The societal costs of metachromatic leukodystrophy (MLD) in the United States and the benefit of a potential new disease modifying therapy to reduce these costs

Bean K,[1] Miller B,[2] Howle K,[3] Wilds A,[3] Walz M,[3] Fields C, [1] and Pang F [1]

[1]Orchard Therapeutics, London, UK and Boston, MA, USA; [2]Precision Health Economics & Outcomes Research, Boston MA, USA; [3] Magnolia Innovation, Hoboken, NJ, USA,

EE547

BACKGROUND & OBJECTIVES

- MLD is an ultra-rare and fatal inherited neurodegenerative disease, caused by a deficiency of the Arylsulfatase A (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).[1]
- At present, US patients with early-onset MLD have no disease modifying treatment options and have very poor survival outcomes, with progressive loss of motor and cognitive abilities, as well as spasticity, seizures, feeding difficulties, typically culminating in a decerebrated state or death before adolescence.
- Due to the debilitating nature of early-onset MLD, parents are often forced to give up work to care for their affected children.[2]
- Future regulatory approval of an autologous haematopoietic stem cell (HSC) gene therapy, arsa-cel (OTL-200), for the treatment of early-onset MLD could result in the availability of an effective disease modifying therapy that enables affected children to retain motor and cognitive function and contribute to society. However, the societal impact of the benefit of this potential treatment has yet to be investigated from a US perspective.
- The Gross Motor Function Classification in MLD (GMFC-MLD) is used to assess the severity of a patient's mobility impairments, with higher levels indicating increased severity.[3] The health states in the economic model used to calculate lost family income and future productivity gains are grounded by the GMFC-MLD levels of motor impairment but include other symptoms of the disease such as dysphagia, seizures, loss of vision, speech and hearing.

Objective:

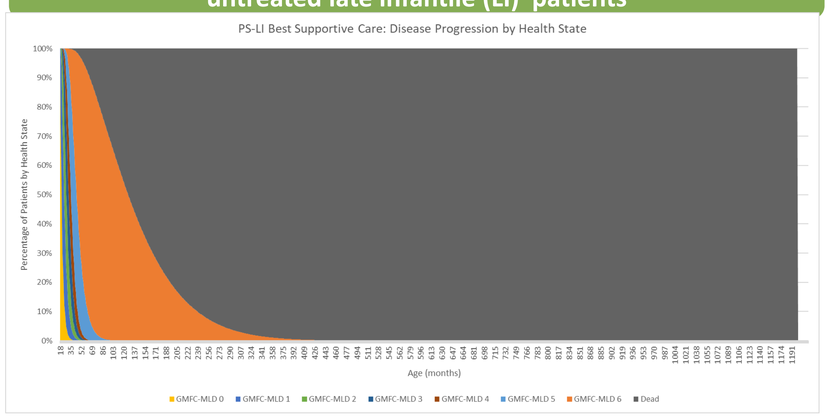
The aim of this study was to determine the average lost family income and out of pocket costs due to caring for an untreated early onset MLD patient and the potential productivity gains associated with disease modifying therapy, from a US perspective.

METHODS

Lost Family income:

- Lost income and out of pocket costs for carers of untreated early-onset MLD patients were calculated from information collected as part of an International MLD Caregiver Survey.
- To align lost family income data with the 7 GMFC-MLD health states in the model, there were sufficient descriptive data to assign untreated patients with MLD into either mild (GMFC-MLD 1 or 2), moderate (GMFC-MLD 3 or 4) or severe GMFC-MLD health states (GMFC-MLD 5 or 6).
- Patients were grouped according to the average scores generated from the Caregiver survey which used a ranking system, where 1 = no problem and 5 = significant difficulty for a variety of symptoms associated with MLD in the preceding 4 weeks like difficulty with walking, swallowing, vision, speech etc. These data align with the descriptions for the GMFC-MLD health states used in the model.
- Caregivers of these patients were then asked if they had forgone a significant amount of income or if their employment status had been affected specifically due to caring for an MLD patient.
- For caregivers employed full-time, loss of earnings for any unpaid missed workdays were included.
- For caregivers employed part-time who had forgone a significant amount of income due to caregiving and their employment status has been affected by caring for someone with MLD, half of the average annual income was added to any missed unpaid days of work.
- Unemployed respondents forgoing significant income and/or whose employment status had been affected by caring for an MLD patient were assumed to lose the median annual income.
- For all respondents who had not forgone significant income or felt their employment status had not been affected, loss of earnings was set to zero.
- The weighted median annual salary for the US based on educational achievement ($55,029) and the number of working days (250) in 2022 were used to calculate both lost family income and future productivity gains.
- Lost family income over a patient's lifetime was calculated based on clinical data from a natural history MLD cohort depicting the amount of time spent in each GMFC-MLD level before death (Figure 1).

Figure 1: Amount of time spent in each GMFC-MLD level for untreated late infantile (LI) patients



Future productivity gains:

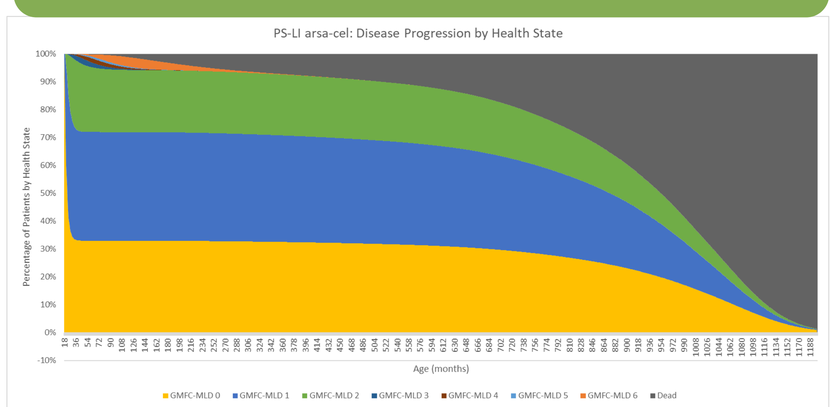
- Future potential productivity gains for treated patients aged 18–64 were calculated using the Human Capital Approach.[4]
- Due to a lack of employment data in MLD patients, published data from cerebral palsy and Down's syndrome served as a proxy for the employment impact of motor/cognitive dysfunction, alongside expected earnings based on US educational achievement.
- For an arsa-cel treated MLD patient with normal cognitive function but who may have some loss of motor function, the published proportion of employment by GMFC stage for cerebral palsy (a condition with fixed motor dysfunction and normal cognition) was used.[5]
- For a treated MLD patient with no motor dysfunction but who may have some cognitive impairment (DQp ≥55 and <70), Down's syndrome employment data was used,[6] as people with Down's syndrome have normal motor function but mild to moderate cognitive impairment.
- Patients with severe cognitive impairment (DQp <55) were assumed to all be unemployed.
- A matrix of unemployment for the GMFC-MLD stages 1–6 with mild/moderate cognitive impairment can be calculated based on the rate of change of unemployment reported for the cerebral palsy group, using the Down's syndrome employment as the baseline (Table 1). The clinical trial data for arsa-cel were then used to determine time spent in the GMFC-MLD health states and extrapolated over the lifetime horizon of the model to generate total costs (Figure 2).

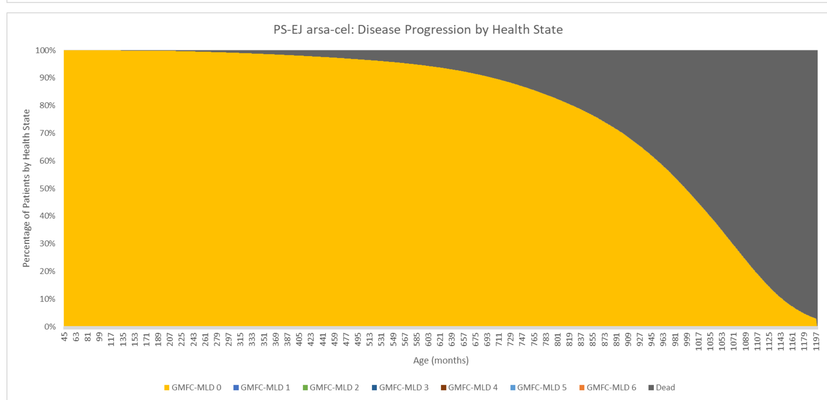
Table 1: Unemployment rates by GMFC-MLD stage and cognitive sub-state

GMFC-MLD	Normal Cognitive Function	Cognitive Impairment (DQ <70)	Severe Cognitive Impairment (DQ <55)
Stage 0	0%	43%	100%
Stage 1	18%	53%	100%
Stage 2	29%	59%	100%
Stage 3	63%	79%	100%
Stage 4	82%	90%	100%
Stage 5	100%	100%	100%
Stage 6	100%	100%	100%

DQ, Development Quotient; GMFC-MLD, Gross Motor Function Classification in Metachromatic Leukodystrophy.

Figure 2: Predicted amount of time spent in each GMFC-MLD level for arsa-cel treated pre-symptomatic late infantile (PS-LI) patients and pre-symptomatic early juvenile (PS-EJ) patients over a lifetime



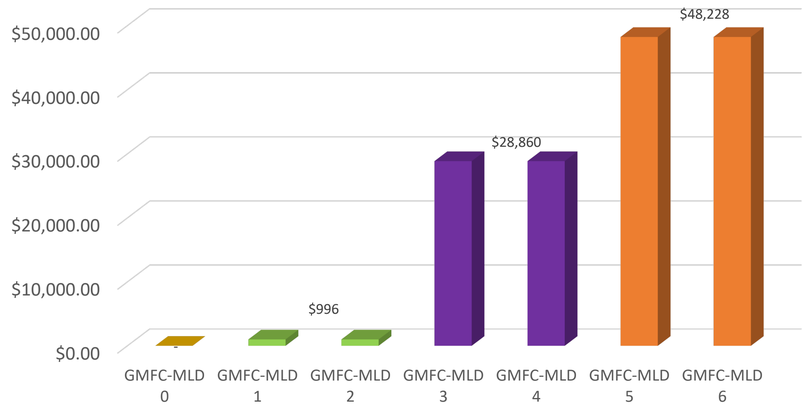


RESULTS

Lost Family income:

- The mean loss of annual income due to caregiving for a patient with MLD increases with GMFC-MLD stage, from $996 for GMFC-MLD 1 and 2 to $48,228 for GMFC-MLD 5 and 6 (Figure 3).

Figure 3: Average loss of annual income due to caregiving for an untreated patient with early onset MLD by GMFC-MLD level

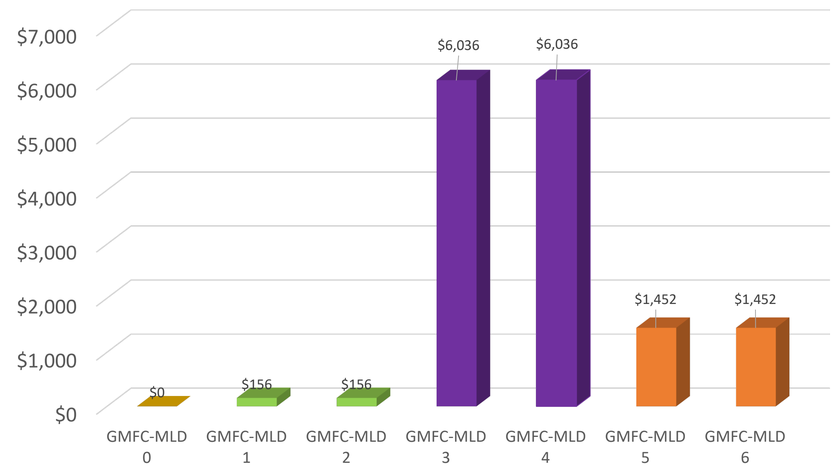


- In untreated patients, the estimated family income lost as a result of caring for an MLD patient ranged from **$348,041** for a late infantile MLD patient to **$423,304** for an early juvenile patient.
- This is because early juvenile patients live longer with their disease than late infantile patients; data from the natural history cohort show that median time to death for late infantile patients was 9.42 years from birth. Whereas 15 years after symptom onset, 68.6% of the EJ cohort were still alive but the majority of EJ patients were > GMFC-MLD 4 five years after symptom onset,[7] and therefore incurring the higher lost family income for a longer period of time.

Out of pocket costs:

Average annual direct non-medical costs are presented in Figure 4. Most of the out-of-pocket costs occurred in GFMC-MLD stages 3 and 4 - at the point where a patient loses the ability to walk. This is logical because house and car adaptations to accommodate a wheelchair, which are not covered by most insurance policies, would occur at this point in the disease.

Figure 4: Average out of pocket costs for untreated patients with early onset MLD by GMFC-MLD level



Future productivity gains:

- Based on the matrix of unemployment in Table 1 and the median annual salary in the US, the total annual productivity gains for treated MLD patients can be calculated and are presented by GMFC-MLD stage in and cognitive function in Table 2.
- As 100% of patients with severe cognitive impairment (DQ <55) are assumed to be unemployed, there would be no productivity gains for any patient with severe cognitive impairment.

Table 2: Total annual productivity gains by GMFC-MLD level and cognitive function

GMFC-MLD 0	GMFC-MLD 1	GMFC-MLD 2	GMFC-MLD 3	GMFC-MLD 4	GMFC-MLD 5	GMFC-MLD 6
Normal Cognitive Function						
$55,029	$45,124	$33,018	$20,631	$9,905	-	-
Cognitive impairment (DQ <70)						
$31,367	$25,864	$22,562	$11,556	$5,503	-	-

- Using the total annual productivity gains presented in Table 2, the potential productivity gains throughout a treated patients working life (18-64 years) can be calculated based on the predicted amount of time spent in GMFC-MLD level over a lifetime, derived from the clinical trials (Figure 2) discounted at 3.0%.
- In early onset MLD patients treated with arsa-cel, the potential productivity gains accrued over a working life were estimated at **$656,906** for late infantile MLD patients and **$908,162** for pre-symptomatic early juvenile patients.
- The difference in productivity gains between the two MLD phenotypes is primarily driven by the fact that 100% of PS-EJ patients remained in GMFC-MLD 0 with normal cognitive function until last follow-up, which was then extrapolated over lifetime as per Figure 2. However, for the late infantile patients treated with arsa-cel, patients stabilised in GMFC-MLD 0, 1 or 2 with normal cognitive function at last follow-up. Productivity gains for patients with some mild motor dysfunction are estimated to be slightly less than those with no motor dysfunction.

SUMMARY & CONCLUSION

- Significant family income is lost through non-treatment of MLD, especially in the later stages of the disease, contributing to the large financial burden of MLD.
- There are significant potential productivity gains for US MLD patients treated with arsa-cel compared to untreated patients who do not have opportunities to enter the workforce.
- The results of this study demonstrate the positive impact of arsa-cel to reduce the societal costs of MLD in the US.

References:
1. Gieselmann *et al.* Neuropediatrics. 2010;41(1):1-6; 2.Pang *et al.* 16th Annual WORLD Symposium; Orlando, Florida, USA (Poster) 2020 3. Palisano *et al.* Phys. Ther. 2000;80(10):974-85 4. Turner *et al.* Fron. Public Health. 2021;9:2296-2565; 5. Verhoef *et al.* J Rehabil Med. 2014;46(7):648-55. 6. Kumin et al. 2015. 7. Fumagalli *et al.* 2021.

Libmeldy (atidarsagene autotemcel, OTL-200) 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-epar-product-information_en.pdf. Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein and Norway. A BLA for arsa-cel has been accepted for Priority Review by the US FDA.