Assessing the Value of the Enzyme Replacement Therapy for Hypophosphatasia (HPP): A Spanish Sub-analysis of a Pan-European Multidisciplinary Multi-Criteria Decision Analysis (MCDA)

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BACKGROUND AND OBJECTIVE

- **Hypophosphatasia (HPP)** is a **rare**, **inherited**, **chronic**, **metabolic**, **systemic** disease caused by deficient activity of tissue-nonspecific alkaline phosphatase (ALP). This deficiency leads to multiple-organ involvement (skeletal, muscular, respiratory, neurological, renal, rheumatic, and dental), with a significant impact on patients' quality of life (QoL) [1–4]. HPP affects individuals across **all age groups**, presenting with a **wide spectrum of clinical manifestations** [5,6].
- Historically, treatment has been based on **supportive and symptomatic care**, including: respiratory support, pain management, fracture care, physical therapy, dental care, nutritional support, and vitamin B6[7,8].
- **Enzyme replacement therapy (ERT)** offers a **targeted treatment approach** for HPP, addressing the underlying disease cause. Asfotase alfa (Strensiq®) is an ERT that was approved by the European Medicines Agency (EMA) for the treatment of HPP in 2015. However, reimbursement decisions vary across countries. As of July 2018, Spain had not approved public funding for asfotase alfa in HPP.
- The **multiple-criteria decision analysis (MCDA**) has been used to improve disease understanding, identify unmet needs, and guide treatment decisions [9-11]. This sub-analysis aims to **identify the value provided by asfotase alfa to HPP patients from a Spanish multi-stakeholder perspective**.

METHODOLOGY

- The study followed the **MCDA good practice guidelines** and the **rare diseases framework**: multidisciplinary panel (n=12), literature review to collect the most relevant evidence, criteria weighting to identify decision-making priorities, value assessment through intervention scoring, and weighted added value assessment.
- The study considered the standard of care in the absence of asfotase alfa (best supportive care) versus asfotase alfa use for patients with HPP.
- This sub-analysis presents the **Spanish perspective on clinical value**, including the results provided by six Spanish experts who participated (2 clinicians, 2 patient advocates, and 2 evaluators). Given the small panel size, findings should be interpreted with caution regarding generalizability.

RESULTS

Criteria Weighting

- "**Disease severit**y" (Rank 1) and "**efficacy/effectiveness**" (Rank 2) were consistently ranked among the highest-priority decision criteria in HPP by the Spanish experts.
- Most of the criteria were weighted above 4 points, **being considered as very relevant in decision-making regarding HPP treatment.**
- No relevant differences were shown across stakeholder profiles.
- The weighting results were aligned with the pan-European panel perception.

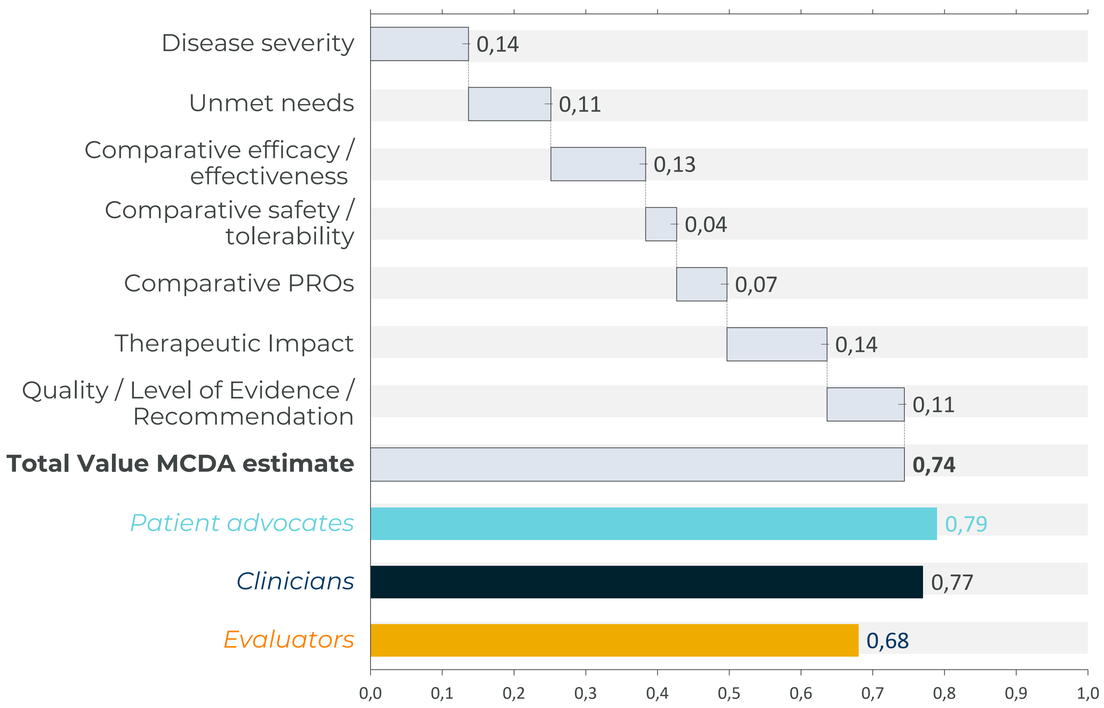
Criteria weighting results in HPP

		5-Point	100-Point	Rank	Key considerations
Hypophosphatasia	***Disease Severity***	4.7 ±0.5	18.5±3.9	1	• HPP was associated with a high disease burden, with the greatest concerns at an early age.
	Unmet Need	4.0±0.6	13.2±5.1	7	• Limited disease awareness, delays in diagnosis and lack of access to disease-modifying treatments.
New treatment comparison	***Efficacy/Effectiveness***	4.5±0.5	18.3±6.1	2	• Patients should initiate treatment when efficacy/ effectiveness criteria indicate a positive benefit-risk balance.
	Safety/Tolerability	4.2±0.8	15.5±3.4	3	• Tolerability is linked to the disease burden and the disability level of the patient.
	Patient-Reported Outcomes	3.5±0.8	9.2±10	6	• PROs are considered less relevant than mortality and morbidity measures.
New treatment	***Therapeutic Impact***	4.2±1.0	15±3.2	4	• New treatment should provide benefits in terms of disease progression and QoL.
	Quality of Evidence/ Level of Recommendation	4.2 ±1.2	10.3±3.3	5	• For decision-making in HPP, long-term data, RWE and GRADE assessments are important.

Criteria Scoring

- HPP was perceived as a **severe, progressive, high-burden disease** affecting individuals of all ages.
- There is an **urgent need** for treatments that address disease progression, ensure efficacy across diverse patient profiles, and maintain a favorable safety profile, particularly given the lack of funded options in Spain that can modify the disease course.
- Asfotase alfa was considered to offer better **efficacy/effectiveness** versus BSC, and it was perceived as a potential "life-changing" option for patients with a high clinical burden. It demonstrated improved **patient-reported outcomes (PROs)**, particularly in infants and children (CHAQ and PedsQL).
- The **safety** profile was **consistently perceived as favorable**, balancing the impact of disease manifestations and treatment-benefit.
- Spanish experts, regardless of stakeholder profile and aligned with the pan-European panel perception (data not shown), considered asfotase alfa to have **demonstrated therapeutic benefits across the diverse patient spectrum, supported by robust and consistent clinical data.**

Value contribution of asfotase alfa versus Best Supportive Care in HPP



CONCLUSION

- In the Spanish context, experts concluded that asfotase alfa offers superior value compared to the BSC (0.74). This value contribution is even much **higher than that reported in other recently financed drugs for rare diseases**, ranging from 0.44 to 0.63. This reinforces its status as a **potentially transformative therapy for HPP** and will inform future decisions regarding access, reimbursement, and policy in Spain.

References:
1. Conti F, et al. Clin Cases Miner Bone Metab. 2017;14(2):230. doi:10.11138/CCMBM/2017.14.1.230; 2. Salles JP. Clin Biochem Rev. 2020;41(1). doi:10.33176/AACB-19-00031; 3. Szabo SM, et al. Orphanet J Rare Dis. 2019;14(1). doi:10.1186/s13023-019-1062-0; 4. Högler W, et al. BMC Musculoskelet Disord. 2019;20(1). doi:10.1186/s12891-019-2420-8; 5. Bishop N. Clin Cases Miner Bone Metab. 2015;12(2). doi:10.11138/ccmbm/2015.12.2.170; 6. Weber TJ, et al. Metabolism. 2016;65(10). doi:10.1016/j.metabol.2016.07.006; 7. Kishnani PS, et al. Orphanet J Rare Dis. 2024;19(1). doi:10.1186/S13023-024-03048-6; 8. Varni JW, et al. Ambul Pediatr. 2003;3(6):329-341. doi:10.1367/1539-4409(2003)003<0329:TPAAPP>2.0.CO;2; 9. Badia X, et al. Expert Opin Orphan Drugs. 2019;7(7-8):363-372. doi:10.1080/21678707.2019.1652163; 10. Orphar-SEFH grupo. MCDA orphan drugs in Spain 2018-2022. [Report]; 11. Romaniuk P, et al. Front Public Health. 2018;6:287. doi:10.3389/fpubh.2018.00287

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