

Value Contribution of Olipudase Alfa Therapy for the Treatment of Non-Central Nervous System Manifestations of Acid Sphingomyelinase Deficiency (ASMD) By Multi-Criteria Decision Analysis (MCDA)

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Introduction and objective

- Acid sphingomyelinase deficiency (ASMD), historically known as Niemann–Pick disease (NPD), is a rare, progressive lysosomal storage disease caused by mutations in the *SMPD1* gene (1).
- ASMD is a life-threatening disorder associated with significant morbidity and mortality, due to both central nervous system (CNS) and non-CNS manifestations (2).
- Most common non-CNS manifestations include interstitial lung disease, hepatosplenomegaly, thrombocytopenia, dyslipidemia, delayed growth and shortness of breath among others(1).
- Currently, the management of ASMD is limited to symptomatic treatment and supportive care.
- Olipudase alfa, a recombinant human ASM, is an enzyme replacement therapy that has recently received the European Commission approval for the treatment of non-CNS manifestations of ASMD (1,3,4).
- Multicriteria decision analysis (MCDA) methodology has demonstrated usefulness in determining the value contribution of health care interventions (5), specially in orphan drugs (6).
- The aim of this study is to determine the value contribution of olipudase alfa compared with placebo in the treatment of non-CNS manifestations of ASMD using MCDA methodology.

Methods

- A targeted literature review was conducted to populate the EVIDEM (v 4.0) Framework adapted to the context of orphan drugs and rare diseases (7), comprised of 9 quantitative and 3 contextual criteria (Table 1). Placebo was selected as comparator due to the lack of treatment alternatives in ASMD.
- MCDA matrix was scored by a multidisciplinary expert panel (n=8) which included the main stakeholders involved in the management of ASMD. The panel was comprised of 5 hospital pharmacists, 2 clinicians, an haematologist and a paediatrician to cover the broad clinical range of symptoms of the disease, and a ASMD patient representative.
- The scoring scale for the qualitative non-comparative criteria ranged from 0 to 5. The qualitative comparative criteria scoring scale ranged from -5 to 5. A qualitative scale with 3 response options was used for contextual criteria: positive, neutral, or negative.
- Mean and standard deviation of the scores were calculated for quantitative criteria. For contextual criteria, the percentage of experts that considered that there was a positive, neutral or negative impact in the Spanish National Health System was calculated.
- The value contribution (VC) for each of the 9 qualitative criteria was determined using the standardized scores (Se) multiplied by the relative weight value of each criterion, obtained from the weighting of 98 evaluators and decision-makers in Spain (8). Olipudase alfa value contribution vs. placebo was calculated by adding up the value contribution of each individual criterion (VCw): VC = Se x VCw.

Table 1: Adapted MCDA Orphan Drug Framework for the study

DISEASE-RELATED CRITERIA	
Disease severity	
Unmet needs	
TREATMENT-RELATED CRITERIA	
Efficacy/effectiveness	
Safety/tolerability	
Patient-reported outcomes (PROs)	
Therapeutic impact	
Other medical costs	
Non-medical/indirect costs	
Quality of evidence and Grade of recommendation	
CONTEXTUAL CRITERIA	
Population priorities and access	
Common goals and specific interests	
System capacity and appropriate use of the intervention	

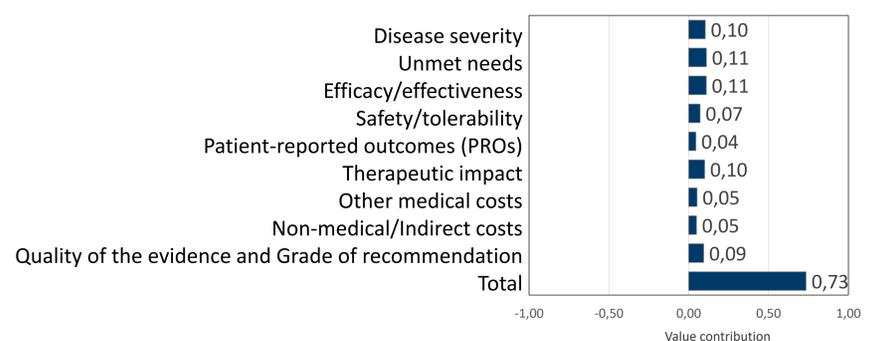
Results

- Scores obtained for each of the quantitative criteria of the evidence matrix comparing olipudase alfa with placebo are shown in Figure 1.
- ASMD was considered a severe disease (mean \pm SD: 4.1 \pm 0.6) due to both neurological and non-neurological clinical manifestations that significantly contribute to the burden of the disease. There is still an unmet need in the treatment of ASMD, given that current treatment is purely symptomatic (4.9 \pm 0.4).
- Experts perceived that olipudase alfa might provide a substantial improvement in efficacy/effectiveness compared to symptomatic treatment and placebo (4.4 \pm 0.7), as it shows a significant improvement in all parameters studied such as the spleen volume or lung functionality. Moreover, olipudase alfa has a favourable safety profile (3.0 \pm 2.6) as most of AEs were mild to moderate.
- Moderate scores were obtained in patient-reported outcomes (PROs) criteria (2.4 \pm 1.8). Although evidence published to date on PROs is not sufficient to conclude the effect of treatment on patient's quality of life, experts considered that olipudase alfa might impact positively in patients' quality of life based on the efficacy and safety results.
- The therapeutic impact provided by olipudase alfa was considered high (4.3 \pm 0.7), as it showed the potential to modify the course of the disease.
- Experts anticipated lower medical costs (2.6 \pm 1.3) for those patients treated with olipudase alfa, due to a potential reduction in hospitalisations, emergency room visits, outpatient visits, and surgical procedures. Participants also perceived savings in indirect costs (2.9 \pm 1.1), as working-age patients treated with olipudase alfa would improve their productivity and reduce the burden of ASMD on caregivers or relatives.
- Evidence supporting olipudase alfa treatment was considered high in the context of orphan drugs (3.9 \pm 1.0).
- The value contribution of olipudase alfa for the treatment of non-CNS manifestations of ASMD versus placebo was 0.73 (Figure 2). Disease severity, unmet need, efficacy/effectiveness and therapeutic impact provided the highest value contribution.
- In contextual criteria, most experts perceived a positive impact on population priorities and access (88%), common goals and specific interests (88%), and system capacity and appropriate use of the intervention (100%).

Figure 1: Scoring results of the quantitative criteria of olipudase alfa vs placebo

Criteria	Mean	Std Dev	Min	Max	n
Disease severity	4,1	0,6	3,0	5,0	8
Unmet needs	4,9	0,4	4,0	5,0	8
Efficacy / effectiveness	4,4	0,7	3,0	5,0	8
Safety / tolerability	3,0	2,6	-1,0	5,0	8
Patient-reported outcomes (PROs)	2,4	1,8	0,0	5,0	8
Therapeutic impact	4,3	0,7	3,0	5,0	8
Other medical costs	2,6	1,3	1,0	5,0	8
Non-medical / Indirect costs	2,9	1,1	2,0	5,0	8
Quality of the evidence and Grade of recommendation	3,9	1,0	2,0	5,0	8

Figure 2: Results of the value contribution of olipudase alfa



Conclusion

- ASMD is a rare disease with significant unmet needs and a high impact on morbidity, mortality, and quality of life of patients and caregivers.
- Olipudase alfa was perceived to provide high added value to the treatment of non-CNS manifestations of ASMD compared to placebo, using MCDA methodology.
- Disease severity, unmet needs, and efficacy/effectiveness and therapeutic impact criteria provided the highest value contribution, considering the high morbidity and mortality of ASMD, the availability only of symptomatic treatment for these patients, and the improvement provided by olipudase alfa treatment in non-CNS manifestations such as splenomegaly, liver and respiratory function.

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