The cost-effectiveness of atidarsagene autotemcel (arsa-cel) for the treatment of early-onset metachromatic leukodystrophy (MLD) in Spain

Bean K[a], Olaye A[a], Miller B[b], Jensen I[b], Muduma G[a], Giro-Perafita A[c], Pang F[a], Badia X[c]

[a] Orchard Therapeutics, London, UK; [b] Precision AG, Boston, US; [c] Omakase Consulting, Barcelona, Spain.

EE434

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 andcells,ine 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.[1]
- Currently in Spain, best supportive care (BSC) is the only available treatment option and does not change the trajectory of the disease.
- Atidarsagene autotemcel (arsa-cel) is an autologous CD34+ haematopoietic stem and progenitor cell (HSPC) gene therapy. HSPCs are collected from mobilised peripheral blood and transduced *ex vivo* with a lentiviral vector, which inserts one or more copies of the human *ARSA* complementary deoxyribonucleic acid (cDNA) into the cell's genome. These genetically modified cells become capable of expressing the functional ARSA enzyme.[2] After a period of conditioning, the modified cells are returned to the patient and these cells and their progeny continue to stably produce the ARSA enzyme.
- Long-term results from the clinical development programme show that arsa-cel provides significant benefit in pre-symptomatic LI and both pre-symptomatic and early-symptomatic EJ patients treated before entering the rapid phase of disease progression, preserving cognitive function and motor development in most patients.[3] This is in comparison to BSC, whereby patients would otherwise be in a vegetative state requiring constant care or experience mortality in the same timeframe from onset of symptoms.[1,3]

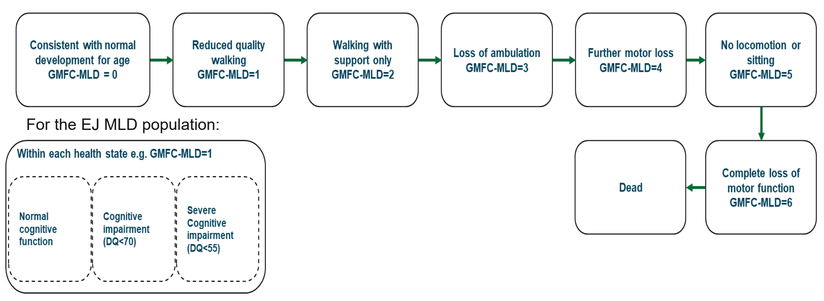
Objective:

The aim of this study was to evaluate the cost effectiveness of arsa-cel compared to best supportive care (BSC) for the treatment of early-onset MLD from the Spanish National Health System (SNS) and societal perspective.

METHODS: MODEL STRUCTURE

- A cost-effectiveness model was developed based on an 8-state partitioned survival framework and Markov structure to model disease progression in MLD grounded by the seven stage Gross Motor Function MLD scale (GMFC-MLD) – Figure 1.
- The GMFC-MLD is a validated measure of motor dysfunction in MLD, which represents all clinically relevant stages from normal (GMFC-MLD 0) to loss of all gross motor function (GMFC-MLD 6).[4]
- For the EJ cohort, cognitive substates were also included to capture the fact that the rate at which cognitive and motor decline occurs varies within this MLD phenotype.

Figure 1: LI and EJ MLD Model structure



- 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 with outcomes measured as Quality Adjusted Life Years (QALYs).
- A discount rate of 3% was applied to both costs and outcomes to adjust for time preference.

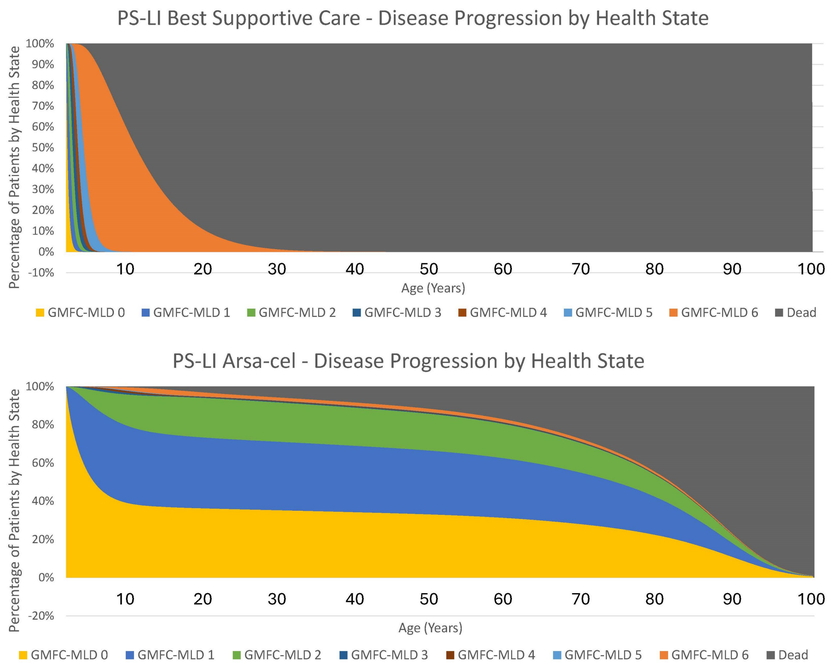
Best supportive care (BSC) transitions:

- Transitions between GMFC-MLD health states for BSC were based on data from an international natural history study conducted at Ospedale San Raffeale, Milan, Italy[1] published literature [5,6] and MLD expert clinical opinion.
- At each model cycle, there is a probability that patients will either transition to the next GMFC-MLD health state, stay in the same health state, or transition to non-MLD related death based on the mean time spent in each GMFC-MLD level from the natural history study.
- This matches the clinical course of MLD in which only deterioration is observed (Figure 2).

Arsa-cel transitions:

- Health state transitions (Figure 2) were based on the following:
  - Patient level data from the arsa-cel clinical trials to calculate mean time spent in each health state. [3]
  - The mechanism of action of OTL-200 which means patients have the potential to experience life-long benefits of treatment.
- Based on the clinical data for arsa-cel, the modelling of patient response was grouped into three distinct categories:
  - full responders – patients who are stable across a broad range of clinical outcomes;
  - partial stable responders – patients who initially experienced some disease progression prior to stabilisation of disease, but who then remained within that health state for the duration of the time horizon of the model;
  - and unstable partial responders - who experienced continued disease progression despite treatment but at a slower rate than was reported for patients in the natural history arm (BSC).

Figure 2: Example of modelled disease progression by GMFC-MLD health state for late infantile (LI) MLD by treatment



METHODS: HEALTH VALUATION

GMFC-MLD Health state utility values:

- Utility values were derived from a vignette study based on the time-trade off method conducted in 201 members of the UK general public to elicit utility values for all 24 health states in the economic model.[7]
- The values were then calibrated using a simple algorithm involving the Spanish EQ-5D value set to reflect the societal preferences for Spain. These values are presented in Table 1.
- Health states worse than death (<0) were permitted to adequately capture the extremely high burden of disease. These values align with health state utility values (HSUVs) from the Spanish EQ-5D tariff where 20% of all predicted health states were less than zero and the worst possible health state is -0.654.

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

	Late Infantile	Early Juvenile		
		Normal cognitive function	Cognitive impairment	Severe cognitive impairment
GMFC 0	Age adjusted general population		0.75	0.46
GMFC 1	0.71	0.91	0.63	0.34
GMFC 2	0.44	0.84	0.56	0.27
GMFC 3	-0.07	0.38	0.10	-0.13
GMFC 4	-0.22	0.00	-0.18	-0.37
GMFC 5	-0.35	-0.09	-0.28	-0.47
GMFC 6	-0.47	-0.14	-0.33	-0.52

Caregiver disutilities:

- There is a considerable physical and psychological burden placed on caregivers of children with MLD.
- Consequently, a disutility of 0.068 per caregiver has been applied to patients from GMFC-MLD 2 and above. This is based on the mean index utility value (0.773) for all respondents completing the EQ-5D in the MLD Caregiver Survey[8] subtracted from the Spanish general population utility at 40 years of age (0.841).
- 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.
- A disutility of −0.57 was included in the model, and this was informed by the utility decrement used in the UK assessment of another gene therapy, Strimvelis, which also requires busulfan conditioning.[9] The base case defaults to a 3-month disutility, because side-effects due to busulfan in the arsa-cel clinical trial programme were short-lived.

METHODS: COSTS

Healthcare resource use:

- HCRU was calculated using a bottom-up micro-costing approach via a structured expert elicitation exercise which was used to estimate the frequency, duration, and proportion of HCRU for MLD patients, including medical visits, equipment, social care use and medication for each GMFC-MLD state.
- Unit costs from the eSalud database were used in conjunction with the HCRU data to calculate monthly medical costs by GMFC-MLD health state ranging from €533 per month for patients in GMFC-MLD 1 to €6,245 per month for patients in GMFC-MLD 6.

Treatment related costs:

- Treatment costs included the list price of arsa-cel (€2,875,000), leukapheresis (€1,035), conditioning (€5,164), administration and hospitalization (€52,583), as well as follow-up transplant costs (€1,092).

RESULTS

- The deterministic cost-effectiveness results for the base case analyses for arsa-cel vs. best supportive care from both a health care system and societal perspective are shown in Table 2.
- The combined cohort is weighted by the proportion of each MLD phenotype in the arsa-cel clinical trial programme (PS-LI:55.9%; PS-EJ: 29.4%, ES-EJ: 14.7%).
- The societal perspective includes lost family income, indirect medical costs and future productivity gains using the Human Capital approach.

Table 2: Deterministic cost-effectiveness results

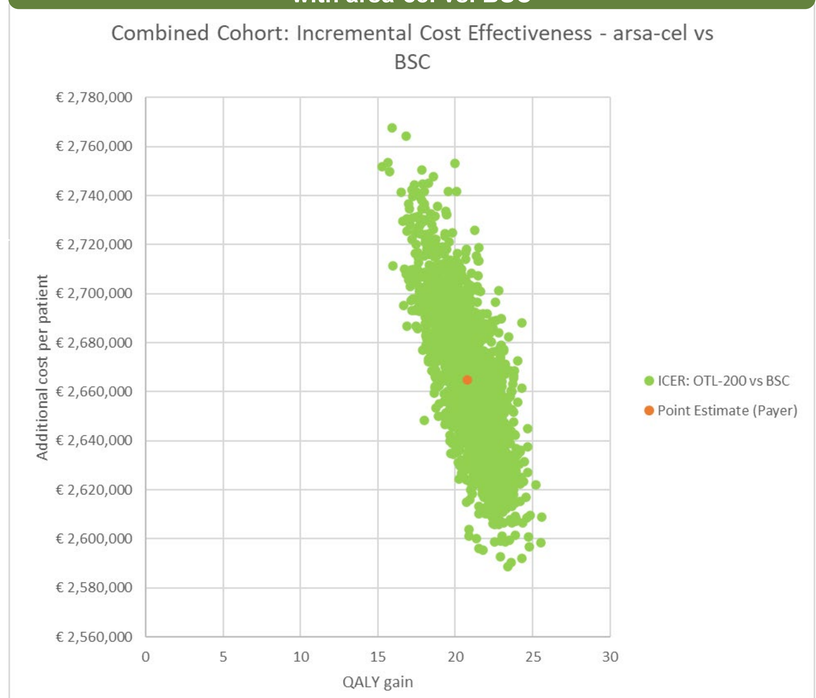
Patient population	Incremental costs	Incremental QALYs	ICER (€/QALY)
Healthcare system perspective:			
PS-LI	€2,638,557	20.53	€128,499
PS-EJ	€2,599,824	26.07	€99,715
ES-EJ	€2,894,582	10.97	€263,899
Combined cohort	€2,664,815	20.76	€128,387
Societal perspective:			
PS-LI	€2,160,881	20.53	€105,236
PS-EJ	€2,074,096	26.07	€79,551
ES-EJ	€2,675,190	10.97	€243,898
Combined cohort	€2,210,990	20.76	€106,522

PS-LI: pre-symptomatic late infantile; PS-EJ: pre-symptomatic early juvenile; ES-EJ: early-symptomatic early juvenile).

Sensitivity analyses:

- Probabilistic sensitivity analyses (PSA) show that the cost-effectiveness results are robust, as the incremental costs and QALYs for arsa-cel vs. BSC are relatively stable when each parameter is sampled simultaneously within it's distribution of variance (Figure 3).

Figure 3: PSA results for the combined cohort of patients treated with arsa-cel vs. BSC



- Scenario analyses testing the impact of key parameters on the cost-effectiveness results are presented in Table 3.
- The discount rate has a large impact on the results – this is to be expected given the majority of costs are incurred upfront, but benefits accrue over a lifetime.
- In addition, if newborn screening (NBS) were to be implemented the cost-effectiveness results improve significantly – this is because better outcomes are achieved for patients treated pre-symptomatically and in advance of predicted onset of symptoms.

Table 3: Scenario analyses to test impact of key parameters on the cost-effectiveness results for the combined cohort (healthcare perspective)

Scenario analyses	Scenario ICER	Base case ICER	Difference from base case
Discount rate of 4.5%	€166,091	€128,387	+ €37,704
Discount rate of 1.5%	€93,204	€128,387	- €35,183
Time horizon reduced to 30 years	€166,772	€128,387	+ €38,385
Alternative phenotype distribution: 31% PS-LI; 38% PS-EJ; 31% ES-EJ	€137,405	€128,387	+ €9,018
Implementation of newborn screening	€99,031	€128,387	- €29,305
Reducing the list price of arsa-cel by 30%	€77,047	€128,387	- €51,340

CONCLUSION

- **This analysis demonstrates that arsa-cel is a cost-effective use of health care resources for the Spanish NHS (SNS) vs. BSC.**
- **Sub-group analyses indicate that arsa-cel is most cost-effective in patients treated pre-symptomatically.**
- **Sensitivity analyses show that the results are robust to uncertainty in the parameter inputs.**
- **Implementation of NBS would further improve the cost-effectiveness of arsa-cel.**

References

1. Fumagalli F *et al*. 2021. *J Inherit Metab Dis*.44(5):1151-1164
2. Arsa-cel SmPC. Accessed Oct 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy#product-info.
3. Calbi *et al.* 2024 *Mol Genet Metab*;46(S1):33-34
4. Elgun *et al.* 2019. *Orphanet J Rare Dis* 14. 136
5. Kehrer et al. 2011. *Dev Med Child Neurol*; 53(2):156–60.
6. Kehrer C *et al. 2011. Dev Med Child Neurol*;53:850-855.
7. Nafees *et al.* 2020. PRO131: *Value in Health.* doi.org/10.1016/j.jval.2020.08.1867
8. Sevin C *et al.* 2022.. *Orphanet J Rare Dis* 17(1):329.
9. NICE HST7. Last accessed Oct 2024. https://www.nice.org.uk/guidance/hst7

Libmeldy (atidarsagene autotemcel, OTL-200) received approval from the European Commission on 17 December 2020, in the UK on 1 February 2021, and the USA as Lenmeldy in March 2024. Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein, Norway, Switzerland, and the USA.