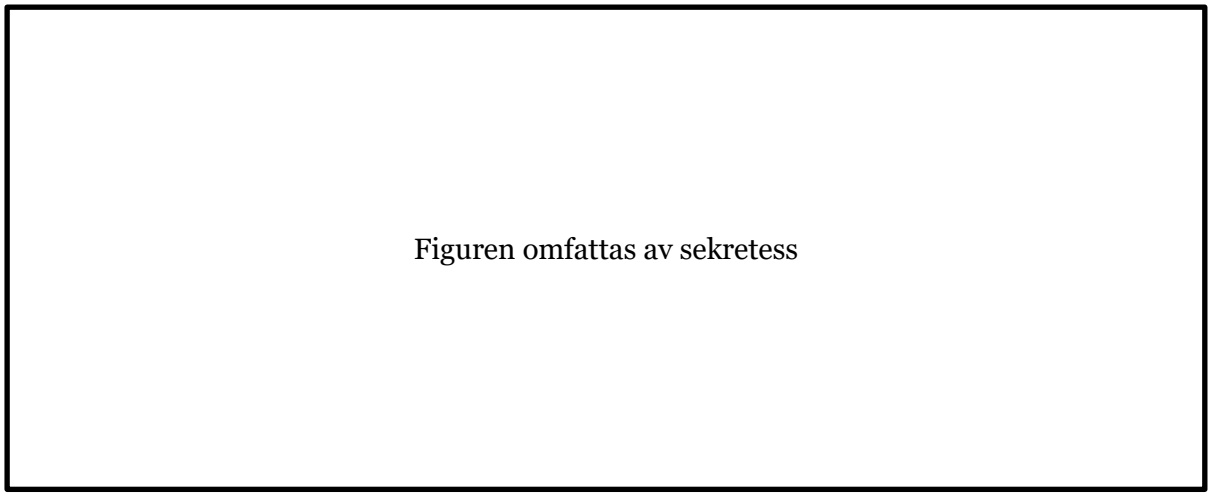
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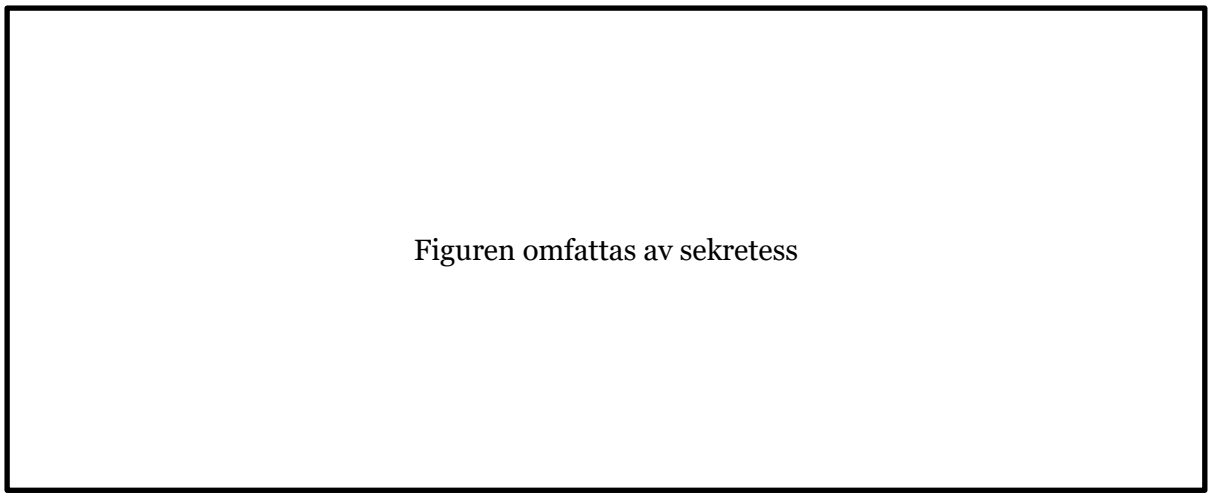
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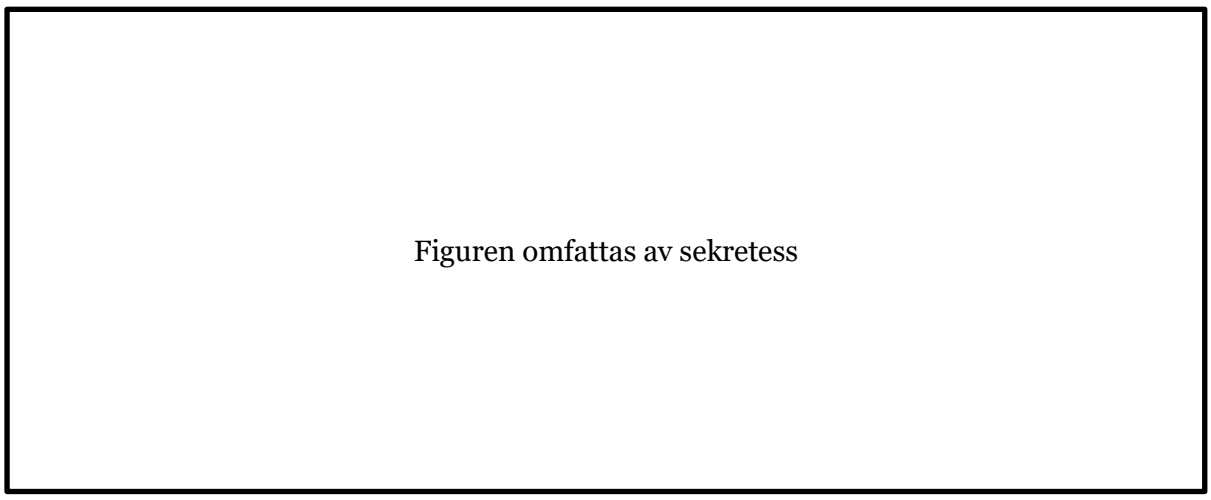
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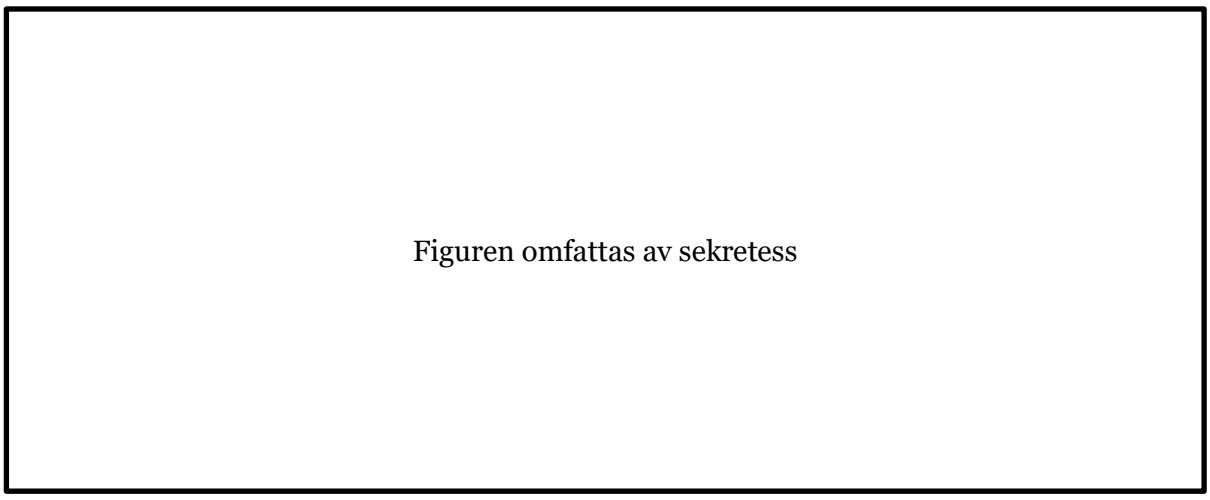
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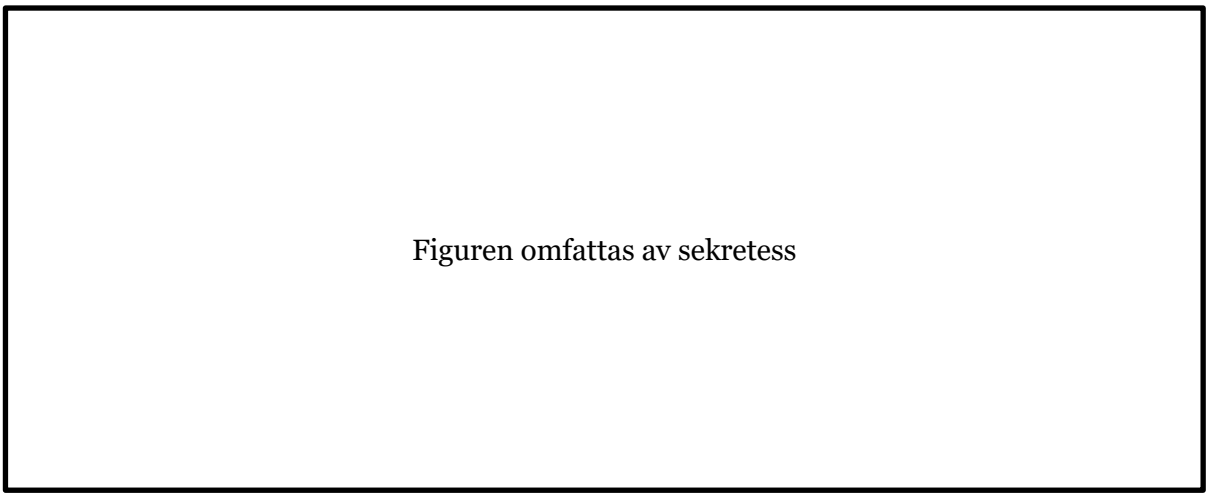
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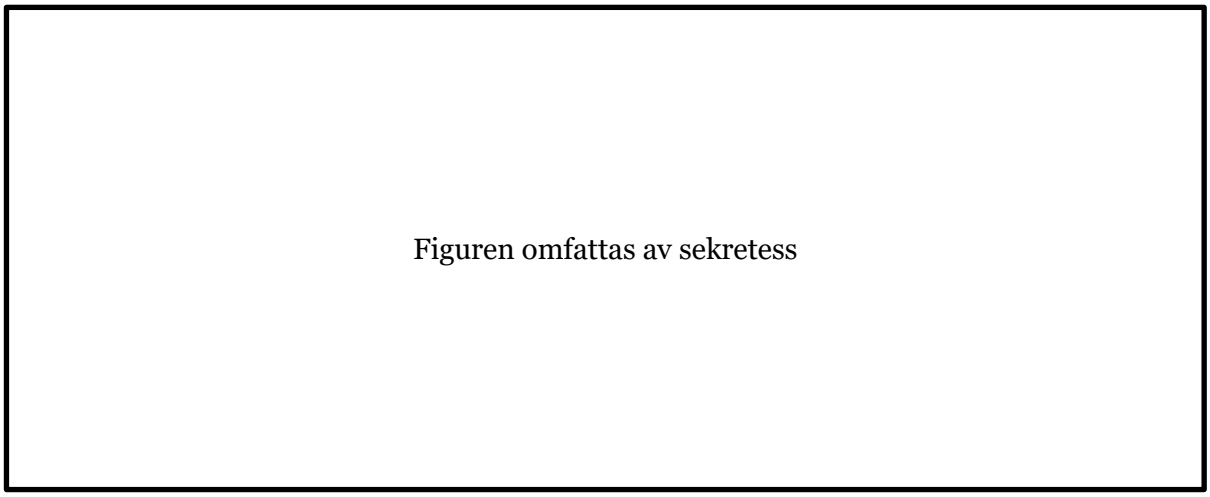
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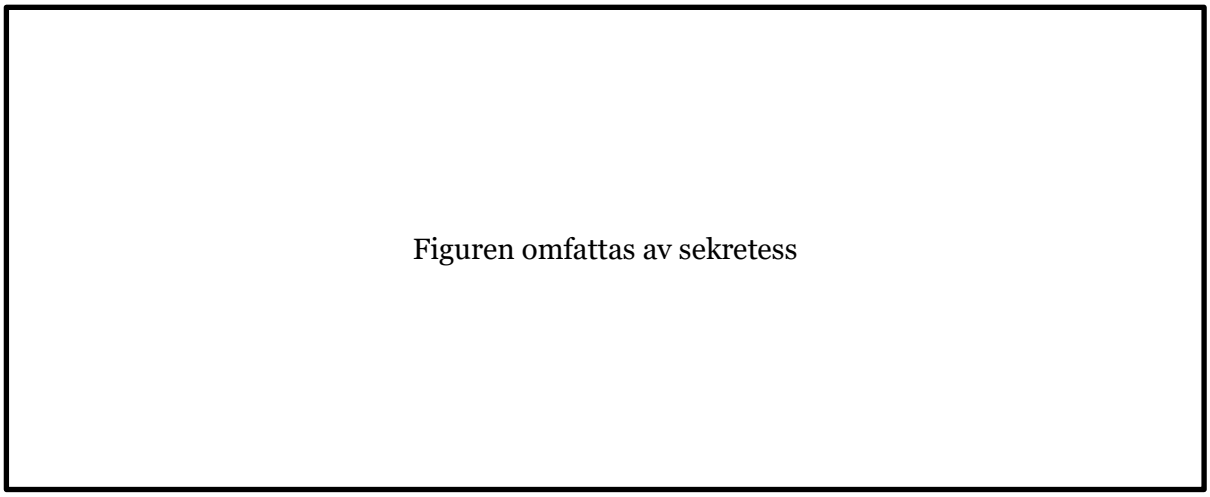
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