Comparing Treatment Options for Fabry Disease: Feasibility Assessment for Network Meta-Analysis

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Background

- Fabry disease is a rare genetic disorder caused by pathogenic variants of the *GLA* gene, leading to a deficiency in the lysosomal α-galactosidase A enzyme.[1]
- Disease progression can lead to premature death, commonly due to renal failure or a cardiac or cerebrovascular event.[2]
- Current treatment options for Fabry disease are enzyme replacement therapies (ERTs, including agalsidase beta, agalsidase alfa, and pegunigalsidase alfa) or chaperone therapy for a subset of patients with amenable mutations (migalastat).[3]
- Comparative studies using agalsidase alfa or agalsidase beta[4,5] have been conducted in the past; however, a network meta-analysis (NMA) summarizing all evidence has not been attempted.

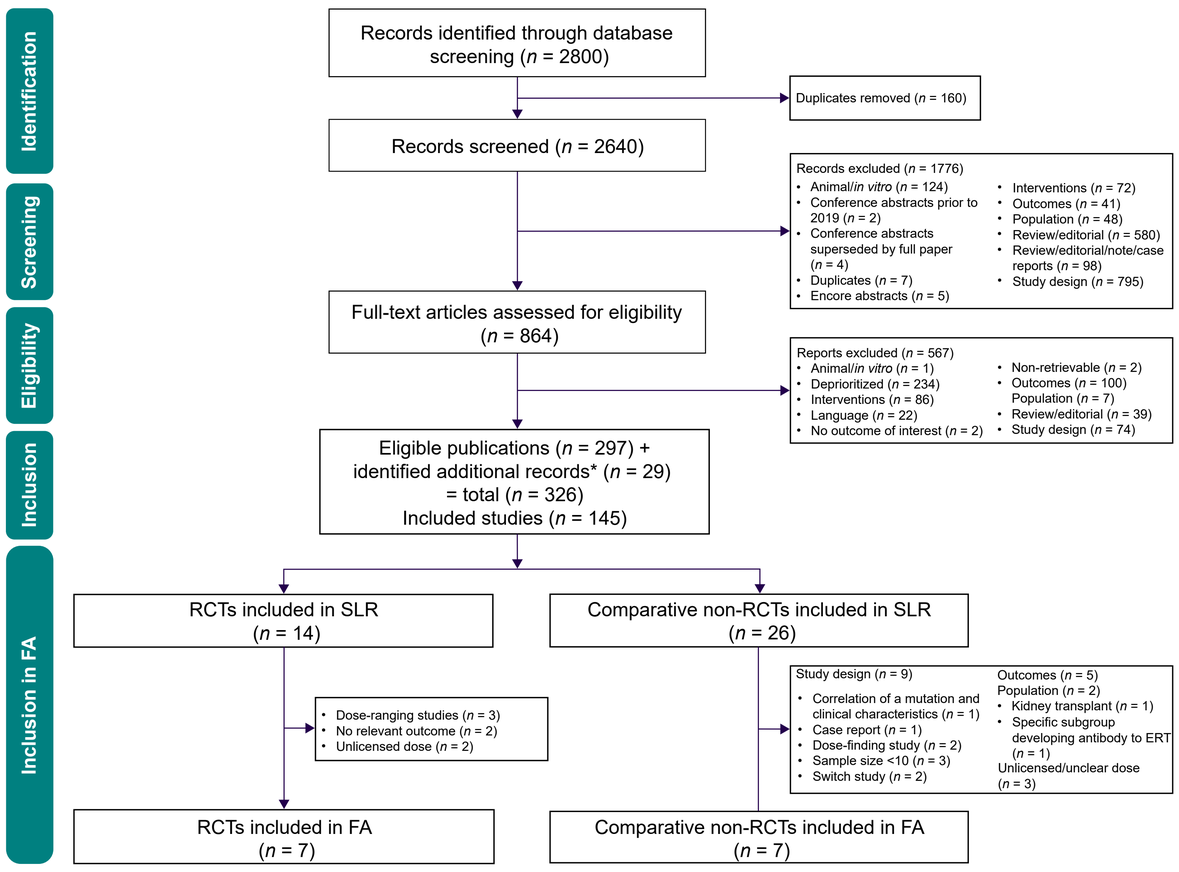
Objective

- To assess the feasibility of estimating the relative efficacy of agalsidase beta compared to other available treatments in Fabry disease by conducting an NMA.

Methods

- A systematic literature review (SLR) was conducted to identify clinical evidence on patients with Fabry disease treated with ERTs or chaperone therapy from January 2000 to August 2022 using the Embase, Medline, Cochrane Library databases, relevant conference proceedings, and Health Technology Assessment websites (Canada, England, Scotland, Wales, and the United States). The SLR included studies of any duration, irrespective of the approved doses of ERTs and chaperone therapy (**Figure 1**).

Figure 1. PRISMA flow diagram of the SLR



*Additional records identified from conference proceedings and bibliographic search.
ERT, enzyme replacement therapy; FA, feasibility assessment; *n*, number of patients; RCT, randomized controlled trial; SLR, systematic literature review

- The publications identified in the SLR were then reassessed based on eligibility criteria for feasibility assessment, described in **Table 1**. The feasibility assessment was conducted per the guidance published by Cope *et al.*[6] and the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research taskforce[7] and the National Institute for Health and Care Excellence-Decision Support Unit Technical Support Document.[8]

Table 1. Eligibility criteria for feasibility assessment for NMA

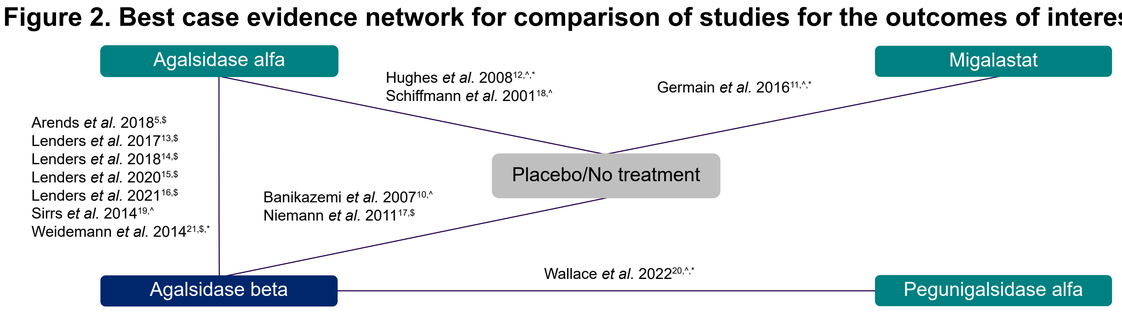
Criteria	Include	Exclude
Population	Patients with Fabry disease	Healthy volunteers and patients without Fabry disease
Intervention/ comparator	At least one of the treatment arms: agalsidase beta 1 mg/kg EoW, agalsidase alfa 0.2 mg/kg EoW, migalastat 123 mg EoD, pegunigalsidase alfa 1 mg/kg EoW or 2 mg/kg E4W	Other than the treatment of interest
Outcomes	Composite endpoint (renal, cardiac or cerebrovascular, or death), all-cause mortality, renal event, cardiac event, cerebrovascular event, CFB for Lyso-GL-3 (plasma and urine separately), eGFR, LVMI, LVPT, LVH, IVS, MSSI, BPI, EQ-5D, and SF-36; any AE, AE leading to discontinuation	Any outcome other than the outcomes of interest listed
Study design/ setting	RCTs and comparative non-RCTs	Before–after switching studies, case studies, editorials, case reports, letters, *in-vitro* studies
Others	Sample size >10	–

AE, adverse event; BPI, Brief Pain Inventory; CFB, change from baseline; eGFR, estimated glomerular filtration rate; EoD, every other day; EoW, every other week; EQ-5D, EuroQol-5 Dimensions; E4W, every 4 weeks; IVS, interventricular septal thickness; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVPT, left ventricular posterior wall thickness; Lyso-GL-3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; NMA, network meta-analysis; RCT, randomized controlled trial; SF-36, 36-Item Short Form Survey

Results

- Among the 326 publications identified during the SLR, 145 were included based on pre-defined SLR eligibility criteria.
- Only randomized controlled trials (RCTs; *n* = 14) and comparative non-RCTs (*n* = 26) of any duration identified from the SLR were evaluated against the NMA feasibility assessment criteria. A total of 26 studies were excluded from the feasibility assessment (**Figure 1**).
- Among the 14 studies included for the feasibility assessment, 13 formed a connected network (**Figure 2**). The study by Hughes *et al*. 2017[9] did not provide a connection to the other studies of interest and thus was removed from the network. Additionally, this study was not assessed further, as the interventions included in this study were not mutually exclusive categories from the interventions included in the network. This study compared ERT therapy as a whole vs placebo.
- A summary of data availability for the included studies based on the outcomes of interest is presented in **Table 2**.

Figure 2. Best case evidence network for comparison of studies for the outcomes of interest



Purple color: intervention of interest; Green color: comparators.
^RCTs; $Non-RCTs (including comparative observational studies); *Studies included in evidence network for left ventricular mass index. RCT, randomized controlled trial

Table 2. Summary of outcomes for which data were available in the included studies

Study name	Treatment arms	Composite endpoint	All-cause mortality	Any renal event	Any cardiac event	Any cerebrovascular events	Change from baseline*									
							Lyso-GL-3	eGFR	LVMI	LVPT	LVH	IVSD	MSSI	BPI	EQ-5D	Any AE	AEs leading to discontinuation
Arends *et al.* 2018[5,^]	Agalsidase alfa vs agalsidase beta	✓															
Banikazemi *et al.* 2007[10,$,&]	Agalsidase beta vs placebo	✓	✓	✓	✓	✓		✓						✓		✓	✓
Germain *et al.* 2016[11,$,&]	Migalastat vs placebo		✓				✓		✓								✓
Hughes *et al.* 2008[12,$]	Agalsidase beta vs placebo								✓								✓
Lenders *et al.* 2017[13,^]	Agalsidase alfa vs agalsidase beta						✓										
Lenders *et al.* 2018[14,^]	Agalsidase alfa vs agalsidase beta						✓	✓				✓					
Lenders *et al.* 2020[15,#]	Agalsidase alfa vs agalsidase beta							✓				✓	✓				
Lenders *et al.* 2021[16,#]	Agalsidase alfa vs agalsidase beta		✓				✓	✓									
Niemann *et al.* 2011[17,#]	Agalsidase beta vs ERT											✓					
Schiffmann *et al.* 2001[18,#,$]	Agalsidase alfa vs placebo							✓						✓			
Sirrs *et al.* 2014[19,$]	Agalsidase alfa vs agalsidase beta	✓															
Wallace *et al.* 2022[20,$]	Pegunigalsidase alfa vs agalsidase beta						✓	✓	✓				✓	✓	✓	✓	
Weidemann *et al.* 2014[21,#]	Agalsidase alfa vs agalsidase beta							✓	✓	✓		✓					

*36-Item Short Form Survey (SF-36) was not reported in any of the included studies; ^Retrospective study; $RCT; #Prospective study.
AE, adverse event; BPI, Brief Pain Inventory; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; EQ-5D, EuroQol-5 Dimensions; IVSD, interventricular septal thickness; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVPT, left ventricular posterior wall thickness; Lyso-GL-3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; RCT, randomized controlled trial

- **Table 3** summarizes the baseline characteristics of studies included in the feasibility assessment.
- The included studies were assessed for their comparability to be included in this NMA based on clinical heterogeneity, which was assessed by comparing baseline characteristics, trial designs, inclusion/exclusion criteria, and evaluation of outcome definitions (**Table 3**).
- The length of follow-up, mean age, and eGFR values varied widely among included studies (**Table 3**).
- Mean urine protein creatinine ratio (0.7–1.3 mg/dL)[10,15,19,21], left ventricular posterior wall thickness (11.1–12.7 mm)[11,12,21], serum creatinine (0.9–1.6 mg/dL)[11,16,19,21], and plasma Lyso-GL-3 (3.1 ng/mL[5], 13.9 ng/mL[11], 77.7 ng/mL[14], and 19.4 ng/mL[15]) were reported in a few studies.
- All studies included adult patients (except one[19]). Few studies included only male patients.[12–14,18] Few studies included only treatment-naïve patients[5,10,14,19] , whereas two studies[15,21] included patients who received prior ERT treatment. The remaining studies included a mixed-treated patient population (both treatment-naïve and prior-ERT-treated patients).[11–13,16–18,20]
- Among the outcomes assessed, only left ventricular mass index (LVMI) resulted in a connected network enabling comparisons across agalsidase beta, agalsidase alfa, and migalastat[11,12,20,21] but only with strong assumptions, including variations in the follow-up period (6 vs 12 months) and LVMI measurement methods (MRI[12,20] vs echocardiogram[11,21]) across studies. Thus, this analysis would have to assume a constant LVMI relative treatment effect and similarity between measurement methods (**Figure 2**).
- For all other outcomes, either the outcomes were reported in only one study, the outcome definition/ measurement method/follow-up differed greatly, the number of events was too low, or the studies did not form a connected network.

Table 3. Baseline characteristics of studies included in feasibility assessment

Study name	Treatment arms	*N*	Follow-up (months)	Age (years) mean	Male (%)	Use of ARB/ACE (%)	eGFR (mL/min/ 1.73 m²) mean
Arends *et al.* 2018[5,^]	Agalsidase alfa vs agalsidase beta	387	60.0*	NR	50.1	36.4	–
Banikazemi *et al.* 2007[10,$,&]	Agalsidase beta vs placebo	82	18.5*	45.9	87.8	35.4	52.8 (58.3)
Germain *et al.* 2016[11,$,&]	Migalastat vs placebo	50	6.0	42.8	48.0	42.0	89.0 (100.3)
Hughes *et al.* 2008[12,$]	Agalsidase beta vs placebo	15	6.0	37.2	100.0	–	103.3
Lenders *et al.* 2017[13,^]	Agalsidase alfa vs agalsidase beta	26	NR	51.0	100.0	–	–
Lenders *et al.* 2018[14,^,@]	Agalsidase alfa vs agalsidase beta	26	94.0*	44.0	100.0	26.0	109.4
Lenders *et al.* 2020[15,#,@]	Agalsidase alfa vs agalsidase beta	47	12.0*	49.0	59.6	–	77.2
Lenders *et al.* 2021[16,#,@]	Agalsidase alfa vs agalsidase beta	28	88.0*	NR	71.4	64.9	102.4
Niemann *et al.* 2011[17,#]	Agalsidase beta vs ERT	–	34.8*	43.0	57.6	30.3	98.3
Schiffmann *et al.* 2001[18,#,$,&]	Agalsidase alfa vs placebo	26	6.0	34.2	100.0	–	88.4 (99.6)
Sirrs *et al.* 2014[19,$,&]	Agalsidase alfa vs agalsidase beta	92	59.0*	47.6	40.2	54.3	79.1 (88.9)
Wallace *et al.* 2022[20,$,&]	Pegunigalsidase alfa vs agalsidase beta	77	24.0*	44.3	61.0	–	73.4
Weidemann *et al.* 2014[21,#,@]	Agalsidase alfa vs agalsidase beta	76	12.0*	45.4	56.6	–	–

^Retrospective study; $RCT; &eGFR measured using MDRD(CKD-EPI) method; @eGFR measured using CKD-EPI method; #Prospective study; *Data reported as median.
ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, chronic kidney disease epidemiology collaboration; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; *N*, number of patients

Limitations

- Only comparative studies were included in the current assessment. There is a possibility that non-comparative studies could provide additional data.

Conclusions

- Based on published evidence, an NMA comparing current treatment options for Fabry disease is not feasible due to heterogeneity among studies, especially on the outcomes included and/or their definition and/or time points evaluated. Disease heterogeneity would pose an additional layer of complexity in the analyses.
- An NMA may be feasible in the future if consistent evidence becomes available to construct a connected network.

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CONFLICTS OF INTEREST
NL, PG, DT, CSL, MM, AC, and RP-J: Sanofi employees; may hold stocks and/or stock options in the company.

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