

Value contribution of olipudase alfa therapy for the management of the non-CNS manifestations of acid sphingomyelinase deficiency by multi-criteria decision analysis

Contribución de valor de olipudase alfa en el tratamiento de las manifestaciones no relacionadas con el SNC del déficit de esfingomielinasa ácida mediante análisis de decisión multicriterio

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Abstract

Introduction: Olipudase alfa, an enzyme replacement therapy, is the first treatment approved for acid sphingomyelinase deficiency (ASMD), a rare lysosomal storage disease. **Objective:** To determine the value contribution of olipudase alfa to treat non-central nervous system (CNS) manifestations of ASMD using MCDA methodology. **Methods:** A literature review was conducted to populate an adapted MCDA framework for orphan-drug evaluation. A multidisciplinary panel of 8 experts were trained in MCDA methodology and scored the evidence matrix. Scoring consistency was explored through a test-retest reliability analysis. **Results:** ASMD was considered a severe disease (mean, 4.1 ± 0.6) with significant unmet needs (4.9 ± 0.4). Experts perceived that olipudase alfa may improve efficacy/effectiveness (4.4 ± 0.7), and has a favorable safety profile (3.0 ± 2.6). Additionally, its therapeutic benefit was considered relevant (4.3 ± 0.7) and patient-reported outcomes (PROs) (2.4 ± 1.8) were rated as moderate. Lower medical costs (2.6 ± 1.3) and indirect cost savings (2.9 ± 1.1) would be expected. Evidence presented was considered adequate (3.9 ± 1.0). The test-retest analysis indicated consistency in the scoring of almost all criteria. Lower correlation scores were observed in criteria with more dispersion as expert's scoring perception was addressed during the discussion session. **Conclusion:** Olipudase alfa may provide a high-value intervention to treat non-CNS manifestations of ASMD.

Keywords: Drugs evaluation. Acid sphingomyelinase deficiency. Olipudase alfa. Multicriteria decision analysis. Rare diseases.

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Resumen

Introducción: Olipudasa alfa es el primer tratamiento indicado para el déficit de esfingomielinasa ácida (ASMD), una enfermedad rara lisosomal. **Objetivo:** Determinar el valor de olipudasa alfa en el tratamiento de las manifestaciones no relacionadas con el sistema nervioso central (SNC) del ASMD utilizando la metodología MCDA. **Metodología:** Se realizó una revisión de la literatura para poblar un marco MCDA adaptado para medicamentos huérfanos. Un panel multidisciplinar de 8 expertos puntuó la matriz de evidencia. Se exploró la consistencia de la puntuación mediante un ejercicio de test-retest. **Resultados:** El ASMD se consideró una enfermedad grave (media de 4.1 ± 0.6), con importantes necesidades no cubiertas (4.9 ± 0.4). Los expertos percibieron una mejora en eficacia/efectividad (4.4 ± 0.7) con un perfil de seguridad favorable (3.0 ± 2.6). Además, su beneficio terapéutico se consideró relevante (4.3 ± 0.7) y los PROs (2.4 ± 1.8) se calificaron como moderados. Se consideró que olipudasa alfa produciría un ahorro de costes médicos (2.6 ± 1.3) y de costes indirectos (2.9 ± 1.1). La evidencia presentada se consideró adecuada (3.9 ± 1.0). El análisis test-retest indicó consistencia en la puntuación en casi todos los criterios, con correlaciones más bajas en los criterios con mayor dispersión. **Conclusión:** Olipudasa alfa proporciona un alto valor al tratamiento de las manifestaciones no relacionadas con el SNC del ASMD.

Palabras clave: Evaluación de medicamentos. Déficit de Esfingomielinasa Ácida. Olipudasa alfa. Análisis de decisión multicriterio (MCDA). Enfermedades raras.

Introduction

Acid sphingomyelinase deficiency (ASMD) is a rare lysosomal storage disorder that leads to the accumulation of sphingomyelin and other lipids in cells and tissues due to an impaired ASM activity¹. The estimated rate of ASMD is 0.4-0.6/100,000 births worldwide². ASMD is a life-threatening disorder associated with significant morbidity and mortality, due to both central nervous system (CNS) and non-CNS manifestations³⁻⁵. Non-CNS manifestations include splenomegaly, impaired pulmonary function limiting diffusion capacity, and hepatomegaly leading to liver failure^{6,7}. ASMD represents a significant burden on both patients and caregivers, affecting both physical and emotional well-being².

Current disease management aims to reduce the impact of individual symptoms to reduce morbidity seeking to improve the patients' quality of life⁵. Until recently, there were no disease-specific treatments for ASMD. Olipudase alfa, a recombinant human ASM, has recently received marketing authorization by the European Commission back in June 2022) for the treatment of non-CNS manifestations in pediatric and adult patients with ASMD⁸. As an enzyme replacement therapy (ERT), olipudase alfa targets the underlying metabolic defect of ASMD by supplementing the deficient enzyme activity. The efficacy and safety profile of olipudase alfa has been demonstrated in the ASCEND study^{9,10}, a multicenter, open-label, randomized, phase 2/3 trial, as well as in the phase 1/2 ASCEND-Peds trial in pediatric population¹¹. Olipudase alfa has obtained the orphan¹² and PRIME¹³ designation by the European Medicines Agency.

Multi-criteria decision analysis (MCDA) methodology allows the assessment in a transparent and systematic

way of the multiple criteria that add value to a medicinal product from the perspective of relevant stakeholders involved in the decision making-process¹⁴. MCDA is widely used in decision-making^{15,16}, specifically in orphan drugs (OD) for rare diseases¹⁷⁻²³. The objective of this study is to determine the value contribution (VC) of olipudase alfa in the treatment of non-CNS manifestations of ASMD using MCDA methodology.

Methods

Study design

The study was designed following MCDA good practices recommendations²⁴. An adaptation of the MCDA value framework developed for the evaluation of OD in Spain was used consisting of 9 quantitative criteria and 3 contextual criteria. Disease-related quantitative criteria included "Disease severity" and "Unmet needs". Treatment-related quantitative criteria were "Efficacy/effectiveness", "Safety/tolerability", "Patient-reported outcomes (PROs)", "Therapeutic impact", "Other medical costs", "Non-medical/indirect costs" and "Quality of evidence". Contextual criteria were "Population priorities and access", "Common goal and specific interests" and "System capacity and appropriate use of intervention". The weighting of 98 evaluators and decision-makers from a previous study was used²⁵. In the absence of approved drugs to treat non-CNS clinical manifestations of ASMD, placebo was selected as a comparator.

To assess scoring consistency and reliability, a retest was performed individually by the same participants 1 week after the workshop session. Change of scoring after the discussion session was allowed.

Literature review

A targeted literature review was performed from March through April of 2022 to identify available evidence for ASMD and olipudase alfa for each of the criteria of the adapted framework. Published evidence was searched using the biomedical databases MEDLINE, Cochrane, and Medes. The search was complemented with information available from grey literature sources. All articles identified through the search were screened by title and abstract. Articles that did not meet the eligibility criteria were excluded from the study. The remaining articles were evaluated by reading the full text.

Evidence matrix development

The information extracted from the literature review was used to populate the MCDA evidence matrix. The scoring scale for the qualitative non-comparative criteria ranged from 0 to 5 (0 being the worst possible score and 5 the best possible one). The qualitative comparative criteria scoring scale ranged from -5 (olipudase alfa being much worse compared to the alternative) to +5 (olipudase alfa much better than the alternative). The evaluation of the contextual criteria was performed using a qualitative scale with 3 response options: positive, neutral, or negative.

Expert panel and study development

The VC assessment was conducted by a multidisciplinary panel including 8 experts, 2 clinicians, 5 hospital pharmacists, and 1 patient representative. The expertise of the 2 clinicians included a hematologist and a pediatrician, to cover the wide range of manifestations of this disease. Hospital pharmacists, 4 of whom were department heads, had extensive experience in OD evaluation and decision-making.

The study was conducted online, using a multi-phased approach throughout April 2022. First, participants received basic training on MCDA methodology. Then, each of the experts scored individually the evidence matrix including their rationale for doing so. Afterwards, the results were presented and discussed online. Subsequently, participants were asked to score again the same evidence matrix considering the reflective discussion.

Data analysis

The value scores for each criterion and the reflections associated were collected individually, transferred to a database, and then analyzed using Microsoft Excel

software. For each quantitative criterion, the mean, standard deviation (SD), and the range of minimum and maximum scores were estimated. The scores of the contextual criteria were analyzed as the percentage of experts who would consider that the medicine would have a negative impact, neutral or positive impact by responding to the definition of each criterion.

The VC for each of the 9 qualitative criteria was determined using the standardized scores (Ss) multiplied by the relative weight value of each criterion (VCw): $VC = Ss \times VCw$. The overall global VC (a value ranging from 0 to 1) was determined from the sum of all individual contributions. Comments and reflections on the experts' scores were analyzed and discussed qualitatively.

A test-retest analysis of global and individual criteria scoring was performed using *Spearman's rank correlation coefficient* with STATA software (version 15 IC; Stata Corporation, College Station, TX, United States). Spearman's rank correlation coefficient measures the strength and direction of the association between the 2 variables ranked (ranging from -1 to +1 being 0 indicative that there is no monotonic association)²⁶. The test-retest analysis aimed to explore how reflective discussion, and therefore data interpretation, may influence criteria scoring. Lower Spearman's rank correlation coefficients would be expected in those criteria with higher dispersion in the first reliability analysis.

Results

Literature review

A total of 279 publications were identified from biomedical databases (n = 265) and grey literature (n = 14). After withdrawing of duplicates, a total of 215 publications were selected for screening. A total of 120 out of 215 publications were discarded based on title and abstract screening as they did not respond to the search objective or did not meet the eligibility criteria. Subsequently, 62 articles were discarded after reading the full text due to the existence of articles with more updated information for the development of the evidence matrix. Finally, the MCDA value framework was populated with information from 33 publications as represented on a PRISMA flow diagram²⁷ as shown in figure 1.

Scoring results and participants insights

Scores obtained for each of the quantitative criterion of the evidence matrix comparing olipudase alfa with placebo are shown on figure 2. Scoring results for contextual criteria are shown on figure 3.

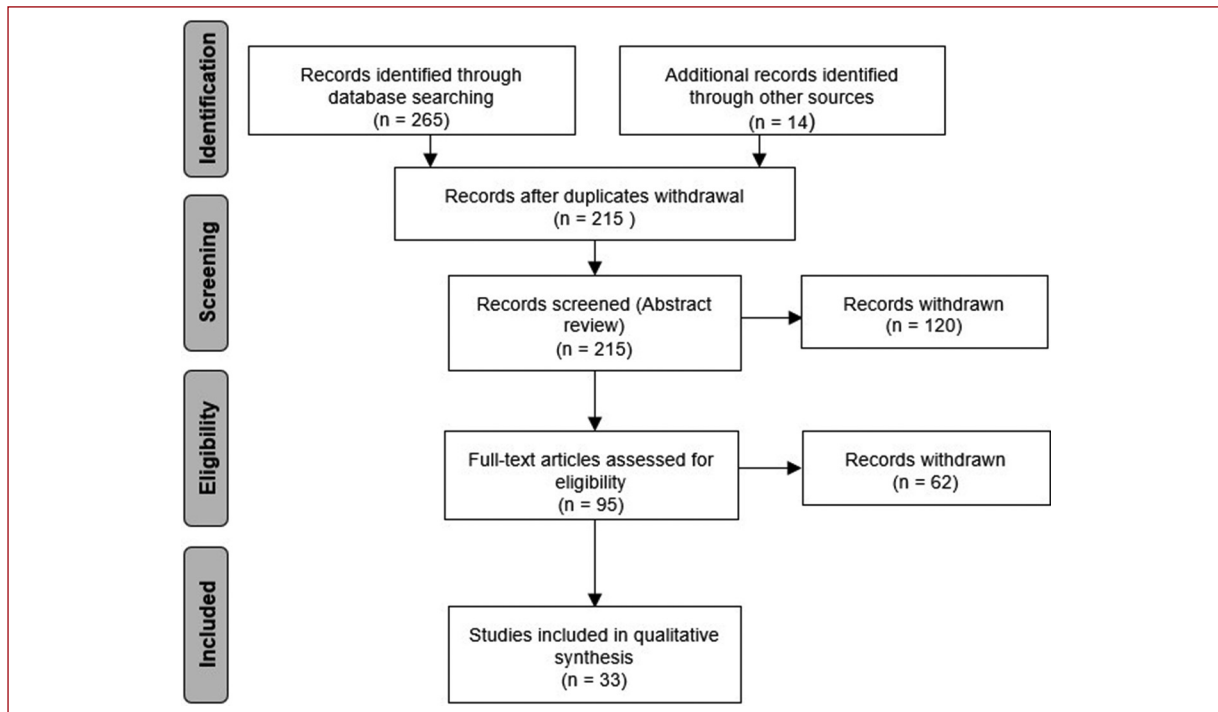


Figure 1. Prisma flowchart showing the diagram results of the literature review.

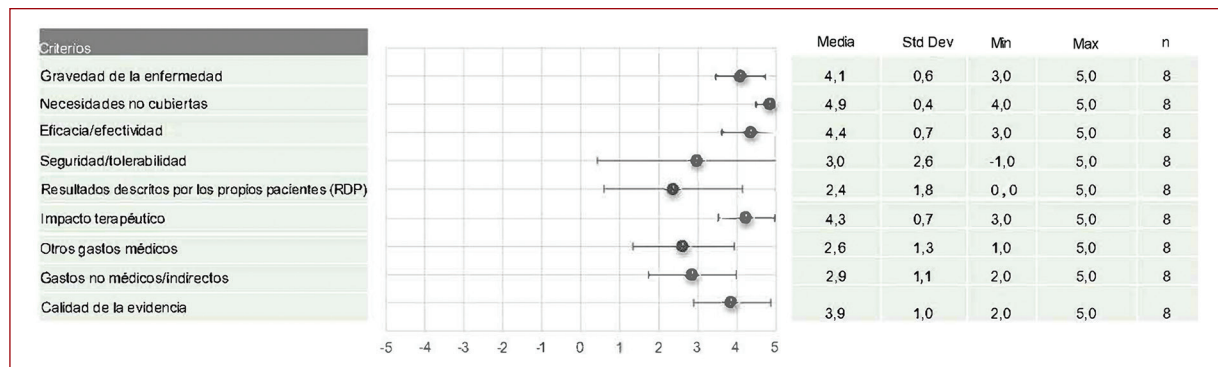


Figure 2. Scoring results of the quantitative criteria of olipudase alfa vs placebo. Dots correspond to the mean of the scores and bars show the SD.

Disease-related criteria

DISEASE SEVERITY

ASMD is perceived as a severe disease (4.1 ± 0.6) due to both neurological and non-neurological clinical manifestations such as liver, spleen, and lung diseases that significantly contribute to the burden and severity of the disease^{4,6}. Experts considered –with a high degree of consensus that– ASMD has a high impact on morbidity and mortality. Severe liver disease and respiratory failure are the leading causes of death in

pediatric and adult patients with ASMD with a mortality rate of 17%^{3,28,29}. In addition, ASMD impacts both the patient and the caregiver's quality of life at a physical, psychological, and emotional level^{2,30}.

UNMET NEEDS OF THE DISEASE

All participants agreed that there is a therapeutic unmet need for the treatment of the non-neurological manifestations of ASMD (4.9 ± 0.4), as the current treatment is purely symptomatic⁵. It is remarkable that 7 out of 8 participants (88%) scored this criterion with the highest score possible.

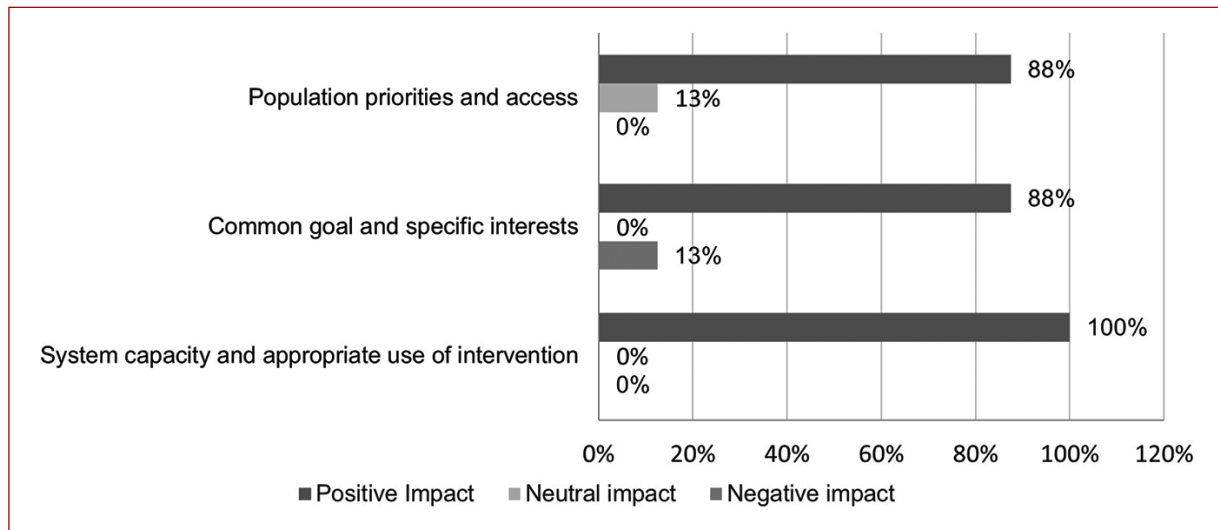


Figure 3. Percentage of participants who considered that the addition of olipudase alfa for the management of the non-NCS manifestations of acid sphingomyelinase deficiency would have an impact (positive, neutral, or negative) on each of the contextual criterion of the adapted multi-criteria decision analysis framework.

Treatment-related criteria

EFFICACY-EFFECTIVENESS

Participants considered olipudase alfa to be more effective compared to symptomatic treatment and placebo (4.4 ± 0.7). Half of the participants (4 out of 8) scored this criterion with the highest score. According to participants, olipudase alfa produces a significant improvement in all clinically relevant parameters studied reducing spleen volume and improving lung function, in both adult and pediatric patients^{9,11}. Experts considered the variables measured in the clinical trials to be related and relevant to the disease.

SAFETY-TOLERABILITY

Most participants considered the adverse events (AEs) associated with olipudase alfa to be manageable and highlighted its good safety profile (3.0 ± 2.6). Treatment was considered well tolerated, as most of AEs were mild to moderate without any treatment-related serious AEs nor AE-related discontinuations in either pediatric or adult patients^{9,11}. High dispersion is observed in this criterion. Although the participants' safety perception was similar as seen in their rationales, some participants scored this criterion comparing olipudase alfa vs placebo (lower scores) while other participants considered the general safety profile of olipudase alfa (higher scores).

THERAPEUTIC IMPACT

Most participants considered the treatment with olipudase alfa to significantly modify the course of the disease, therefore considering the therapeutic impact in ASMD as very relevant (4.3 ± 0.7). Olipudase alfa was shown to reverse multisystemic clinical features of ASMD resulting in clinically relevant improvements that would reduce the burden of the disease, with the potential to improve survival^{7,9,11}.

PATIENT REPORTED OUTCOMES (PROs)

Most participants agreed that the limited evidence published to this date on PROs is not sufficient to conclude how the effect of olipudase alfa treatment impacts the patient's quality of life, granting a score of 2.4 ± 1.8 . However, some of the participants considered that olipudase alfa may have a positive impact positively in patients' quality of life based on the efficacy and safety results, as well as considering their own clinical experience.

OTHER MEDICAL COSTS (EXCLUDING PHARMACOLOGICAL COSTS)

Participants considered that olipudase alfa could have a positive impact reducing other medical costs associated with patients with ASMD (2.6 ± 1.3). Although little evidence was available, participants considered

that the higher efficacy and acceptable safety and tolerability profile of olipudase alfa could be translated into important savings for the Spanish NHS translated into fewer and shorter hospitalizations, emergency room visits, outpatient visits, surgical procedures, and use of medicines associated with ASMD.

Non-medical/indirect costs

Overall, participants considered that treating patients with olipudase alfa would have a positive impact on non-medical/indirect costs (2.9 ± 1.1). Although little evidence is available, participants agreed that working age patients treated with olipudase alfa would be able to work, thereby improving productivity. The burden of ASMD on caregivers or relatives would also be reduced. This could be enhanced by providing a home support program for lysosomal diseases.

Quality of Evidence

The quality of evidence for olipudase alfa was considered high by all participants (3.9 ± 1.0). Most participants considered that the studies supporting olipudase alfa, both the ASCEND⁹ and the ASCEND-Peds¹¹, are well-designed, with a low risk of bias considering the characteristics of a rare disease. The forthcoming publication of long-term efficacy and safety results had a positive impact on their score.

Contextual criteria

Scoring results from contextual criteria are shown on figure 3.

Population priorities and access

Most participants (88%) considered that the use of olipudase alfa would have a positive impact, which is fully consistent with the priorities of current national health system. One participant considered that its impact would be neutral since, although there are specific strategies for rare diseases³¹⁻³⁴, there is no clear priority for this drug, assuming it would suppose a significant budgetary impact.

Common goal and specific interests

The introduction of new medicines to treat ASMD would have a positive impact according to expert ratings (88%). However, 1 participant considered that this

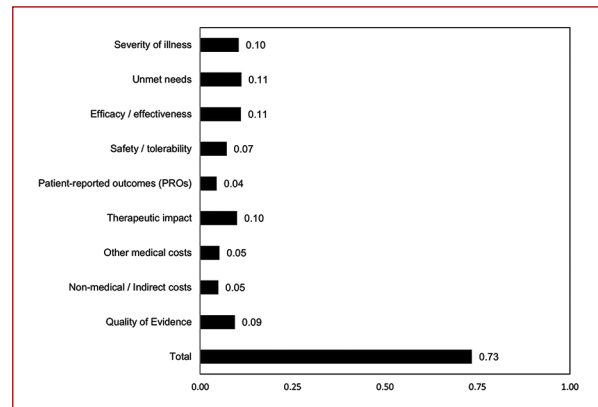


Figure 4. Global value contribution of olipudase alfa vs placebo to treat non-nervous central manifestations of acid sphingomyelinase deficiency.

would have a negative impact as the Spanish authorities have some reservations when it comes to funding high impact drugs.

System capacity and appropriate use of the intervention

All experts (100%) considered olipudase alfa as a new therapeutic option for the non-CNS manifestations of ASMD. In addition, all participants agree that the NHS is sufficiently prepared to ensure the appropriate use of olipudase alfa as it already has some experience using other lysosomal enzyme therapies and there are health professionals with expertise in these types of diseases.

Global VC of olipudase alfa

The global VC of olipudase alfa vs placebo is shown on figure 4.

The global VC of olipudase alfa to treat ASMD is perceived as positive compared to placebo (score, 0.73). Overall, olipudase alfa was considered to add value to all the criteria included in the framework from the perspective of all stakeholders.

Reproducibility assessment

Consistency of the scoring was explored by performing a retest of the same analysis 1 week after the discussion session. Change of scoring was allowed between analyses, to assess how the arguments of the discussion and, therefore, data interpretation may

Table 1. Results of the test-retest analysis using the Spearman's rank correlation coefficient

Criteria	Test value scoring		Retest value scoring		Spearman's rank correlation coefficient
	Mean	SD	Mean	SD	
Disease severity	4.1	0.6	4.3	0.5	0.873
Unmet needs	4.9	0.4	5	0.0	1
Efficacy/effectiveness	4.4	0.7	4.5	0.8	0.843
Safety/tolerability	3	2.6	4.1	0.6	0.756
PROs	2.4	1.8	1.6	1.6	0.756
Therapeutic impact	4.3	0.7	4.4	0.7	0.850
Other medical costs	2.6	1.3	2.9	1.2	0.379*
Non-medical/indirect costs	2.9	1.1	3.3	0.5	0.810
Quality of evidence	3.9	1.0	3.9	1.0	0.7534
Overall criteria value scoring	-	-	-	-	0.9833

*NS: not significant; PRO: patient reported outcomes.

influence criteria scoring. Results of the retest reliability analysis and Spearman's rank correlation coefficient are shown on [table 1](#).

Global criteria scoring was consistent between the analyses performed, with a correlation coefficient of 0.98. Nevertheless, when the scores were analyzed per each particular criterion, lower correlation coefficients (< 0.8) were seen for the following criteria: "Safety/tolerability" (0.756), and "Other medical costs" (0.379), with slightly higher mean value scores, "Quality of the evidence" (0.753), with same mean value scoring, and the "PROs" criterion (0.756), with lower mean value scores. The VC of olipudase alfa in the retest was 0.77.

Discussion

Olipudase alfa has been compared to the symptom-based treatment of ASMD using reflective MCDA methodology by a multidisciplinary panel of experts experienced in the management of ASMD and decision making, including a patient's representative. The adapted framework to the context of OD was selected and adjusted for 12 criteria relevant to the context of ASMD.

The results suggest that olipudase alfa provides a high value for the management of the non-CNS manifestations of ASMD. Hence, the overall value score of olipudase alfa was 0.73. A total of 3 criteria contributed the most to the value of olipudase alfa: "Disease severity", "Unmet needs", and "Efficacy/effectiveness". The

criteria that contributed to a lesser extent were "PROs" and "Non-medical/indirect costs".

ASMD was perceived as a severe disease with a high unmet need for effective treatment. There was a broad consensus regarding the improvements in efficacy and therapeutic impact that olipudase alfa provides. However, long-term data are limited and therefore the impact on survival cannot yet be determined. Regarding the criterion "Safety/tolerability", there was general consensus that olipudase alfa has a good safety profile, with manageable AEs (mild to moderate) and no drop-outs during the study. Regarding PROs, most patients agree that the current evidence is limited, nevertheless, due to its efficacy and safety profile, participants perceived that it would have a positive impact on the patients' quality of life. Regarding direct and indirect costs, experts considered that the use of olipudase alfa would have a positive impact by reducing the number of hospitalizations and improving productivity.

Concerning contextual criteria, participants agreed that there is a certain degree of sensitivity towards orphan diseases in Spain, as well as a positive impact on priority access, as an important therapeutic gap would be covered in patients with ASMD on olipudase alfa. In addition, participants considered that the national health system is sufficiently prepared to guarantee its appropriate use as it has previous experience in enzymatic replacement therapies for lysosomal diseases.

Medical decision-making has an additional level of complexity because it is influenced by several non-clinical factors and perceptions³⁵. This is reflected in the higher dispersion observed in the scoring of some criteria like “Safety/tolerability”, “PROs” or “Other medical costs”. In these criteria, the scores varied considerably among participants due to differences in the perception and/or interpretation of data. For instance, some participants scored the “PROs” criterion based on their clinical experience on top of the evidence included in the matrix. In the “Safety/tolerability” criterion, some participants compared the safety profile of olipudase alfa to placebo giving low or negative values to this criterion while others assessed the safety and tolerability profile based on olipudase alfa clinical trials giving high scores to these criteria. In the criterion “Other medical costs”, some participants highlighted in the discussion that although few evidence was available, both the safety and efficacy profile of olipudase alfa would be translated into direct costs saving thanks to fewer and less severe complications.

We should mention that the Spearman’s correlation coefficient for these criteria showed that scores given by participants in the retest analysis varied after reaching consensus in the discussion session, thus decreasing the dispersion observed in the first analysis (Table 1). For example, in the Safety/tolerability criterion there was a large dispersion in the first scoring due to different perceptions, giving different scores to similar rationales. Thanks to the reflective capability of the MCDA methodology, the differences seen in the perceptions of the experts were harmonized increasing agreement among participants. Therefore, the scores in the retest reliability analysis showed less variability. These results highlight the positive impact of the reflective discussion among participants on the perception and interpretation of data, highlighting whether retest should be performed routinely in the healthcare setting.

MCDA is increasingly being used for the evaluation of OD and rare diseases^{14,17-19,36}. For instance, Guarga et al.²³ developed an MCDA framework for the assessment of OD in the Catalan Health System. Also, the Rare Diseases and OD Working Group of the Spanish Society of Hospital Pharmacy (Orphar-SEFH) uses the MCDA methodology to draft the Assessment Reports in OD²².

Several studies have been published regarding the use of reflective MCDA to assess the VC of drugs in the management of hematological and non-hematological diseases^{18,20,21,37,38}. Olipudase alfa, a new drug for the management of the non-CNS manifestations of ASMD, has one of the highest VC s found in the literature.

A high VC for olipudase alfa could be explained by the lack of available therapeutic alternatives for a severe disease such as ASMD, therefore with relevant unmet needs regarding efficacy and considering the positive therapeutic impact of olipudase alfa for the management of ASMD.

This study is no stranger to limitations. The first limitation would be the number of experts included in the expert panel (n = 8). Nevertheless, experts included have extensive experience in the management of ASMD and decision making. Also, a small panel sized facilitates discussion obtaining a more detailed analysis of the VC of olipudase alfa in each criterion. We should also mention that the patient perspective was considered in the study, as a patient’s representative was included in the expert panel. As in all MCDA studies, the results depend, to some degree, on the composition of the expert panel, on their value judgments, and experience. To mitigate the risk of bias, training on MCDA methodology was provided to all participants before the scoring, and a test-retest reliability analysis was conducted to assess the reproducibility and consistency of the results only 1 week after the workshop session. Moreover, the lack of evidence in the literature for some criteria is also a limitation. Therefore, a follow-up to this the study when additional studies and long-term data become available would be required.

Conclusions

These results show the high added value of olipudase alfa for the management of the non-CNS manifestations of ASMD from a multidisciplinary perspective. The reflective and clarifying ability of the MCDA has proven to be a useful tool in decision-making regarding newly available treatments for rare diseases. Treatment with olipudase alfa could significantly improve the clinical course of ASMD, a life-threatening disorder whose non-neurological manifestations produce a high disease burden for both the patients and their families.

Funding

This study was developed by Omakase and funded by Sanofi.

Conflicts of interest

JV has received honoraria for talks, travel grants, and for being a member of Sanofi and Takeda advisory boards and has received research funding from Sanofi.

MRA has received speaking fees from Janssen, Sobi, Galapagos, Abbvie, Ipsen, Biogen, CSL Behring, Takeda, and has participated in MCDA analyses funded by Zogenix, Biomarin and Sanofi. AGM has received honoraria for his participation in scientific meetings and advisory boards from Sanofi, as well research funding from Sanofi. EG has received honoraria for consultant/advisory panel activities for Sanofi, and research support from Sanofi and Takeda, and for being involved in training activities in lysosomal diseases also Sanofi and Takeda. Also, he has declared registration and travel fees for participating in congresses/conferences held by Sanofi, Takeda, Pfizer, and GSK. JLP declared no conflicts of interest related to this article. JLT has received funding for being involved in presentations/professional meetings for 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. MRA, AGM, EG, JLP, JLT, and JV received funding from Sanofi related to the hours dedicated to this project. MB, AG, and XB work for Omakase Consulting, which have received funding from Sanofi to develop this project.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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