AGENZIA ITALIANA DEL FARMACO

SCIENTIFIC REPORT

Libmeldy®

(atidarsagene autotemcel)

Italian Medicines Agency

20 May 2022

Characteristics of the medicinal product:

Marketing Authorization procedure: centralized European.
Type of negotiation: Orphan drug for rare disease.
ATC category: A16AB (Enzymes – this group includes autologous cells modified *ex-vivo* to express specific enzymes)
Marketing Authorization holder: Orchard Therapeutics (Netherlands) B.V.

Therapeutic indication:

Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:

- in children with 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.

Indication reimbursed:

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, with the addition of the criteria defined in section 5.1 of the SmPC with regard to the symptomatic population.

Posology:

The single dose of Libmeldy® to be administered is defined based on the patient's weight at the time of infusion.
The minimum recommended dose is 3×10^6 CD34+ cells/kg, to be administered via intravenous infusion. In clinical trials, doses up to 30×10^6 CD34+ cells/kg have been administered.
The maximum volume of Libmeldy to be administered should remain < 20 % of the patient's estimated plasma volume.
Libmeldy is intended for autologous use and should only be administered once.

Pack eligible for reimbursement by the NHS:

Table 1

Pack	Legal status	Specialists	Class	AIFA note	PT/PHT
Libmeldy 2-10 x 10^6 cells/mL	OSP	Qualified treatment center with expertise in haematopoietic stem cell transplantation (HSCT)	H	-	NO

Mechanism of action:

Libmeldy is an *ex vivo* genetically modified CD34+ autologous haematopoietic stem and progenitor cell (HSPC) gene therapy. Autologous CD34+ HSPCs are collected from patient bone marrow (BM) harvest or from mobilized peripheral blood (mPB) and transduced with a lentiviral vector (ARSA LVV), which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome so that genetically modified cells become capable of expressing the functional ARSA enzyme. When administered to the patient following the administration of a myeloablative conditioning regimen, the genetically modified cells engraft and are able to repopulate the haematopoietic compartment. A subpopulation of the infused HSPCs and/or their myeloid progeny is able to migrate across the blood brain barrier to the brain and engraft as central nervous system (CNS) resident microglia and perivascular CNS macrophages as well as endoneural macrophages in the peripheral nervous system (PNS). These genetically modified cells can produce and secrete the functional enzyme ARSA, which can be taken up by surrounding cells, a process known as cross-correction, and used to break down, or prevent the build-up, of harmful sulfatides. Following a successful and stable engraftment in the patient, the effects of the product are expected to be persistent.

Disease classification

METACHROMATIC LEUKODYSTROPHY (MLD)

MLD is a very severe, progressive neurological disease with an ominous prognosis and extremely poor quality of life for all affected patients. It is a rare disease with autosomal recessive transmission, belonging to the heterogeneous group of lysosomal storage disorders, caused by mutations in the arylsulfatase A (ARSA) gene that result in the corresponding enzyme deficiency. ARSA deficiency results in accumulation of the undegraded substrate in lysosomes of neural tissues, which in turn leads to microglial damage, progressive demyelination, neurodegeneration, and

subsequent loss of motor and cognitive functions and early death, especially in patients with early disease onset.

MLD can present in a variety of clinical forms, age of onset, and rate of disease progression. The ***classification*** is mainly based on the criterion of age of onset of the first symptoms:

- MLD with late infantile onset (LI, ***Late Infantile***, onset of the disease before 30 months);
- MLD with juvenile onset (Juvenile) (30 months < onset < 17 years) which was further distinguished into Early Juvenile MLD onset (EJ, ***Early Juvenile***, 30 months < onset < 7 years) and Late Juvenile MLD onset (LJ, ***Late Juvenile***, 7 years ≤ onset < 17 years);
- MLD with **adult onset** (onset after the age of 17 years).

The ***clinical course*** of the disease can be divided into a pre-symptomatic stage, characterized by normal motor and cognitive development, followed by onset of first symptoms and a period of developmental plateau, which is short in early-onset forms, and longer and more variable in late-onset forms. The latter condition offers more opportunities for therapeutic intervention before irreversible cell damage and the subsequent onset of the symptomatic phase of rapid disease progression. In the absence of treatment able to modify the disease pathophysiology, the disease inevitably leads to loss of motor and cognitive functions and eventually to death, although its course and duration are highly variable, particularly in late-onset MLD variants.

The most common form of MLD, *Late Infantile* onset, is characterized by muscle atrophy, weakness, muscle rigidity, developmental delay and progressive vision loss, seizures, impaired swallowing, paralysis, and dementia. Motor impairment (i.e., the loss of acquired motor skills) can occur as early as 12 months of age, starting with a slowing of motor skill development in infants. Death occurs in early childhood. In patients with the late infantile form, survival at 5 years after the onset of symptoms is 25% and survival at 10 years is 0%; for those with the juvenile form (average age at diagnosis 10 years), survival at 5 and 10 years is 70% and 44%, respectively. An increase in the survival rate in the vegetative state has been observed since 1970, mainly due to improvements in supportive care. However, almost all patients with the most severe form of MLD with late-infantile onset are quadriplegic and in a vegetative state before the end of the second year of life; similarly, most patients with the early-onset juvenile form of MLD are quadriplegic and in a vegetative state within 12 to 18 months after the onset of the first symptoms.

Epidemiological profile

The paucity of published MLD epidemiology data makes it difficult to accurately estimate the global prevalence and incidence of MLD; however, a systematic review of the available literature has revealed approximately 1.1 cases (all variants) of MLD per 100,000 live births in the European Union. In addition, European studies suggest that approximately 40-60% of patients have the Late Infantile variant, 20%-40% have the Juvenile variant (Early + Late), and approximately 18%-20% have the adult variant. According to ISTAT data, new births in Italy are about 400,000 per year, and therefore, about 4 new cases per year are expected in the Italian population. Of these, about 80% will be affected by the Late Infantile/Early Juvenile variant (LI/EJ 3.2 patients/year).

Therapeutic framing

There are currently no specific treatments for MLD whose efficacy and safety has been conclusively established. The only available treatment on which there is more data at present is allogeneic haematopoietic stem cell transplantation (HSCT), although the results are inconsistent and controversial. Allogeneic HSCT can only be considered as a therapeutic alternative for part of the target population of Libmeldy's indication (i.e., pre-symptomatic and early symptomatic *Early Juveniles*), as the disease progresses too quickly in the more severe *Late Infantile* forms.

It must also be taken into account that, compared to gene therapy with Libmeldy, the results on the efficacy of allogeneic HSCT are still controversial because the response in terms of motor function is more variable and there seems to be no benefit for symptoms related to the peripheral nervous system (PNS). Furthermore, there are risks related to allogeneic transplantation especially in terms of transplant rejection and GVHD (*Graft Versus Host Disease*).

Other therapeutic approaches, such as intrathecal *Enzyme Replacement Therapy* (ERT) or other lentiviral vectors, are currently being tested.

Although multiple strategies including HSCT, ERT or gene therapies with AAV have been explored, none of these appear to be entirely effective in treating patients with MLD.

Clinical Efficacy

The clinical efficacy of Libmeldy is based on the integrated analysis of the outcomes of 29 patients with early-onset MLD treated as part of the Registration Study 201222, a non-randomized, open-label, prospective study conducted in 20 patients, and of 3 expanded access programs, which enrolled 9 patients. All studies were performed at a single center (San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) in Milan, Italy).
Of the 29 total patients (16 LI and 13 EJ), 20 were pre-symptomatic and 9 early symptomatic.
The co-primary efficacy endpoints of the integrated analysis included:
(a) the total Gross Motor Function Measure (GMFM) scale score at Year 2 after treatment. The pre-specified effect size was a delay in progression of 10% in the total GMFM scale score in treated subjects as compared to a historical control group of untreated MLD patients of the same age enrolled in the natural history (NHx) study conducted by the SR-TIGET center in Milan;
(b) ARSA activity in peripheral blood mononuclear cells (PBMCs) and cerebrospinal fluid (CSF). The pre-specified effect size was a significant [≥ 2 SD, standard deviation] increase of residual ARSA activity measured in the peripheral blood lymphomonocytes (PBMCs) at 2 years as compared to pre-treatment values.
Secondary endpoints included (i) Gross Motor Function Classification (GMFC-MLD) (analysis of disease stages at different ages in treated patients compared to untreated historical control subjects); (ii) brain MRI (total score measured two years after treatment); (iii) neuropsychological tests (assessment of the effect of Libmeldy on patients' cognitive and verbal functions by measuring the intelligence quotient [IQ] and developmental quotient [DQ] through neuropsychological tests performed at 2 years, 2.5 years and 3 years after treatment, respectively); (iv) *Nerve Conduction Velocity* (NCV); (v) ARSA activity in the CSF; (vi) neurological evaluations; and (vii) survival.

All LI subjects in the study and some EJ subjects were identified after a sibling had developed symptoms with subsequent diagnosis of MLD, leading the other family members to perform genetic testing for the diagnosis.
A study with the cryo-preserved formulation of Libmeldy (Study 205756) was also performed, which has enrolled 9 patients.

Efficacy - motor skills

Subjects with early-onset MLD treated with Libmeldy in the pre-symptomatic phase showed normal motor development and a stabilisation or slowing of the progression of motor dysfunction, as measured by the *Gross Motor Function Measure* (GMFM) scale, a scale that measures the ability to ambulate independently.
Using an age-adjusted ANCOVA model in GMFM evaluation and treatment, the mean difference between treated pre-symptomatic LI patients and untreated LI patients of the same age in the NHx study was 71.0 % after 2 years and 79.8 % after 3 years. Similarly, the mean difference between treated pre-symptomatic EJ patients and untreated EJ patients of the same age was 52.4 % after 2 years and 74.9 % after 3 years. These treatment differences were statistically significant ($p \leq 0.008$) in favor of Libmeldy. Although not statistically significant, a clear difference in total GMFM score was also observed between treated and untreated early symptomatic EJ patients of the same age (28.7 % after 2 years; p value = 0.350 and 43.9 % after 3 years; p value = 0.054).
Overall, Libmeldy showed remarkable efficacy in pre-symptomatic LI and EJ subjects also in cognitive performance (based on IQ measurement), which was within the normal ranges of healthy subjects for the vast majority of treated subjects in the pre-symptomatic phase throughout the duration of follow-up.

Efficacy - Enzyme activity

In all Libmeldy-treated patients, restoration of ARSA activity in the hematopoietic system was observed through progressive reconstitution of enzyme levels in peripheral blood mononuclear cells (PBMCs), which reached values within the physiological reference range within 3 months of treatment and remained stable within - or above - the physiological range throughout the duration of follow-up.
In particular, a statistically significant increase in ARSA activity was observed in PBMCs 2 years after treatment compared to pre-treatment baseline in both pre-symptomatic (20.0-fold increase; p value < 0.001) and early symptomatic patients (4.2-fold increase; p value = 0.004).
Regarding the secondary outcomes of the Registration Study 201222, the results for GMFC-MLD, VCN, neuropsychological tests, and parent-reported outcomes were consistent with the effects seen on GMFM.

Safety and tolerability

With regard to treatment safety, although the number of patients in the Libmeldy safety dataset was limited, the safety profile was in line with that of myeloablative conditioning regimens used in stem cell transplantation.
The only adverse event specifically attributed to Libmeldy was the development of anti-ARSA antibodies, which occurred infrequently (in only 5 patients), with no significant impact either in terms of patient safety or in terms of reduced clinical efficacy of the product.
The median duration of follow-up in the pivotal study at the date of submission of the dossier was 5.4 years (range: 2.98 to 7.51 years).
Additional data will be collected post-marketing to confirm efficacy and safety up to 15 years of follow-up.

Mortality

For *Late Infantile* patients, at the last visit reported in the study report, the median follow-up for all treated subjects was 5.4 years (range 2.98-7.51 years) and all subjects were alive (100% overall survival). Therefore no median survival time is available.
For *Early Juvenile* patients, 2/11 (18%) Libmeldy-treated subjects died of disease progression and 3 of 12 (21%) in the TIGET NHx Study died at the time of interim analysis. However, none of the *pre-symptomatic EJ* treated subjects died. A difference with *borderline* statistical significance was observed for overall survival of LI subjects compared with NHx controls (unstratified Log-rank p value = 0.062) and EJ subjects (estimated HR 1.85; Log-rank p value = 0.537). The effect on survival is substantial, particularly in pre-symptomatic patients.

Recognition of innovativeness

On the basis of the criteria for the classification of innovative drugs and innovative oncology drugs identified in AIFA Determination No. 1535/2017 pursuant to Article 1, paragraph 402 of Law No. 232 of 11 December 2016, the therapeutic innovativeness of the drug is recognized for the reimbursed indication with an expected validity of 36 months, from 08/04/2022 to 07/04/2025. For further details, please refer to the innovativeness assessment report published on AIFA's website at: https://www.aifa.gov.it/en/farmaci-innovativi).

Table 2

MEDICINAL PRODUCT	ACTIVE SUBSTANCE	NHS INDICATIONS	THERAPEUTIC INNOVATION	G.U. DATE (EFFICACY)	EXPIRATION DATE
Libmeldy®	Antidarsagene autotemcel	MLD	Innovative	08/04/2022	07/04/2025

Cost of treatment

Table 3

Active substance	atidarsagene autotemcel
ATC V level	A16AB21
Specialities	Libmeldy®
Pack	Libmeldy 2-10 x 10^6 cells/mL dispersion for infusion
Public price (excluding VAT)	€ 4,744,900
Ex-factory price before statutory reductions, excluding VAT	€ 2,875,000
Recommended dose in SmPC	1 infusion
Number of packs for the duration of the treatment	The dose to be administered and the total number of bags to be used are defined according to the total number of CD34+ cells supplied, also taking into account the weight of the patient at the time of treatment
Ex-factory cost gross of statutory reductions for the duration of the treatment per patient paid by the NHS, excluding VAT	€ 2,875.000
Negotiated conditions	Compulsory discount on the ex-factory price to be granted to public health facilities, including private health facilities accredited with the National Health Service, in accordance with the terms laid down in the negotiation agreement.

Economic Evaluations

The company presented a cost-effectiveness analysis in which Libmeldy® therapy was compared to best supportive care (BSC). Table 6 shows the main features of the pharmacoeconomic model presented by the company.

Table 4

Population under analysis	Children with Late Infantile (LI) or Early Juvenile (EJ) forms, without clinical manifestations of the disease, and children with the early juvenile form, who still have the ability to walk independently (GMFC ≤ 1) and before the onset of cognitive decline (IQ ≥ 85)
Perspective of the analysis	National Health Service
Comparators	BSC
Time horizon	Lifetime
Discount rate	3% per annum for costs and benefits
Health Outcome	QALYs (Quality adjusted life years) and life years gained

Model type	Partitioned survival Markov model, with one-month cycles
Source of efficacy data	Clinical Study 20122 (NCT01560182) Expanded Access Programmes
Utility data sources	Utility values were collected by Orchard Therapeutics in a preference study conducted in the UK - Utility scores of the general population were obtained from the EQ-5D population index values (Time Trade Off – TTO value set, specific to Italy). Due to the lack of EQ-5D index values for the general population under the age of 18, the EQ-5D index values for the population aged between 18 and 24 were used.
Cost data sources	DRG fee schedule, Specialist and outpatient services fee schedule, analysis conducted by San Raffaele Hospital
Type of costs included	Cost items include: drugs, diagnostic tests, specialist medical examinations, hospital admissions, visits to general practitioners and emergency rooms, medical supplies and social services. Libmeldy® administration costs include pre-transplant screening to confirm patient's eligibility, intital admissions to perform baseline assessments and haematopoietic stem cell harvesting of patients, myeloablative conditioning of patients, transplantation of genetically corrected stem cells and follow-up monitoring/hospitalisation
Sensitivity analysis	Univariate, probabilistic and scenario analysis

Assessment of the quality of the pharmacoeconomic analysis

The quality of the cost-effectiveness analysis was assessed using a readjusted checklist from that of Philips et al. 2004. Out of a total of 31 criteria, 23 were considered fully met, 4 partially met, and 1 criterion was found to be not applicable.

Review of the cost-effectiveness analysis by the Office of Economic Evaluations (UVE)

In light of the model review process provided by the company, the main assumptions of the economic evaluation presented are listed below:

Table 5

Recruitment	Sources and justifications	Managing uncertainty
The effect of Libmeldy® therapy will last a lifetime in pre-symptomatic *full responder* LI and EJ patients because it is able to repopulate the brain with stem cells containing corrected copies of the ARSA gene, capable of self-replicating and synthesizing the missing arylsulphatase A enzyme, thus preventing the onset of clinical manifestations of the disease	Conceptualization of the model by a panel of experienced MLD clinicians	Scenario analysis see Table 7 p.1 and p. 5

Libmeldy® will interrupt disease progression to GMFC-MLD 2 in pre-symptomatic LI and EJ patients with partial response and GMFC 3 for patients with early symptomatic EJ partial response for life because some patients may experience stabilisation of disease progression after irreversible damage has occurred. Once gene corrected cell engraftment and improved ARSA enzyme levels have occurred, further disease progression can be prevented. The cells grafted into these patients are able to release ARSA enzymes at a sufficient rate and concentration to prevent further cellular damage	Conceptualization of the model by a panel of experienced MLD clinicians	Scenario analysis see Table 7 p. 2
Libmeldy® requires some time for the effects to become apparent for symptomatic EJ patients, given the time required for cells with the correct ARSA gene to engraft in the brain and for the synthesis of the enzyme arylsulphatase A to take place. Pre-symptomatic LI and EJ patients will be treated before the onset of symptoms, so that engraftment occurs before the onset of symptoms	Opinion of a panel of experienced MLD clinicians	Scenario analysis see Table 7 p. 3
Libmeldy® will slow down the progression of the disease in LI and EJ partial responder patients rather than halt it because some irreversible damage may occur in these patients before the cells with the correct ARSA gene engraft and the levels of the enzyme arylsulphatase A increase, leading to some degree of disease progression. However, progression would occur at a slower rate than in untreated patients.	Conceptualization of the model by a panel of experienced MLDclinicians	Scenario analysis see Table 7 p. 4

Changes made to the pharmacoeconomic model submitted by the company

Based on the model submitted by the company in open format, the following changes were made:

1. The price of Libmeldy® was imputed net of statutory reductions and net of the mandatory discount on the ex-factory price, applied according to the terms defined in the negotiation agreement, based on the number of patients expected to be treated.
2. A combined cohort of patients was considered (pre-symptomatic LI 62.5% ; pre-symptomatic EJ 18.75% ; early symptomatic EJ 18.75%).

Results of pharmacoeconomic evaluation after the revision

Taking into account the revision of the cost-effectiveness model and adopting the most conservative assumptions from the health care perspective, i.e., the most pessimistic assumptions with respect to the efficacy of the new therapy, the results of the analysis in terms of incremental cost-effectiveness (ICER) are as follows:

Table 6

Expected discounted values	BSC [A]	atidarsagene autotemcel [B]	Difference [Δ=B-A]	ICER
Total costs	[redacted]	[redacted]		
Years of life	9.5	27.6	18.1	**€ 117,443**
QALYs	-3.7	19.6	23.3	**€ 91,465**

Scenario analysis by the Office of Economic Evaluations (UVE)

A scenario analysis was performed in order to recalculate the ICER of atidarsagene autotemcel vs. BSC from the perspective of the NHS, varying certain parameters and assumptions of the cost-effectiveness model provided by the company. Table 9 presents the results of the scenario analysis. In almost all simulations performed, the ICER is around the value of the base case, with the exception of two scenarios with a maximum ICER of € 236,526/QALY and a minimum ICER of € 56,139 per QALY, respectively.

Table 7

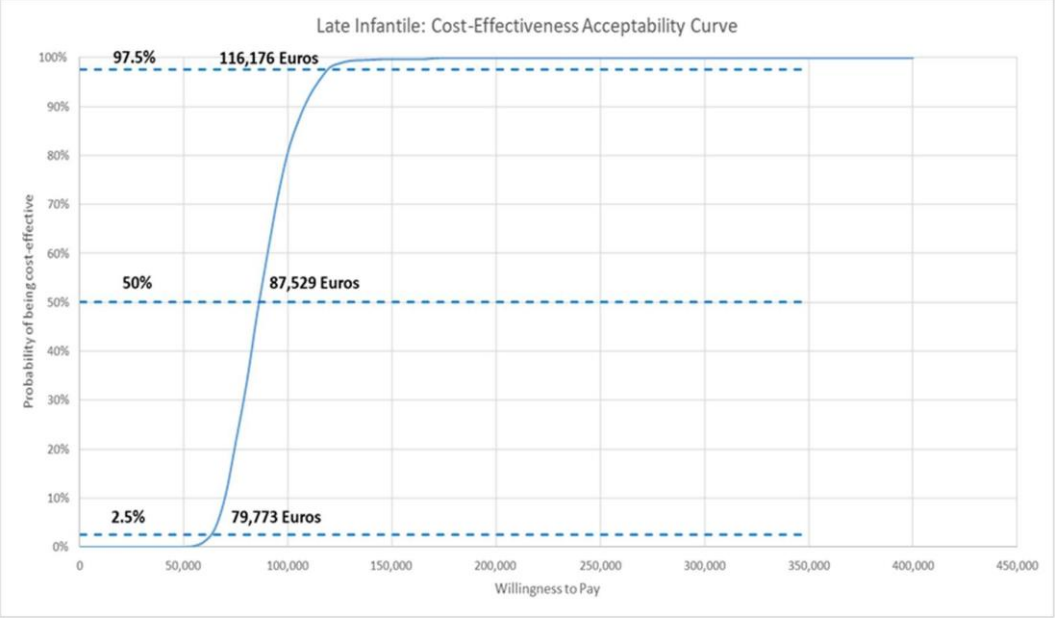
	Base Case Assumption	Input parameter UVE	ICER (QALY)
1	The effect of Libmeldy® therapy will last lifetime in pre-symptomatic *full responder* LI and EJ patients	**Late Infantile** Time to Progression (months) Applied to GMFC-MLD 0 patients = 120 months	**€ 122,173**
		Pre-symp. Early Juvenile Time to Progression (months) Applied to GMFC-MLD 0 patients = 120 months	**€ 137,713**
2	Libmeldy® will interrupt disease progression to GMFC-MLD 2 in pre-symptomatic LI and EJ patients with partial response and GMFC 3 for patients with early symptomatic EJ partial response for life (100 years)	**Late Infantile**: Duration of stabilisation (years)=20	**€ 108,822**
		Pre-symp. Early Juvenile: Duration of stabilisation (years)=20	**€ 94,945**
		Symp. Early Juvenile: Duration of stabilisation (years)=20	**€ 97,099**
3	Libmeldy® requires some time for the effects to become apparent for symptomatic EJ patients (6 months)	**Symp. Early Juvenile**: Time to OTL-200 engraftment (months): 12 months	**€ 92,278**
4	Libmeldy® slows disease progression in LI and EJ *partial responder* patients	Progression modifier : 2 LI Pre-Symp Symp	 **€ 95,801** **€ 92,382** **€ 92,270**
		Progression modifier: 5 LI Pre-Symp Symp	 **€ 95,342** **€ 91,521** **€ 90,404**
5	Time horizon of Economic Model (Lifetime)	Time horizon = 10 years	**€ 236,526**
6	Natural history data source:	Elgun, 2019	**€ 93,337**
		Kehrer, 2011	**€ 93,274**

7	A higher number of patients are treated as a result of screening programmes	Negotiated Agreement	**€ 56,139**
8	Proportion of patients in the combined population: pre-symptomatic LI 62.5%: pre-symptomatic EJ 18.75%; early symptomatic EJ 18.75%.	Late Infantile (Pre-Symptomatic) = 2.5% Early Juvenile (Pre-Symptomatic) = 2.5% Early Juvenile (Symptomatic) = 95%	**€ 156,278**
		Late Infantile (Pre-Symptomatic) = 70% Early Juvenile (Pre-Symptomatic) = 15% Early Juvenile (Symptomatic) = 15%	**€ 90,267**
		Late Infantile (Pre-Symptomatic) = 33.33% Early Juvenile (Pre-Symptomatic) = 33.33% Early Juvenile (Symptomatic) = 33.33%	**€ 96,374**

Cost-effectiveness acceptability curve (CEAC)

The uncertainty of the incremental cost-effectiveness results is represented by means of the acceptability curve, through which the probability that the treatment is cost-effective compared to the considered therapeutic alternative is illustrated at different levels of identified threshold values.

Figure 1. Acceptability curve of antidarsagene autotemcel vs. BSC



Price and reimbursability regulatory process

Table 8

Stages of the regulatory process	Date/ Reference period
Submission of the application for reimbursement and price	10 December 2020
Opinion of the HTA Secretariat	16 February 2021
Opinion of the CTS	17, 18, 19 March 2021 06 -09, 12 April 2021

Approval of the monitoring register forms https://www.aifa.gov.it/en/registri-e-piani-terapeutici1	05, 06, 07 May 2021
Recognition of therapeutic innovativeness https://www.aifa.gov.it/en/farmaci-innovativi	06-09, 12 April 2021
Opinion of the CPR	15, 16 and 17 December 2021
Duration of the negotiation agreement	24 months
Resolution of the Board of Directors	24 February 2022
Publication in the Official Journal	7 April 2022
First approved version of the technical-scientific report	14 April 2022
Final approved version of the technical-scientific report	09 May 2022

Monitoring logs

In this section, in-depth analyses of the data collected through the monitoring registry of Libmeldy® will be published when they are requested by AIFA Commissions, or foreseen as a result of price and/or reimbursability renegotiation procedures.

Comments from the company holding the AIC for Libmeldy®

In view of the extreme rarity of the disease and the known epidemiological data, the base case reflects the number of patients eligible for treatment during the reporting period. Should different epidemiological data emerge - for example, as a result of the activation of screening campaigns - this report will be updated accordingly.