Poster #347

Indirect treatment comparisons of pegunigalsidase alfa vs other therapies for left ventricular mass index in Fabry disease

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Introduction

- Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by mutations in the galactosidase alpha gene, leading to α-galactosidase A (α-Gal A) deficiency and multi-organ complications[1,2]
- Left ventricular mass index (LVMi) is a key diagnostic and prognostic marker for FD-related complications, including cardiac and renal events[3,4]
- Approved treatments for FD include enzyme replacement therapies (ERTs; agalsidase alfa, agalsidase beta, and pegunigalsidase alfa)[1,2,5,6] and chaperone therapy (migalastat for amenable mutations)[1,2]
- The BALANCE trial compared LVMi outcomes for pegunigalsidase alfa and agalsidase beta, but no direct comparisons exist for agalsidase alfa or migalastat[7]
- In the absence of direct evidence, indirect treatment comparisons (ITCs) such as network meta-analysis (NMA) are used; however, due to patient heterogeneity in FD, advanced methods addressing treatment effect modifiers (TEMs) may improve ITC reliability[8-11]

Objective

- The objective of this study was to indirectly compare mean change from baseline (CFB) in LVMi for pegunigalsidase alfa with agalsidase alfa and migalastat in patients with FD by NMA and by simulated treatment comparison (STC) to adjust for TEMs and prognostic variables (PVs)

Methods

- Relevant interventional and real-world evidence (RWE) studies for FD treatments were identified via systematic literature reviews (SLRs) conducted in 2022 and updated in April 2023, following NICE and Cochrane guidelines[12,13]
- A feasibility analysis confirmed the suitability of NMA and STC to adjust for differences in trial populations including prior treatment status, migalastat-amenable mutations, and baseline LVMi
- A Bayesian NMA was conducted using Markov chain Monte Carlo (MCMC) simulation via the R2jags package in R[14,15], and unanchored STCs adjusted for differences between pegunigalsidase alfa and comparator trials[16]
  - A regression model for LVMi was fitted to individual patient data from BALANCE, PB-102-F01/F02/F03, and BRIDGE trials[17-19], including covariates such as ERT timing, sex, phenotype, baseline LVH, estimated glomerular filtration rate (eGFR), proteinuria, and migalastat-amenable mutations
- LVMi served as a proxy for LVH as comparator RCTs did not report LVH prevalence

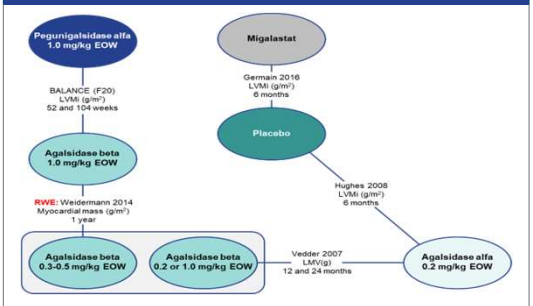
Results

- There were 56 original studies from 120 records that were identified in the interventional SLR, including 18 RCTs and 38 non-RCTs/single-arm trial studies

NMA

- After conducting a feasibility analysis of the identified interventional and RWE studies, further studies were excluded due to not meeting Population, Intervention, Comparator, Outcomes, and Study design criteria and a total of five studies (four RCTs and one RWE study) investigating ERTs, migalastat, or placebo formed the network of evidence for change from baseline in LVMi (**Figure 1**)[17,22-24]
- The RWE study, Weidemann 2014[25] linked the standard dose of agalsidase beta with lower dosages of agalsidase beta

Figure 1. Network for NMA of mean CFB in LVMi



Notes: CFB in LVMi at 52 weeks was selected from BALANCE to facilitate comparisons with agalsidase beta and alfa at similar timepoints; the network could only be connected if the standard and lower dosages of agalsidase beta were pooled, making the unlikely assumption they are equivalent in efficacy and safety; As Vedder 2007[23] reported only LVM, LVMi was estimated using the average BSA of the BALANCE cohort (1.91 m²), which included patients from the USA and European countries such as Germany and France;[17] however, Vedder 2007[23] focused exclusively on patients from the Netherlands and Norway. Given the average BSA in these regions (1.87 m²) was nearly identical to the overall BALANCE cohort, a sensitivity analysis was deemed unnecessary.

Results (continued)

- **Table 1A** displays the mean differences in CFB in LVMi for each comparator vs pegunigalsidase alfa (grey content), indicating a nominal trend favoring pegunigalsidase alfa
- On average, patients treated with pegunigalsidase alfa may experience less deterioration or greater improvement in LVMi compared to other treatments
- Since the 95% credible intervals (CrIs) of the mean differences include the null effect (0), no statistical difference in the efficacy of either treatment in terms of their effect on LVMi can be concluded
- The probability of pegunigalsidase alfa being more effective than each comparator (calculated by the number of MCMC simulations where the treatment effect of pegunigalsidase alfa is more effective than the treatment effect of each comparator) reflect these observations as all probabilities are more than 75% (**Table 1B**)
- **Figure 2** shows the sensitivity analysis excluding the RWE study, Weidermann 2014,[25] and lumping the different dosages of agalsidase beta into one node resulted in slightly or negligibly decreased mean differences, and decreased width of all corresponding 95% CrIs, reflecting the fact that the RWE study no longer adds additional uncertainty to the NMA
- While a nominal trend favored pegunigalsidase alfa, the 95% CrIs in the sensitivity analysis included the null effect, indicating no statistically significant difference in LVMi outcomes between pegunigalsidase alfa and the comparator; this is to be expected as the included trials were non-inferiority trials

Table 1. NMA results

A) Mean differences (95% CrI) in CFB in LVMi (column vs row)

	Placebo	Agalsidase alfa	Agalsidase beta (low dose)	Agalsidase beta	Migalastat	Pegunigalsidase alfa
Placebo	-	-14.11 (-49.75, 21.64)	-26.99 (-76.46, 22.42)	-31.27 (-83.63, 21.13)	-6.41 (-40.48, 27.59)	-35.13 (-87.61, 17.54)
Agalsidase alfa	14.11 (-21.64, 49.75)	-	-12.90 (-51.09, 25.18)	-17.17 (-59.58, 25.29)	7.78 (-41.44, 57.17)	-21.00 (-63.73, 21.68)
Agalsidase beta (low dose)	26.99 (-22.42, 76.46)	12.90 (-25.18, 51.09)	-	-4.30 (-24.38, 15.89)	20.59 (-39.53, 80.82)	-8.12 (-28.80, 12.64)
Agalsidase beta	31.27 (-21.13, 83.63)	17.17 (-25.29, 59.58)	4.30 (-15.89, 24.38)	-	24.85 (-37.58, 87.43)	-3.82 (-8.91, 1.26)
Migalastat	6.41 (-27.59, 40.48)	-7.78 (-57.17, 41.44)	-20.59 (-80.82, 39.53)	-24.85 (-87.43, 37.58)	-	-28.69 (-91.38, 34.01)
Pegunigalsidase alfa	35.13 (-17.54, 87.61)	21.00 (-21.68, 63.73)	8.12 (-12.64, 28.80)	3.82 (-1.26, 8.91)	28.69 (-34.01, 91.38)	-

B) Probabilities of pegunigalsidase alfa being more effective than comparators

	Placebo	Agalsidase alfa	Agalsidase beta (low dose)	Agalsidase beta	Migalastat
Pegunigalsidase alfa	90.44%	83.24%	77.82%	93.03%	81.53%

Notes: Mean differences >0 imply there is a nominal trend favoring the row treatment compared to the column treatment (i.e., on average, patients receiving the row treatment may experience less deterioration or more improvement in LVMi compared to the column treatment); if the 95% CrIs of the mean differences include the null effect (0), there is no evidence to conclude there is a difference in the efficacy of the treatments; Hughes 2008[22] did not report any associated variance measure for the mean change in LVMi; imputation was carried out using the average of the variances reported in BALANCE[7] and Vedder 2007[23] to estimate the variance of the CFB in LVMi from Hughes 2008[22]

STC

- **Figure 2** presents the results for the unanchored STCs as well as the forest plots for the NMA base case and sensitivity analysis for agalsidase alfa, placebo, and migalastat vs pegunigalsidase alfa
- No unanchored STCs were performed to compare agalsidase beta vs pegunigalsidase alfa as BALANCE[7] provides the most robust comparison

Agalsidase alfa vs pegunigalsidase alfa

- Results (**Figure 2A**) nominally favored pegunigalsidase alfa without statistical significance, aligning with trends observed in the NMA

Placebo vs pegunigalsidase alfa

- Results (**Figure 2B**) nominally favored pegunigalsidase alfa without statistical significance, aligning with trends observed in the NMA

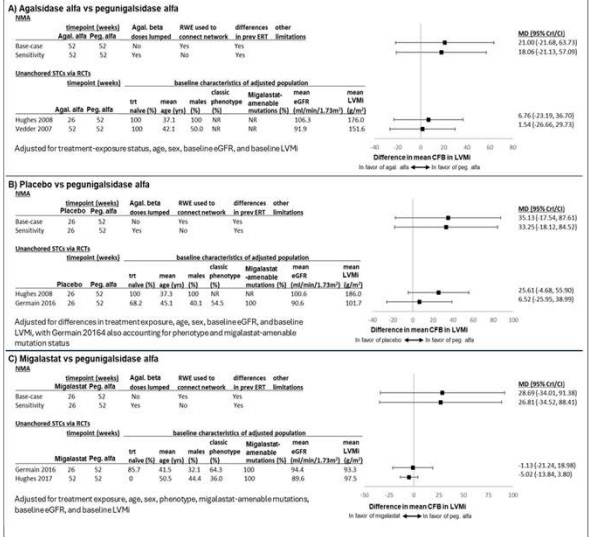
Migalastat vs pegunigalsidase alfa

- Germain 2016[24] included a mostly treatment-naïve population with migalastat-amenable mutations and evaluated the LVMi at 26 weeks
- BALANCE[7] did not report LVMi before 52 weeks for pegunigalsidase alfa, thus an unanchored STC at a mutual timepoint was not possible; however, when compared with the treatment-naïve population harboring migalastat-amenable mutations in Germain 2016[24], the mean difference nominally favored migalastat, without statistical significance
- Hughes 2017[26] allowed for a comparison at 52 weeks in a previously treated population with migalastat-amenable mutations, again showing a nominal but non-significant advantage for migalastat, which is not consistent with NMA trends

Conclusions

- **The results of this ITC, when considered alongside published clinical trial data, suggest that pegunigalsidase alfa demonstrates comparable efficacy to other treatment options for FD in terms of LVMi**
- **There were limitations associated with each method of ITC; notably, differences in trial populations, follow-up time, and limited covariate data made it difficult to conduct robust ITCs**

Figure 2. NMA and STC results



Agal. Alfa, agalsidase alfa; Agal. beta, agalsidase beta; Peg. alfa, pegunigalsidase alfa

Limitations

- The ITCs included studies from 2001 to 2022, a period during which FD management transformed considerably, and reporting of baseline characteristics was inconsistent across studies, resulting in significant challenges in assessing between-study heterogeneity
- There were differences between key TEMs (eg, timepoints and population) in BALANCE and comparator trials that violated underlying assumptions of NMA, notably:[7,22-24]
  - Pegunigalsidase alfa was directly compared with agalsidase beta in a 100% previously treated population, while ITCs vs. agalsidase alfa and placebo were informed by comparator RCTs in a treatment-naïve population, and vs. migalastat by an RCT of mostly treatment-naïve patients who harbored migalastat-amenable mutations
  - Patients in BALANCE may have been at a more advanced stage compared to comparator trials, due to the eligibility criteria on historical estimated GFR slope
- While the NMA did not account for differences in these key TEMs, the unanchored STCs attempted to adjust for these and other TEMs and PVs using a pooled set of patients who received pegunigalsidase alfa in three trials (BALANCE, PB-102-F01/F02, BRIDGE);[17-19] however, only a small proportion of these patients were treatment-naïve, and thus adjustments for differences in treatment-exposure status were uncertain
- Although the STCs attempted to adjust for differences in populations and timepoints that NMAs did not account for, they may still be biased due to unmeasured confounders or different timepoints

Abbreviations: α-Gal A, α-galactosidase A; Agal., agalsidase; BSA, body surface area; CFB, change from baseline; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; FD, Fabry disease; GL-3/GB3, globotriaosylceramide; ITC, indirect treatment comparison; LVM, left ventricular mass; LVMi, LVM index; lyso-GB3, globotriaosylsphingosine; MCMC, Markov Chain Monte Carlo; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; Peg., pegunigalsidase; PV, prognostic variable; RCT, randomized controlled trial; RWE, real-world evidence; SLR, systematic literature review; STC, simulated treatment comparison; SUCRA, surface under the cumulative ranking curve; TEM, treatment effect modifier

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