Cost-utility analysis of pegunigalsidase-alfa compared to agalsidase-alfa and agalsidase-beta for the treatment of adult patients with Fabry Disease in Greece

EE 307

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Introduction

- Anderson-Fabry Disease (FD) is a rare, progressive X-linked lysosomal storage disorder leading to significant morbidity (1). It is caused by mutations in the GLA gene, which results in deficiency of the α-galactosidase A (α-Gal A) enzyme and subsequent accumulation of globotriao-sylceramide (Gb3) in lysosomes (1,2).
- Current ERTs, agalsidase-alfa and agalsidase-beta can lead to clinically relevant improvements in natural disease course, improving morbidity and mortality, although disease progression occurs in some cases (3). Infusion-related reactions (IRR) are also possible and may result in treatment discontinuation. In addition, their administration may induce the production of anti-drug antibodies (ADAs), limiting treatment efficacy and long-term benefits of the treatment (4-7). Migalastat, an oral pharmacological chaperone is also indicated for FD patients who have an amenable mutation.
- The emergence of a new treatment that provides sustained efficacy, improved safety, and reduced immunogenicity, leading to a low risk of ADA development is of utmost need.
- Pegunigalsidase alfa, approved in the EU and USA, is a PEGylated α-Gal A ERT with prolonged half- life, and designed to have reduced immunogenicity and potentially improved tolerability (8-10).

Objective

- This research aims to assess the cost-utility of pegunigalsidase-alfa compared to agalsidase-alfa and agalsidase-beta for the treatment of adult patients (≥18 years) with FD in Greece.

Methods

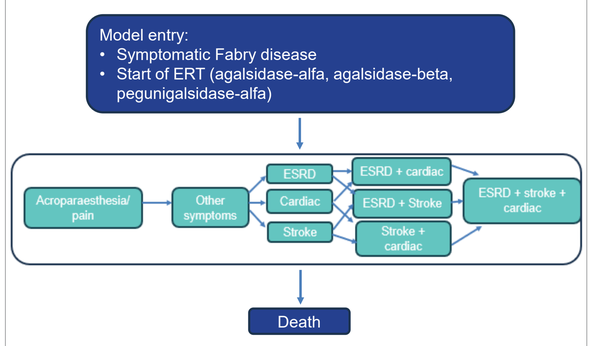
- A global cost-utility Markov model was adapted to compare pegunigalsidase-alfa with agalsidase-alfa and agalsidase-beta from the Greek National Health Sickness Fund (EOPYY) perspective, over a lifetime, with annual cycle length and applying 3.5% discount rate on cost and health outcomes.

  – The model includes the following health states along with their combinations: acroparesthesia/ pain, other symptoms (see footnote at Figure 1), end stage renal disease (ESRD), cardiac complications, stroke, and death (11) (Figure 1).

  – Within each health state there is a series of possible events, whereby the distribution of these events contributes to the costs associated with the respective health state.

  – Health outcomes are captured by each health state representing a category of complications that occur with FD.
- Migalastat, an oral treatment option for FD in patients over 16 years of age with an amenable mutation was excluded from this analysis given that the comparable population is limited to patients with amenable mutations and the uncertainty surrounding indirect treatment comparison results (12).
- A network meta-analysis (NMA) and simulated treatment comparison (STC) was conducted to assess effectiveness across all ERTs (12).
- A structured resource use questionnaire was developed to validate global data where necessary and to assess local inputs from Greek nephrology and neurology experts.
- Health outcomes were expressed in quality-adjusted-life-years (QALYs), whereas costs were expressed in euros, 2024 values (€, 2024)
- Cost parameters included: drug acquisition cost, administration cost, health state management and management of adverse events (AEs).
- The base-case cost utility analysis, the incremental costs and incremental QALYs were assessed to calculate the incremental cost-effectiveness ratio (ICER).
- Scenario analyses with different time horizons, discount rates, sources from utilities, treatment-experienced patient population were explored.
- In order to account for first-order uncertainty on input parameter values, a one-way deterministic sensitivity analysis (DSA) was performed. The parameters varied by 20% to derive the upper and lower values.
- Probabilistic sensitivity analyses (PSA) was performed to explore uncertainty in the results with 1,000 iterations (Figure 4).

Figure 1. Model structure



Acroparesthesia/pain: Neuropathic pain in the extremities; **Other symptoms:** Clinical signs and/or symptoms of left ventricular hypertrophy, chronic kidney disease stage 1-4, or white matter lesions **ESRD:** Chronic kidney disease stage 5, dialysis, or kidney transplant, **Cardiac complications**: Atrial fibrillation, any other rhythm disturbance needing hospitalization, pacemaker or implantable cardiac defibrillator implantation, cardiac congestion requiring hospitalization, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft

Model Inputs

- **Patient characteristics** were sourced from BALANCE (3) and were validated by Greek clinical experts. At baseline; mean starting age: 44.5, mean weight: 79 kg and proportion male: 61.3%.
- **Baseline patient distribution** at diagnosis, across health states was sourced from Greek clinical experts to depict Greek patient population (Table 1).
- **Clinical inputs:** Given the short follow-up of BALANCE trial (two-years), it was not possible to use the trial data to estimate the transition probabilities. The transition probabilities were sourced from Rombach et al., 2013 (11).
- Similar efficacy was assumed across all ERTs (conservative assumption), reflecting the uncertainty of the relative efficacy of pegunigalsidase alfa vs. agalsidase beta directly estimated in BALANCE trial, as well as pegunigalsidase alfa vs. other comparators indirectly estimated via NMA and STC in terms of change from baseline in estimated glomerular filtration rate (eGFR) and left ventricular mass index (LVMI).
- **Treatment-emergent adverse events (TEAEs)** of any grade occurred in >10% of patients were considered. For the pegunigalsidase alfa and agalsidase beta arms, AE rates were sourced from the BALANCE (3), whereas AE rates in agalsidase alfa arm were assumed to be the same as agalsidase beta. Additional sources on AE rates have been explored on scenario analysis (Table 4)
- **HRQoL inputs**: EQ-5D-5L data were collected and were mapped to EQ-5D-3L following NICE guidelines (13).
- **AE disutilites** as obtained from published literature were applied in AEs (14-20).
- **Mortality:** Complication-specific mortality from Rombach et al., 2013 (11) was used in addition to the adjusted age and sex mortality from the Greek life tables (21).
- **Cost inputs**: Total costs include drug acquisition costs, drug administration costs, health state costs, AE costs and terminal care.

  – The dosing schemes of intervention and comparators were based on their Summary of Product Characteristics (SPCs), with their adherence rates being sourced from BALANCE trial (3).

  – Drug acquisition costs were based on ex-factory prices accounting for all legal discounts. Ex-factory prices are published in the drug price bulletins from the Ministry of health (22,23).

  – The model included drug wastage of residual vial contents to best reflect clinical practice, based on local clinical experts. In the model base case, a simplistic approach was adopted to account for wastage: The required number of vials was rounded up to the nearest integer, with a 10% minimum threshold of dose rounding applied. When more than two vials were available, the model considered the one with the cheapest cost per mg.

  – Drug administration cost (€80) was applied in each intravenous administration, corresponding to the daycare clinic tariff (24).

  – Healthcare resource use to calculate health state costs was informed by Greek nephrology and neurology experts. It was combined with their unit costs to assess the annual health state costs at Year 1 and Year 2+ (Table 2). Specifically:

  – The cost associated with a healthcare professional (HCP) visit is estimated at €10 (25).

  – Reimbursement costs for medical exams, as sourced by EOPYY website, were used to calculate monitoring costs (26).

  – The Greek catalogue of Diagnosis Related Group (Gr-DRG) was used to calculate the hospitalization costs of symptoms and acute complications (Table 2) (27).

  – Resource utilization for the management of TEAEs in Greece was also assessed from local clinical experts. The unit cost of each AE was applied to the AE rates from BALANCE trial (3) and, in turn, the total AE cost per treatment arm, per cycle was calculated.

Table 1. Patient distribution across health states, at baseline

Health State	Distribution (%)
Acroparesthesia/pain	17.0%
Other symptoms	61.6%
ESRD	0.0%
Cardiac complications	18.1%
Stroke	3.4%
ESRD and cardiac	0.0%
Cardiac and stroke	0.0%
ESRD and stroke	0.0%
ESRD, cardiac, and stroke	0.0%
Total	**100%**

Source: Greek nephrology & neurology experts

Results

- Over lifetime, treatment with pegunigalsidase-alfa results in €2,774,411 total costs per patient, whereas treatment with agalsidase-alpha and agalsidase-beta result in €2,790,943 and €3,160,879 respectively (Table 3).
- Treatment with pegunigalsidase-alfa results in less adverse event costs compared to agalsidase-alpha and agalsidase-beta arms.
- Treatment with pegunigalsidase-alfa yielded 11.278 QALYs, whereas agalsidase-alfa/agalsidase-beta yielded 11.187 QALYs (Table 3).
- The incremental difference in QALYs (0.091) between the treatment arms was driven by lower AEs disutilities in pegunigalsidase-alfa arm.
- **Scenario analysis** showed that the base case results remain in all the scenarios, including the scenario of treatment-experienced patients (Table 4).
- **DSA** showed that in both pairwise comparisons, the drug acquisition costs would be the key drivers of the results (Figure 2, Figure 3).
- **PSA** confirmed the robustness of base case results, as the majority of iterations fell within the south-west quadrant of CE plane (Figure 4).

Figure 2. Tornado graph vs. agalsidase alpha

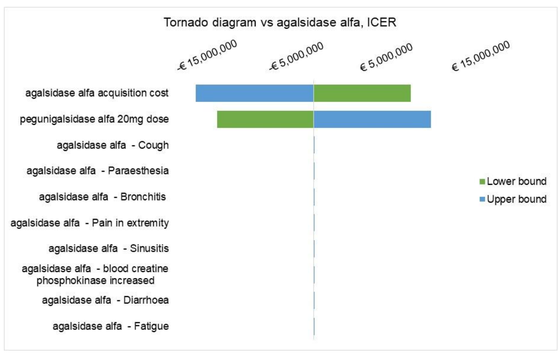
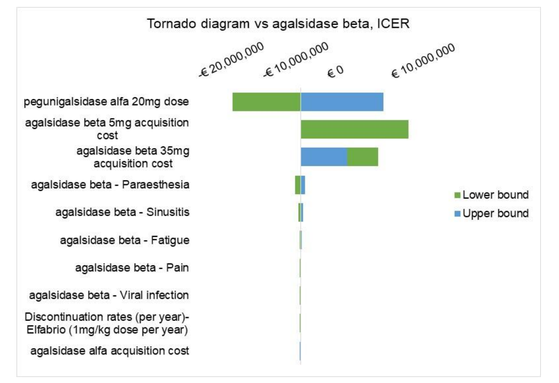


Figure 3. Tornado graph vs. agalsidase beta



Limitations

- In the absence of trial data, transition probabilities were based on the Dutch Registry. A conservative approach assumed similar efficacy across ERTs, though the Dutch data may not be generalizable to the Greek population.
- Given that wastage is the accepted method of drug administration in FD in Greece, the round-up approach was used to calculate wastage as the base-case analysis, which may increase the model's sensitivity to patient weight.

Table 3. Base-case & scenario results of the pairwise comparisons with pegunigalsidase-alfa (€, 2024)

Base case analysis

Treatment option	QALYs	Costs	ΔQALYs	ΔCosts	ICER
Pegunigalsidase alfa	11.278	€ 2,774,411			More effects & Less costs with Pegunigalsidase alfa
Agalsidase alfa	11.187	€ 2,790,943	0.091	- €16,532	
Agalsidase beta	11.187	€ 3,160,879	0.091	-€386,468	

Table 4. Scenario analyses results of the pairwise comparisons with pegunigalsidase-alfa (€, 2024)

Scenario description		Vs Agalsidase alfa	Vs Agalsidase beta
Time horizon	10 -20 - 40 years	More effects & Less costs with Pegunigalsidase alfa	
Discount rate	0% - 1.5% - 5%	More effects & Less costs with Pegunigalsidase alfa	
Utility source	Arends (28) Rombach (3)	More effects & Less costs with Pegunigalsidase alfa	
AE source for ERTs	ATTRACT (29)	More effects & Less costs with Pegunigalsidase alfa	
Exposed population	Exposed population	More effects & Less costs with Pegunigalsidase alfa	
Risk reduction	On all complications	More effects & Less costs with Pegunigalsidase alfa	
Risk reduction	On eGFR	More effects & Less costs with Pegunigalsidase alfa	
Risk reduction	Pre-treated using LVMI for risk reduction	More effects & Less costs with Pegunigalsidase alfa	

Conclusion

- Treatment with pegunigalsidase-alfa results in less costs and higher QALYs as health outcomes, compared to currently used ERTs for adult patients with FD in Greece.

Figure 4. Cost – effectiveness plane

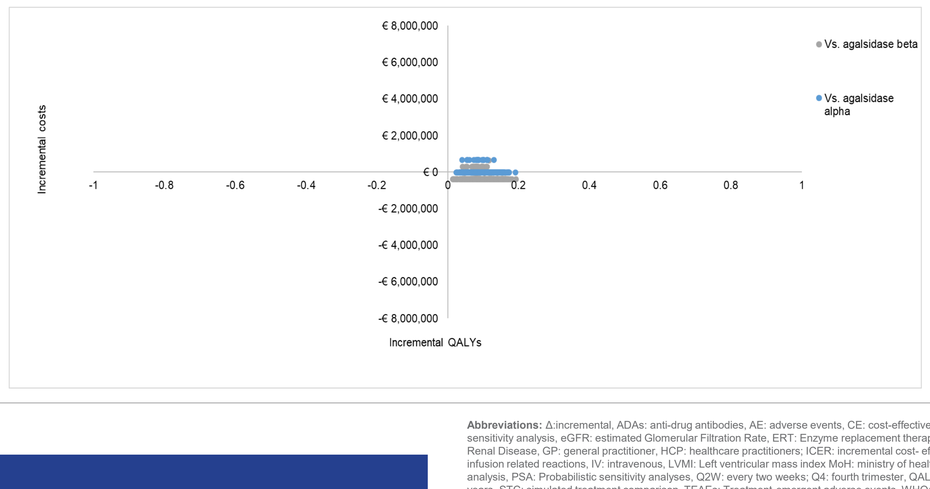


Table 2. Health State costs at year 1 and year 2+ (€, 2024)

	Year 1	Year 2+			
Health State	Hospitalisation (acute complications)	Monitoring Costs	HCP visits costs	Acute complication follow-up costs	Total Cost Year 2+
Pain	€ -	€ 277	€ 135	€ -	**€ 412**
Other symptoms	**€ 1,389**	€ 277	€ 120	€ -	**€ 397**
ESRD	**€ 5,653**	€ 277	€ 231	€ 26,618	**€ 27,126**
Cardiac complications	**€ 1,311**	€ 277	€ 231	€ 931	**€ 1,438**
Stroke	**€ 1,189**	€ 277	€ 231	€ 269	**€ 776**
ESRD & cardiac complications	**€ 6,964**	€ 277	€ 208	€ 27,549	**€ 28,033**
Stroke & cardiac complications	**€ 2,500**	€ 277	€ 208	€ 1,200	**€ 1,684**
ESRD & stroke	**€ 6,841**	€ 277	€ 208	€ 26,887	**€ 27,371**
ESRD & stroke & cardiac complications	**€ 8,153**	€ 277	€ 208	€ 27,818	**€ 28,302**

Other symptoms: white matter lesions: 35%, LVH: 40%, CKD stage 1-4: 25%;
ESRD: CKD stage 5 (100%), Renal transplant: 30%;
Cardiac complications: Atrial fibrillation/ any other rhythm disturbance needing hospitalization: 17.5%, pacemaker: 1.5%, or cardiac defibrillator implantation:0.8%, cardiac congestion requiring hospitalization: 17.5%, myocardial infarction:17.5%, percutaneous coronary intervention: 3%, or coronary artery bypass graft: 1.75%

Abbreviations: Δ:incremental, ADAs: anti-drug antibodies, AE: adverse events, CE: cost-effectiveness, DSA: deterministic sensitivity analysis, eGFR: estimated Glomerular Filtration Rate, ERT; Enzyme replacement therapies, ESRD: End stage Renal Disease, GP: general practitioner, HCP: healthcare practitioners; ICER: incremental cost- effectiveness ratio, IRR: infusion related reactions, IV: intravenous, LVMI: Left ventricular mass index MoH: ministry of health, NMA: network meta-analysis, PSA: Probabilistic sensitivity analyses, Q2W: every two weeks; Q4: fourth trimester, QALYs: quality adjusted life years, STC: simulated treatment comparison, TEAEs: Treatment-emergent adverse events, WHO: world health organization, WTP: willingness to pay

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