HTA130

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).
- **Until recently, the management of ASMD was 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 ±SD: 4.1±-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±0.4).
- Experts perceived that olipudase alfa might provide a substantial improvement in **efficacy/effectiveness** compared to symptomatic treatment and placebo (4.4±0.7), as it shows a significant improvement in all parameters studied such as the spleen volume or lung functionality. Moreover, olipudasa alfa has a favourable **safety profile** (3.0±2.6) as most of AEs were mild to moderate.
- Moderate scores were obtained in **patient-reported outcomes** (PROs) criteria (2.4±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±0.7), as it showed the potential to modify the course of the disease.
- Experts anticipated lower **medical costs** (2.6±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±1.1), as working-age patients treated with olipudase alpha 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±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

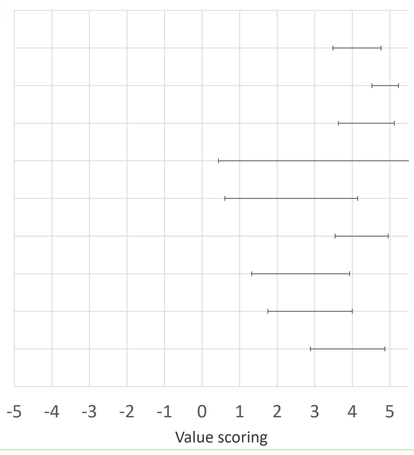
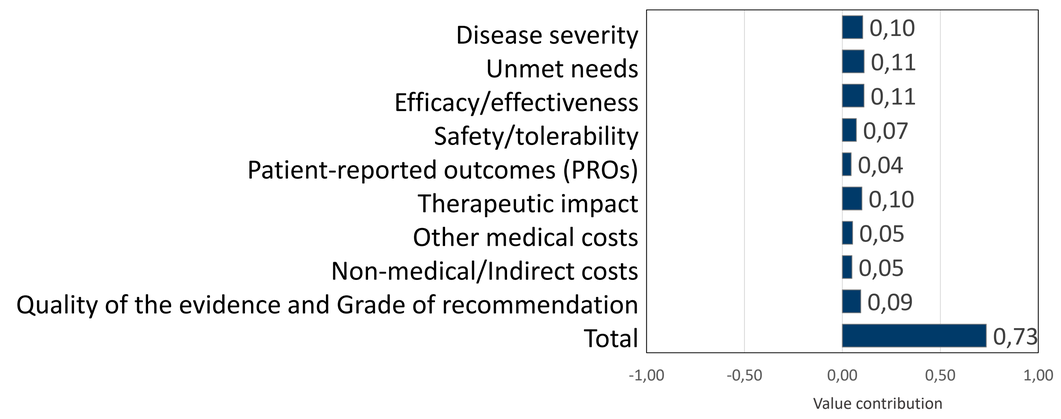


Figure 2: Results of the value contribution of olipudase alfa



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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Conflict of interest: MRA has received speaking fees from Janssen, Sobi, Galapagos, Abbvie, Ipsen, Biogen, CSL Behring, Takeda and I has participated in MCDA analyses funded by Zogenix International Ltd, Biomarin International and Sanofi .AGM has received honoraria for scientific meetings and advisories from Sanofi and research funding from Sanofi. EG has received honoraria for consultant/advisory panel activities for Sanofi, research support for Sanofi and Takeda ,training activities in lysosomal diseases for Sanofi and Takeda and registration and travel fees to congresses/conferences for Sanofi, Takeda, Pfizer, and GSK. JLP declares no conflicts of interest related to this article. JLT has received funding for presentations/ professional meetings from Pfizer and Sanofi. DV declares the following non-personal conflicts of interest as ASMD Spain has received funding for the development of outreach projects and congress development. JV has received honoraria for talks, travel grants and attendance at advisory boards from Sanofi and Takeda and research funding from Sanofi. MRA,AGM,EG,JLP,JLT,JV received funding from Sanofi related to the hours dedicated to this project. MB and XB work for Omakase Consulting, which have received funding from Sanofi to develop this project