Cost-effectiveness of Atidarsagene Autotemcel (Arsa-cel) gene therapy for treating Metachromatic Leukodystrophy (MLD) in Ireland, Belgium, and the Netherlands as a part of Beneluxa Initiative

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INTRODUCTION

- MLD is an ultra-rare and fatal inherited neurodegenerative disease caused by a deficiency of the ARSA enzyme, resulting in a build-up of toxic sulfatides. This leads to rapid motor and cognitive decline and premature death, particularly in early-onset MLD (late infantile [LI] and early juvenile [EJ]).
- Previously, the standard of care for early-onset MLD consisted of the best supportive care (BSC) in Ireland, Belgium, and the Netherlands.
- However, arsa-cel, an autologous CD34+ haematopoietic stem cell (HSC) gene therapy now offers an effective treatment option. HSCs are collected from mobilized peripheral blood and transduced with a lentiviral vector carrying the human ARSA cDNA, enabling the cells and their progeny to stably express the ARSA enzyme.
- Long-term clinical results showed arsa-cel provided significant benefits in pre-symptomatic (PS) LI and both PS and early-symptomatic (ES) EJ patients, preserving cognitive function, motor development, and slowing brain demyelination in most patients compared to best supportive care, which often leads to a vegetative state or mortality. [1,2]
- The Beneluxa Initiative enables joint assessment and negotiations of access to innovative medicines for Belgium, the Netherlands, Luxemburg, Austria, and Ireland. Arsa-cel underwent this process between 2021 and 2022 and was assessed by Belgium, the Netherlands, and Ireland.

Objective: **This study aimed to present the cost-effectiveness results of arsa-cel compared to BSC for patients with early-onset MLD in Belgium, the Netherlands, and Ireland.**

METHODS

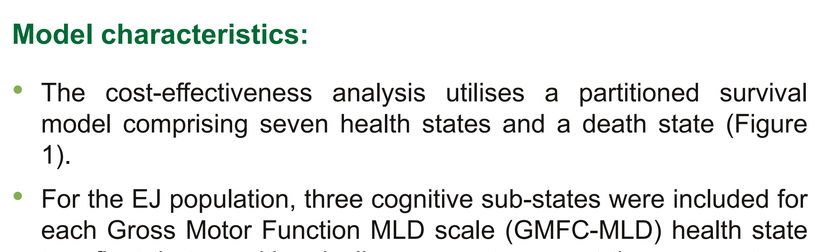
Patient population:

- The patient population considered in this model comprised PS-LI, PS-EJ, and ES-EJ MLD subgroups vs. best supportive care.

Model characteristics:

- The cost-effectiveness analysis utilises a partitioned survival model comprising seven health states and a death state (Figure 1).
- For the EJ population, three cognitive sub-states were included for each Gross Motor Function MLD scale (GMFC-MLD) health state to reflect that cognitive decline may not occur at the same rate as motor function loss in EJ MLD. Importantly, including cognitive sub-states enables the capture of the impact cognitive ability has explicitly on a patient's health-related quality of life (HRQoL). [2,3]
- Since there are no other effective treatments for early-onset MLD besides arsa-cel, established clinical management consisting of BSC was used as the comparator for Belgium, the Netherlands, and Ireland.
- A monthly model cycle was chosen to capture the changes in gross motor function and cognitive decline seen in the rapidly deteriorating phase of the disease in patients receiving BSC.
- The time horizon for the model was a lifetime horizon.
- The analysis was conducted from a healthcare payer perspective for Belgium and Ireland.
- The model adopted a societal perspective for the Netherlands:
  - Societal perspective included lost family income and productivity gains using the friction cost method. Out of pocket costs were excluded.

FIGURE 1. LI and EJ MLD Model structure



Model inputs:

- Clinical trial data, published literature, national registry data, and expert opinions informed transition probabilities for both arsa-cel and best supportive care.
- Discount rates and costs specific to each country were applied in the analysis.
- Table 1 details the cost input data by country and Table 2 outlines the key assumptions applied in the model.
- Utilities were derived from a study using vignette and time trade-off methods and subsequently rescaled using the EQ-5D to align with national tariff standards and reflect each country's preferences (Table 3).

TABLE 1. Cost data used in the economic model

Total costs	Belgium	Netherlands	Ireland
Total drug costs	€3,047,500	€2,875,000	€2,716,875
Additional costs per patient (administration costs)	€104,770	€103,882	€106,202
Total monthly MLD-related medical costs (0-18 years; MLD 1 till MLD 6 in hospital)	€258 – €14,090	€960 – €17,099	€815 – €47,305
Total monthly MLD-related medical costs (19+ years; MLD 1 till MLD 6 in hospital)	€649 – €14,049	€890 – €17,057	€608 – €47,214

TABLE 2. Key assumptions used in the model

Assumption:	Source:
Percentage of phenotype in combined cohort: Belgium: PS-LI 32.4%, PS-EJ 33.8%, ES-EJ 33.8% Netherlands: PS-LI 20.3%, PS-EJ 35.4%, ES-EJ 44.3% Ireland: PS-LI 65.9%, PS-EJ 19.2%, ES-EJ 14.9%	• The percentage distribution of patients across MLD phenotype subgroups is based on country specific epidemiological data and clinical expert opinion.[3,4,5]
Classification of response into three groups: "full responder", "stable partial responder" and "unstable partial responder"	• The response classification was introduced based on all outcomes reported in the arsa-cel clinical development program.[3]
The 'progression modifier' parameter simulates the slowed disease progression in unstable partial responders compared to untreated patients. It was calculated from the ratio between the average time to progression in natural history patients and that reported for arsa-cel patients.	• These estimates are based on clinical trial data, the OSR-TIGET natural history study, and confirmation from MLD clinical experts.[1,2,3,7]
To account for cognitive decline that can occur before or after motor function loss, cognitive sub-states were developed for each GMFC-MLD stage: normal cognition (DQ >70), moderately impaired cognition (70 ≤ DQ ≥ 55), and severely impaired cognition (DQ <55).	• These sub-states were based on published literature and clinical expert opinion from OSR-TIGET investigators with experience in managing NHx patient cohorts. [2,3]
Increased mortality risk per GMFC state capture the increasing probability of dying of non-MLD causes as a result of being affected by MLD: GMFC-MLD 1: 1.4 GMFC-MLD 2: 1.4 GMFC-MLD 3: 2.0 GMFC-MLD 4: 2.0 GMFC-MLD 5: 9.92	• These sub-states were based on published literature and clinical expert opinion [3,8]

TABLE 3. Utility values by GMFC-MLD health state for Belgium and the Netherlands [3,6]

Health states	Late Infantile	Early juvenile		
		Normal cognitive function	Cognitive impairment	Severe cognitive impairment
GMFC-MLD 0	Age adjusted general population		0.73	0.53
GMFC-MLD 1	0.67	0.88	0.67	0.47
GMFC-MLD 2	0.58	0.80	0.58	0.38
GMFC-MLD 3	0.25	0.46	0.24	0.04
GMFC-MLD 4	-0.01	0.20	-0.01	-0.22
GMFC-MLD 5	-0.04	0.18	-0.04	-0.24
GMFC-MLD 6	-0.08	0.14	-0.08	-0.28

RESULTS

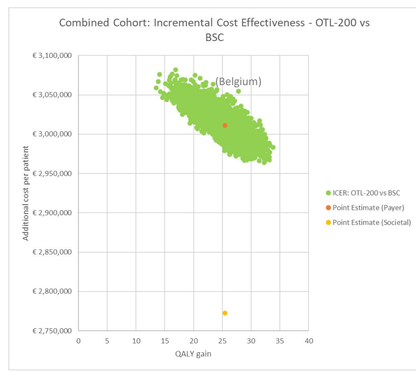
- The deterministic base case analysis results show that arsa-cel was associated with higher costs and offered significant gains in life years and in QALYs to patients compared to BSC over the lifetime model horizon (see Table 4).
- The same pattern of results was seen across all country settings and analyses, and across the individual subgroups and combined cohort.
- The scenario analysis including a societal perspective, newborn screening, and caregiver disutility yielded the following ICERs:
  - €41,965 for Belgium
  - €38,803 for The Netherlands
  - €45,772 for Ireland

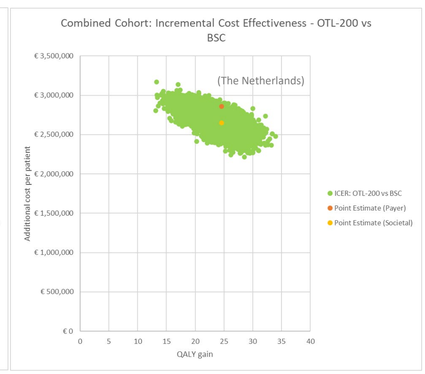
TABLE 4. Base case results over lifetime horizon

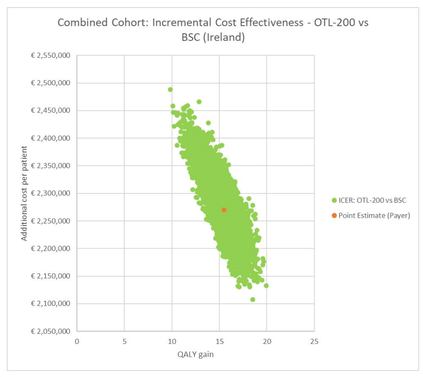
Patient population	Incremental costs	Incremental QALYs	ICER (€/QALY)
Combined cohort			
Belgium	€3,011,290	25.47	€118,234
Netherlands (vs BSC)	€2,649,787	24.59	€107,777
Ireland	€2,269,761	15.48	€146,642
Scenario 2: Societal perspective, newborn screening, and caregiver disutility			
Belgium	€1,619,604	38.59	€41,965
Netherlands	€1,529,495	39.42	€38,803
Ireland	€968,950	21.17	€45,772

- The proportional QALY shortfall represents the ratio of health lost due to the disease (absolute QALY shortfall) to the total potential health without the disease. It is calculated by dividing the absolute QALY shortfall by the potential QALYs for individuals without MLD. The proportional QALY shortfall for MLD **is 0.999**, with 1.0 being the highest (poorest) possible value. [4, 5, 9, 10]
- Scenario analyses examining the impact of different parameter values showed that the discount rate, the time horizon, and the assumptions around the duration of the treatment effect had the most impact on the ICERs.Varying the percentage of responders in the PS EJ subgroup had the most effect on the ICER in Belgium and The Netherlands.
- The PSA results suggest that the ICER for arsa-cel vs. BSC is relatively stable across different scenarios. This indicates a robust model where the results are not highly sensitive to parameter changes (Figure 2). In Belgium, the societal perspective lowers the ICER compared to the payer perspective, while the payer perspective only marginally increases the ICER in The Netherlands.

FIGURE 2. Cost-effectiveness planes







INSIGHTS

- Current health economic guidelines that apply to a standard pharmaceutical product may underestimate the potential benefit of arsa-cel, as this is a one-off treatment for an ultra-rare condition.
- QALY shortfall data highlight the extremely high burden of disease faced by MLD patients. The standard WTP thresholds associated with these guidelines typically do not take this into account.
- When considering the cost-effectiveness thresholds maintained in the three Beneluxa countries, it's reassuring to see that arsa-cel aligns with the ICERs for other ultra-rare therapies that have been successfully reimbursed.
- The cost-effectiveness of arsa-cel improves if newborn screening is included in the analysis.

CONCLUSION

- **Arsa-cel yields lifelong quality of life improvement.**
- **Different modelling requirements and inputs among the three included countries cause variable cost-effectiveness. Broader considerations significantly reduce all ICERs in the adopted scenario analyses, underscoring arsa-cel's value.**

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