

The cost-effectiveness of atidarsagene autotemcel for the treatment of Metachromatic Leukodystrophy (MLD) in Italy

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BACKGROUND & OBJECTIVES

Background

- MLD is an ultra-rare and fatal inherited neurodegenerative disease, leading to a deficiency of the ARSA enzyme resulting in a build-up of toxic sulphatides. This leads to rapid motor and cognitive decline and premature death, particularly in early-onset MLD (late infantile and early juvenile). The burden of disease of early onset MLD is rated amongst the highest of all debilitating genetic conditions.
- There are three forms of MLD based on the age of symptom onset: late infantile (LI < 30 months); juvenile (>30 months to 16 years), which is further subdivided into early juvenile (EJ >30 months to <7 years) and late juvenile (LJ >7 to 16 years), and finally adult (> 17 years).
- The prognosis for patients without treatment is very poor, with the median time from symptom onset to loss of all voluntary movement with only head control remaining reported as 1.12 years for LI MLD and 2.7 years for EJ MLD.¹
- Atidarsagene autotemcel (arsa-cel) is an autologous CD34+ haematopoietic stem and progenitor cell (HSPC) gene therapy. HSPCs are collected from patient bone marrow (BM) harvest or from mobilised peripheral blood (mPB) and transduced ex vivo 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.
- Arsa-cel is approved in Europe for the treatment of MLD characterized by biallelic mutations in the 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

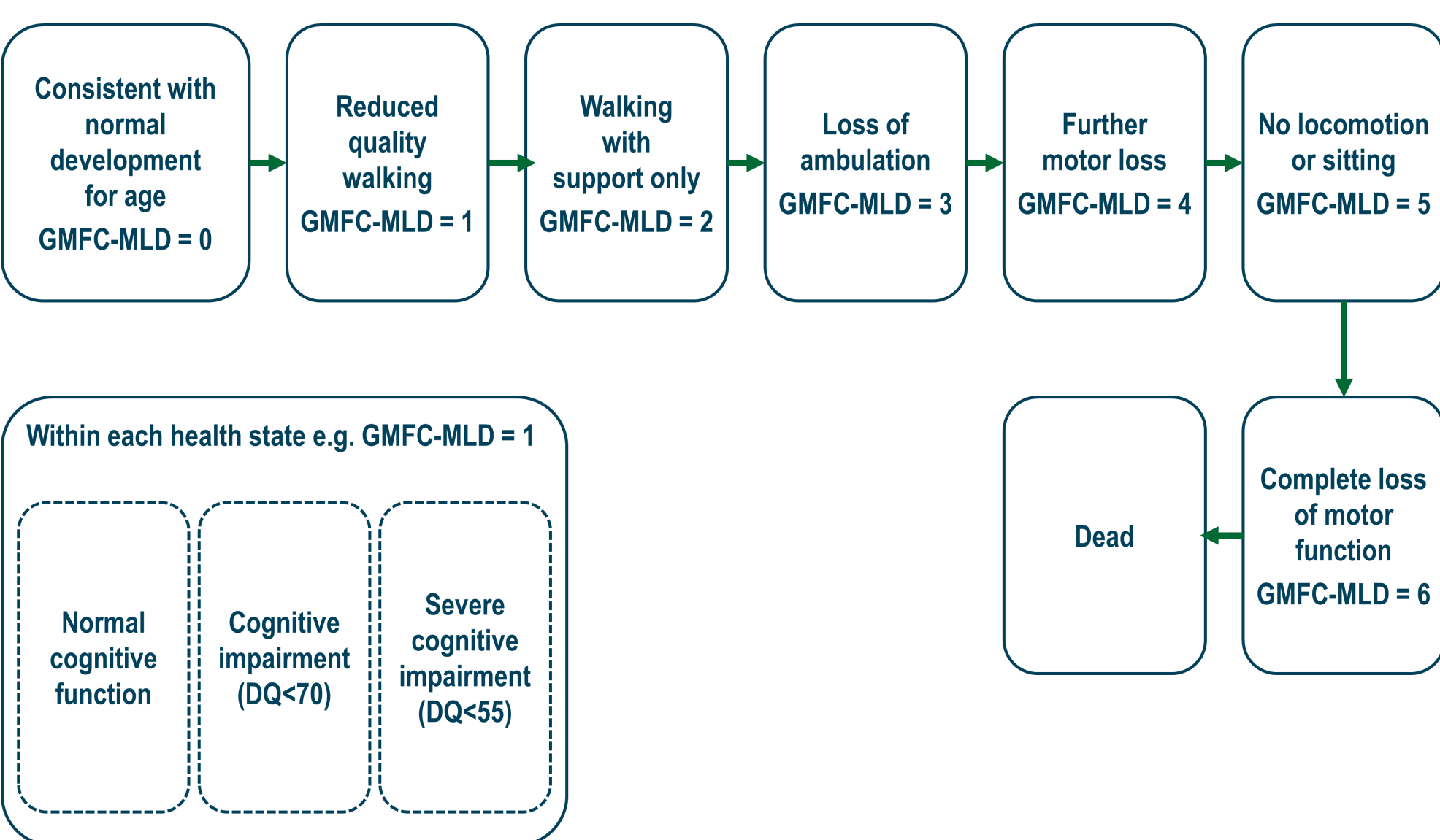
Objective

- The aim of this study was to determine the long-term cost-effectiveness of arsa-cel compared to best supportive care for the treatment of MLD, using the Italian NHS as the base setting.

METHODS: FRAMEWORK

- A de novo cost-effectiveness model was developed based on an 8-state partitioned survival framework and Markov structure. This approach has been used for a number of health technology assessments and is deemed to be a reliable method for modelling diseases with motor function progression involvement.
- For the LI MLD population there were eight possible health states based on the Gross Motor Function MLD scale (GMFC-MLD). However, for the EJ population, three cognitive sub-states (normal/mild, moderate and severe) were included for each GMFC health state to reflect the fact that cognitive decline may not occur at the same rate as motor function loss in EJ MLD.

Figure 1: Model structure



METHODS: HEALTH STATE MODEL TRANSITIONS

Best supportive care

- Transitions between GMFC-MLD states were based on the OSR-TIGET natural history cohort (matched for age and variant), published literature^{1,3} and MLD expert clinical opinion.

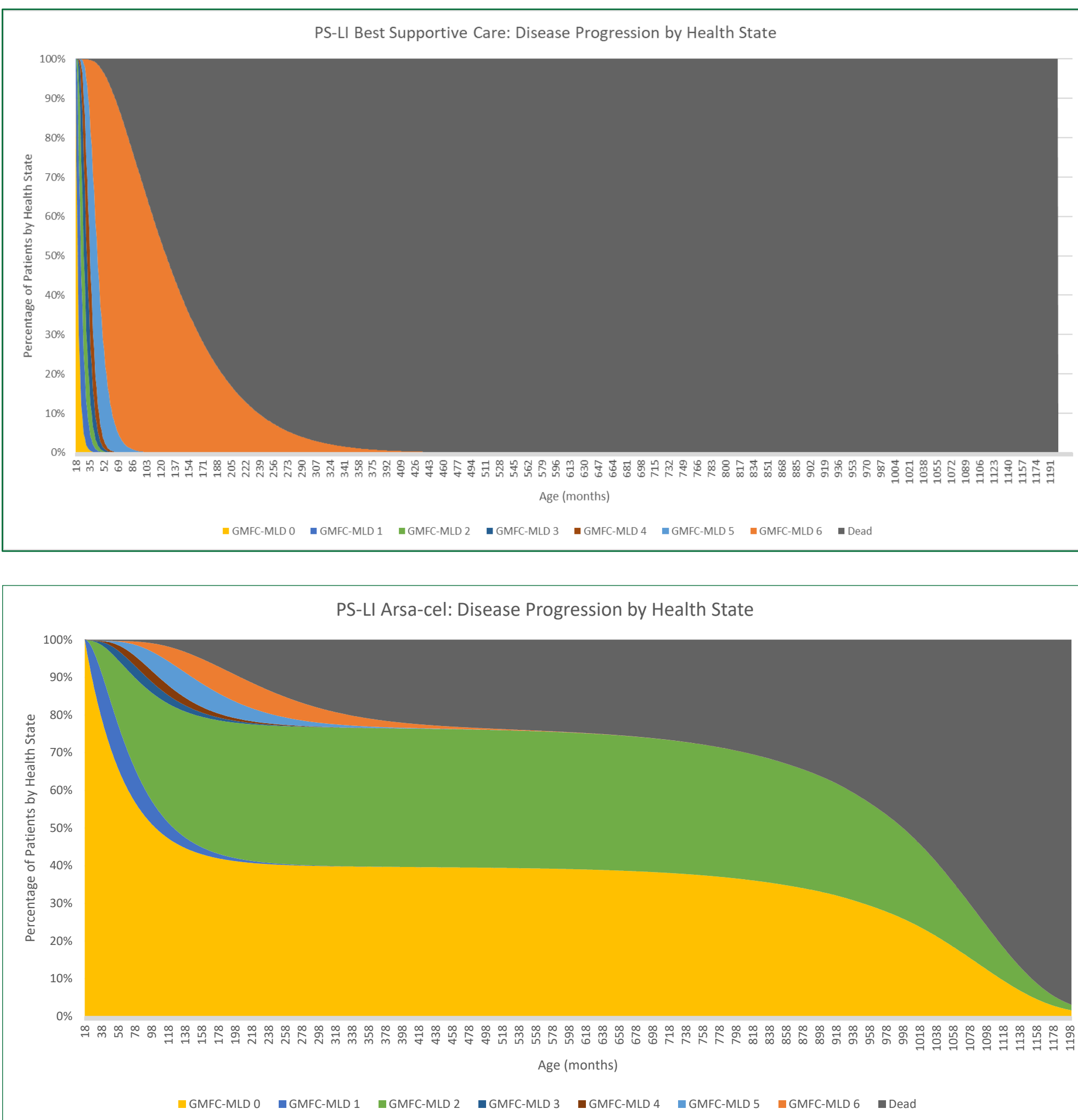
Arsa-cel

- Full responders:** Assumes patients never develop signs and symptoms of disease and are in GMFC 0 for lifetime horizon leading normal health lives in line with the general population.
- Stable partial responders:** Some patients may have an initial decline in clinical outcomes post gene therapy, for up to 2 years, but then once accumulated sulphatides have been broken down, their disease stabilises and remains stable across multiple outcome measures.

Arsa-cel transitions (cont.)

- Stable partial responders (cont.):** Alternatively, a patient could be classified as a partial responder if the patient had early symptoms at time of treatment and remained at that state without any disease progression for the duration of follow-up. The term “stable partial responder” is simply nomenclature to differentiate between the people with no signs of the disease (full responders), and patients who have had some disease progression prior to stabilisation.
- Unstable partial responders:** Assumes progression through GMFC-MLD states at a slower rate than best supportive care - calculated as a ratio of the difference in time to transition from each GMFC health state to the next from the arsa-cel clinical trials and the OSR TIGET natural history data for only those LI and EJ patients that received treatment but continued to progress, as well as clinical expert opinion.

Figure 2: Example of GMFC-MLD output for late infantile (LI) MLD by treatment



- The time horizon for the model was a lifetime horizon with outcomes measured as Quality Adjusted Life Years (QALYs).

METHODS: HEALTH VALUATION

Health states

- There were no health-related quality of life data collected in the clinical trials of arsa-cel.
- A vignette study was conducted in 201 members of the UK general public to elicit utility values for all 24 health states in the economic model.⁴
- For each of the 24 health states (6 infantile and 18 juvenile), comprehensive descriptions or vignettes of each health state were developed using the literature and qualitative clinician interviews.
- The valuation of each of the health states was then elicited during face-to-face interviews using the time trade off (TTO) method.
- Health states worse than death were permitted to adequately capture the extremely high burden of disease but were constrained by the worst possible health state from the Italian value set of the EQ-5D (-0.571)⁵ to allow for comparison with other health technology assessments.
- Utility values for each of the health states are presented in Table 1.

Table 1: Utility values for each GMFC health state used in the cost-effectiveness analysis

	Late Infantile	Early Juvenile		
		Normal cognitive function	Moderate cognitive impairment	Severe cognitive impairment
GMFC 0	Age adjusted general population		0.75	0.51
GMFC 1	0.71	0.9	0.65	0.42
GMFC 2	0.44	0.82	0.57	0.34
GMFC 3	-0.07	0.43	0.18	-0.05
GMFC 4	-0.22	0.12	-0.13	-0.36
GMFC 5	-0.35	0.05	-0.2	-0.43
GMFC 6	-0.47	0.01	-0.26	-0.49

Disclaimers/Author Disclosures

- Atidarsagene autotemcel (arsa-cel) was licensed to GlaxoSmithKline (GSK) in 2014, and subsequently transferred in 2018 to Orchard Therapeutics (OTL).
- Libmeldy (atidarsagene autotemcel) received approval from the European Commission on 17 December 2020, and in the UK on 1 February 2021. Libmeldy SmPC: https://www.ema.europa.eu/en/documents/product-information/libmeldy-smpc-product-information_en.pdf. Libmeldy is approved in European Union, UK, Iceland, Liechtenstein and Norway. Atidarsagene autotemcel is an investigational therapy in the US.
- AO, SB, and FP are employees of Orchard Therapeutics and receive equity-based compensation from the company.
- FF, VC, and AA are investigators of clinical trials for MLD sponsored by Orchard Therapeutics, the license holder of arsa-cel. FF and VC have acted as ad-hoc consultants for an Orchard Therapeutics advisory board and have received reimbursement for travel costs.
- MG has left San Raffaele Hospital and is now an employee at Evotec.
- RD, JJ, and BM are employees of Precision Health Economics & Outcomes Research. Precision HEOR contributed to the design of the model number funded by Orchard Therapeutics.
- SC was paid a consulting fee by Orchard Therapeutics to carry out work on this study.

METHODS: HEALTH VALUATION (CONT.)

Caregiver disutilities

- There is a considerable physical and psychological burden placed on caregivers of children with MLD. A disutility has been applied to patients from GMFC 2 and above and is based on the mean index utility value (0.773) for all respondents, including European respondents, completing the EQ-5D in the MLD Caregiver Survey subtracted from UK General Population Utility at 40 years of age (0.882). This disutility was assumed to last for 30 years.

Adverse event disutilities

- Adverse events associated with busulfan conditioning were temporary and most resolved spontaneously, however a short-term disutility associated with complications due to conditioning was also included in the cost-effectiveness analysis.

METHODS: COSTS

Healthcare resource use

- A structured discussion involving international and Italian MLD clinical experts was used to estimate frequency, duration, and proportion of health care resource use for MLD patients, including medical visits (e.g., paediatrician, physiotherapist), equipment use (e.g., enteral feeding pump, aspirator) social care use and medication (e.g., anti-spasmodic and anti-epileptics drugs) for each GMFC-MLD state.

Treatment related and health state costs

- Treatment costs included arsa-cel, leukapheresis (cell harvest), conditioning, administration and hospitalization, as well as follow-up transplant costs.
- Costs were from a variety of sources including hospital Diagnostic-related-groups (DRGs) and outpatient Tariffs of the Lombardy Region, Orthopedic Aids tariffs of the Lazio Region, Federfarma database (medicines).

RESULTS: COST-EFFECTIVENESS RESULTS

- The incremental cost-effectiveness ratios (ICERs) were calculated for the individual variants (pre-symptomatic LI, pre-symptomatic EJ and early symptomatic EJ patients) and combined population (i.e., a weighted average of the individual variants in Italy) for arsa-cel vs BSC using a differential discount rate of 3.0% for costs and benefits.

Table 1: Incremental cost-effectiveness ratios (ICERs)

	Life years (LY)	QALYs	Incremental LYs	Incremental QALYs	ICER (€/QALY)
PS-LI					
Arsa-cel	27.1	21.1	18.9	24.5	€85,712
BSC	8.2	-3.4			
PS-EJ					
Arsa-cel	29.4	24.0	17.3	27.6	€69,640
BSC	12.1	-3.6			
ES-EJ					
Arsa-cel	27.8	10.1	16.4	14.9	€163,570
BSC	11.4	-4.8			
Pooled					
Arsa-cel	27.6	19.6	18.1	23.3	€91,465
BSC	9.5	-3.7			

RESULTS: SENSITIVITY ANALYSES

- A number of deterministic and probabilistic sensitivity analyses were conducted to explore the robustness of the ICERs.
- Scenario analyses looking at the impact of different parameter values showed that the discount rate, the time horizon and the assumptions around duration of treatment effect had the most impact on the ICERs.

DISCUSSION & CONCLUSION

- This model has used a pragmatic approach for the parameter inputs using natural history and clinical trial data where possible. Where inputs were unable to be sourced from literature or study data (e.g., duration of stabilisation, cognitive distributions by GMFC-MLD stage etc.) clinical expert input was used.
- The results indicate that treatment of early onset MLD with arsa-cel results in substantial health gains with incremental QALYs ranging from 14.9 to 27.6 discounted QALYs depending on the variant treated and ICERs which are comparable to those of other highly specialized technologies that are currently reimbursed by AIFA^{6,7}.
- Limitations of this study include the small sample size of the clinical studies used, which is typical of research with ultra-rare diseases. Another limitation is that follow-up duration is relatively short compared with the lifetime model horizon.

Conclusion

- There are no official cost-effectiveness thresholds in Italy; however, this study shows that arsa-cel is a cost-effective treatment option for MLD based on cost-effectiveness estimates of other drugs for rare diseases that are currently funded by the Italian health system.

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