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Matching-adjusted indirect comparisons (MAICs) and network meta-analyses (NMAs) of the oral small-molecule chaperone migalastat versus intravenous enzyme replacement therapies (ERTs) for clinical measures in Fabry disease

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Introduction

- In Fabry disease, *GLA* gene variants affect α-galactosidase A enzyme function, compromising the clearance of glycolipids.[1]
- Resultant progressive damage can lead to multiorgan involvement and potentially life-threatening cardiac, cerebrovascular and renal complications,[2] known as Fabry-associated clinical events (FACEs).[3]
- Treatment options include:
  - Intravenous ERT (agalsidase beta or pegunigalsidase alfa in Europe[4,5] and the USA,[6,7] or agalsidase alfa in Europe[8])
  - The oral small-molecule chaperone migalastat, which is approved in patients with amenable *GLA* variants and who are aged ≥12 years in Europe[9] or are adults in the USA.[10]
- ATTRACT (NCT01218659) was a Phase III 18-month randomised-controlled trial (RCT) with a 12-month open-label extension (OLE); the RCT compared migalastat with agalsidase alfa or agalsidase beta (well-established ERTs) in patients with amenable *GLA* variants.[11]
- Our objectives were to augment the direct comparisons from ATTRACT by indirectly comparing migalastat with (i) pegunigalsidase alfa (the most recent ERT) for key cardiac and renal measures using data from the RCT phase of ATTRACT, and (ii) any ERT for long-term risk of FACEs using data from the RCT and OLE phases of ATTRACT.

Methods

Study selection and data extraction

- Relevant publications and studies were identified from a published systematic literature review (SLR) of ERT and chaperone therapy in patients with Fabry disease covering January 2000 to August 2022[12] and a complementary targeted literature review (TLR) covering August 2022 to 9 January 2024 (**Table S1**).
- Clinical measures of interest included:
  - Change from baseline in LVMi with pegunigalsidase alfa
  - Annualised rate of change in eGFR slope with pegunigalsidase alfa
  - FACEs with any ERT, for which data were extracted from digitised Kaplan–Meier plots.

Indirect treatment comparisons (ITCs)

Feasibility assessment

- A feasibility assessment indicated that ITCs, including population-adjusted methods (MAICs) and standard NMAs, could be performed, with the approach taken dependent on data availability (**Table S2**).

MAIC analyses

- The LVMi and eGFR slope analyses used patient-level data for participants with amenable *GLA* variants receiving migalastat or ERT during the 18-month randomised phase of ATTRACT (the modified intent-to-treat population).
- The FACE analyses used patient-level data for participants with amenable *GLA* variants receiving migalastat during the 18-month randomised phase and/or the 12-month OLE.
- The migalastat-treated population was adjusted for between-trial differences in patient baseline characteristics.
- Matching was performed with the comparator arm study population (unanchored MAIC) or overall study population (anchored MAIC)
  - Matching variables (as available) were age, sex, ACEi/ARB use, baseline eGFR and previous ERT duration.
- ESS was calculated as:

$$\frac{\left(\sum_{i=1}^{N} w_i\right)^2}{\sum_{i=1}^{N} {w_i}^2}$$

where w_i is the weight assigned to patient i, and N is the original number of patients with patient-level data.

Model selection

- Model selection for the anchored MAICs and NMAs involved comparing the deviance information criteria (DIC) of fixed- and random-effects models; for comparable DIC values (differing by <5 points), the fixed-effects model was chosen.

Assumptions

- For the anchored MAICs and NMAs, networks rested on the assumption of similar efficacy of agalsidase alfa and agalsidase beta.

Limitations

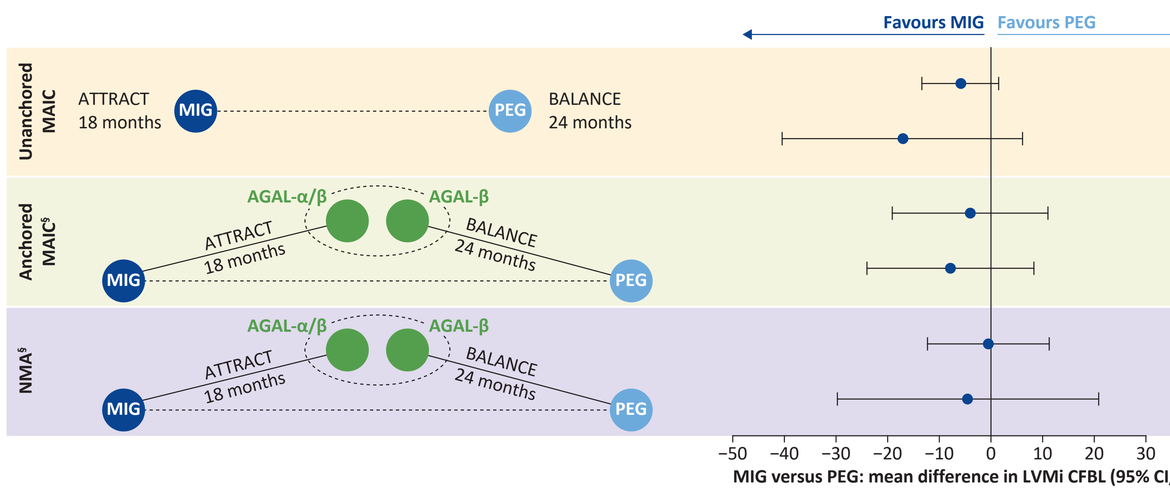
- There was little overlap between patient populations in most comparisons; this resulted in a small ESS for the MAICs and implies that the NMAs should be used for reference only.
- Data unavailability meant that matching based on *GLA* variant amenability was not feasible and FACEs could not be analysed for pegunigalsidase alfa.
- Some available data were also ambiguous. Although FACE risk was significantly lower with migalastat versus agalsidase alfa from the FOS registry, this finding should be considered with caution, as the median time to FACE derived from the digitised Kaplan–Meier curve (35.6 months) did not match that reported in the text (78.65 months).
- For the anchored MAICs and NMAs, networks rested on the assumption of similar efficacy of agalsidase alfa and agalsidase beta.

Results

- In addition to the RCT and OLE phases of ATTRACT, nine studies investigating pegunigalsidase alfa, agalsidase alfa or agalsidase beta were identified from the SLR or TLR for inclusion in the ITC analyses (two RCTs, one clinical trial with a switch-over design, three open-label clinical trials [including two OLEs] and three observational studies).[13–22]

ITCs of change from baseline (CFBL) in LVMi for migalastat and pegunigalsidase alfa

- Change from baseline in LVMi between migalastat and pegunigalsidase alfa was assessed using data from ATTRACT[11] and BALANCE[23] (**Table S3**)
  - LVMi was assessed using echocardiogram at month 18 in ATTRACT and cardiac magnetic resonance imaging at month 24 in BALANCE.

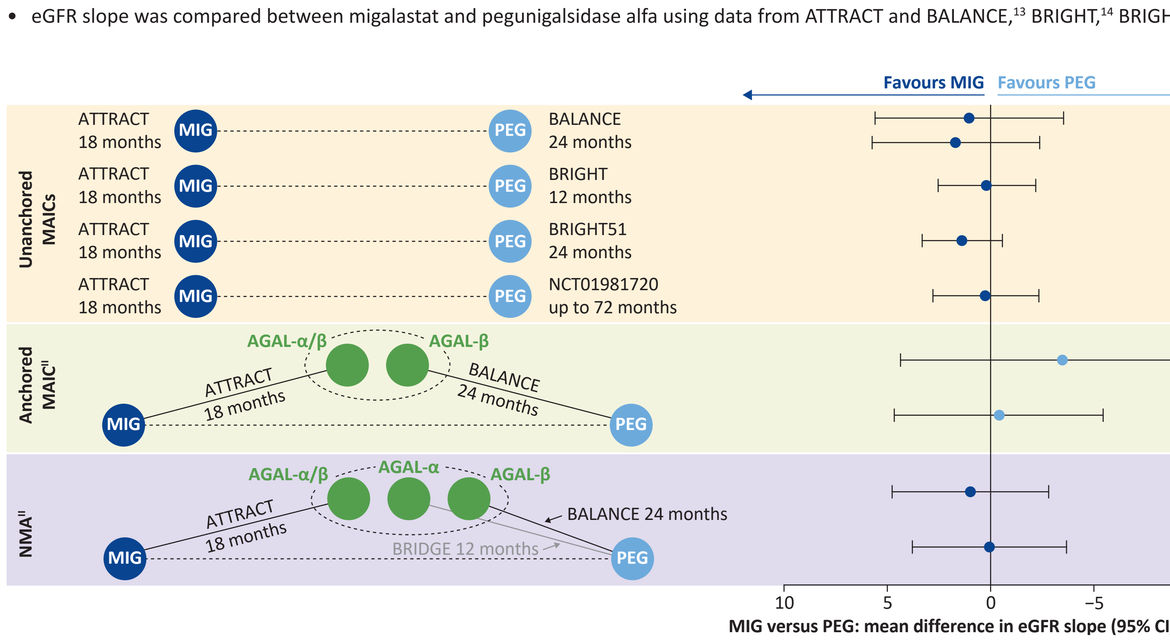


	Comparison (ATTRACT vs)	ESS	MIG versus PEG: mean difference in LVMi CFBL (95% CI/95% CrI)*
Unanchored MAIC	BALANCE (scenario 1)†	7	−5.94 (−13.38, 1.50)
	BALANCE (scenario 2)‡	3	−17.18 (−40.42, 6.05)
Anchored MAIC§	BALANCE (scenario 1)†	10	−4.06 (−19.15, 11.10)
	BALANCE (scenario 2)‡	14	−7.90 (−23.98, 8.24)
NMA§	BALANCE (all patients)	–	−0.51 (−12.30, 11.28)
	BALANCE (patients with LVH – sensitivity analysis)	–	−4.60 (−29.83, 20.81)

The left panel shows network connections, with solid lines representing direct comparisons and dashed lines representing indirect comparisons; agalsidase alfa and agalsidase beta were assumed to have similar efficacy. Times (in months) indicate length of follow-up for the analyses. The right panel shows the results. As matching using all variables resulted in a low ESS, previous ERT duration or baseline eGFR were excluded to increase ESS.†,‡
*95% CI for unanchored MAIC, 95% CrI for NMA and anchored MAIC; †Scenario 1 used age, sex, ACEi/ARB use and baseline eGFR as matching variables; ‡Scenario 2 used age, sex, ACEi/ARB use and previous ERT duration as matching variables; §DICs were comparable and therefore a fixed-effects model was chosen.
AGAL-α, agalsidase alfa; AGAL-β, agalsidase beta; CFBL, change from baseline; CI, confidence interval; CrI, credible interval; LVH, left ventricular hypertrophy; MIG, migalastat; PEG, pegunigalsidase alfa.

ITCs of eGFR slope for migalastat and pegunigalsidase alfa

- eGFR slope was compared between migalastat and pegunigalsidase alfa using data from ATTRACT and BALANCE,[13] BRIGHT,[14] BRIGHT51,[15] NCT01981720[16,17] and BRIDGE[18] (**Table S4**).

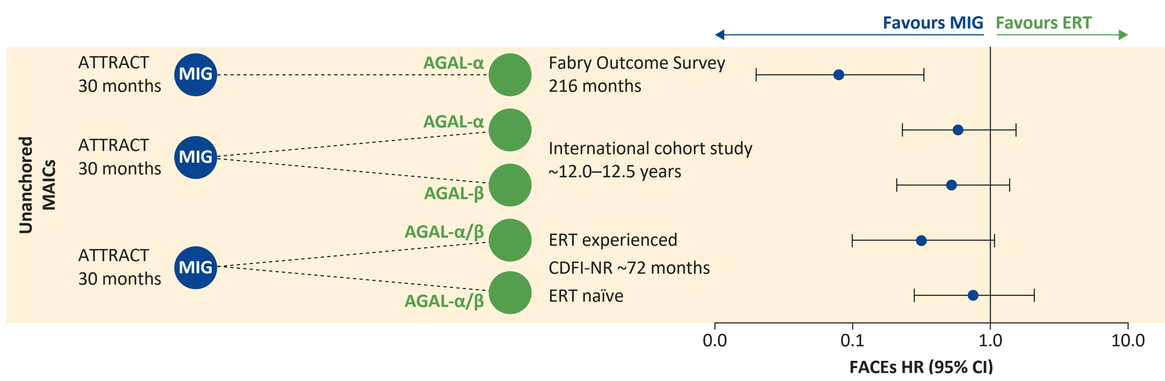


	Comparison (ATTRACT vs)	ESS	MIG versus PEG: mean difference in eGFR slope (95% CI/95% CrI)*
Unanchored MAICs	BALANCE (scenario 1)†	7	1.02 (−3.55, 5.59)
	BALANCE (scenario 2)‡	3	1.70 (−2.37, 5.76)
	BRIGHT§	13	0.17 (−2.19, 2.53)
	BRIGHT51§	14	1.37 (−0.60, 3.33)
	NCT01981720§	9	0.22 (−2.34, 2.77)
Anchored MAIC‖	BALANCE (scenario 1)†	10	−3.48 (−11.27, 4.33)
	BALANCE (scenario 2)‡	14	−0.40 (−5.45, 4.64)
NMA‖	BALANCE	–	0.97 (−2.83, 4.75)
	BALANCE and BRIDGE (sensitivity analysis)	–	0.05 (−3.69, 3.77)

The left panel shows network connections, with solid lines representing direct comparisons and dashed lines representing indirect comparisons; agalsidase alfa and agalsidase beta were assumed to have similar efficacy. Times (in months) indicate length of follow-up for the analyses. The right panel shows the results. For BALANCE, as matching using all variables resulted in a low ESS, previous ERT duration or baseline eGFR were excluded to increase ESS.†,‡
*95% CI for unanchored MAIC, 95% CrI for NMA and anchored MAIC; †Scenario 1 used age, sex, ACEi/ARB use and baseline eGFR matching variables; ‡Scenario 2 used age, sex, ACEi/ARB use and previous ERT duration matching variables; §Matching omitted ACEi/ARB use and previous ERT duration (not reported); ‖DICs were comparable and therefore a fixed-effects model was chosen.

ITCs of FACE risk for migalastat and agalsidase alfa/beta

- Long-term risk of a FACE with migalastat was compared with agalsidase alfa, agalsidase beta or agalsidase alfa/beta using data from ATTRACT and its OLE and the Fabry Outcome Survey (FOS) registry,[19] an international retrospective cohort study,[20] the Canadian Fabry Disease Initiative study[21] and a placebo-controlled RCT of agalsidase beta[22] (**Table S5**)
  - As both the RCT and OLE phases of ATTRACT were included, only single-arm data were available and therefore unanchored MAICs were performed
  - No studies of pegunigalsidase alfa reported FACEs
  - After matching, the ESS (N=2) for comparison with the agalsidase beta RCT[22] was deemed too low for meaningful analysis.



	Comparison (ATTRACT plus OLE vs)*	Migalastat versus	ESS	FACEs HR (95% CI)†
Unanchored MAICs	Fabry Outcome Survey	Agalsidase alfa	12	**0.08 (0.02, 0.33)**
	International cohort study	Agalsidase alfa	39	0.59 (0.23, 1.54)
	International cohort study	Agalsidase beta	33	0.53 (0.21, 1.39)
	CFDI-NR cohort 1a (ERT experienced)	Agalsidase alfa or agalsidase beta	22	0.32 (0.10, 1.07)
	CFDI-NR cohort 1b (ERT naïve)	Agalsidase alfa or agalsidase beta	28	0.76 (0.28, 2.08)

The left panel shows the network connections, with dashed lines representing indirect comparisons. Times (in months or years) indicate length of follow-up. The right panel shows the results. FACEs data and follow-up times for comparator studies were extracted from digitised Kaplan–Meier curves. In the international cohort study, the Kaplan–Meier analysis was performed using a subpopulation of propensity-score-matched patients; therefore, baseline characteristics of the matched groups may differ.
*Matching variables were age, sex, ACEi/ARB use and eGFR (the FOS publication did not report ACEi/ARB use;[19] therefore, this variable was not included in the unanchored MAIC); †Statistically significant result shown in **bold**.
CFDI-NR, Canadian Fabry Disease Initiative National Registry; HR, hazard ratio.

Conclusions

- In unanchored and anchored MAICs of patients with Fabry disease, effective sample size (ESS) tended to be small and the anchored MAICs had limitations around the assumption of similar efficacy of agalsidase alfa and agalsidase beta
  - For change in left ventricular mass index (LVMi) and estimated glomerular filtration rate (eGFR) slope, all comparisons numerically favoured migalastat over pegunigalsidase alfa apart from the anchored MAIC for eGFR slope
  - For long-term FACE risk, unanchored MAICs numerically favoured migalastat over agalsidase alfa and/or beta.
- Challenges relating to data availability are reflected in the methodology and results
  - Matching was conducted using age, sex, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEi/ARB) use, baseline eGFR and previous ERT duration, although most comparisons used fewer variables due to data availability or the need to remove a variable (baseline eGFR or previous ERT duration) to increase ESS.
- Overall, these results show that ITCs of Fabry disease treatments have utility; further uses may include informing treatment decisions and reimbursement policies.

References

1. Ortiz A *et al. Mol Genet Metab* 2018;123:416–27.
2. Waldek S *et al. Genet Med* 2009;11:790–6.
3. Hughes DA *et al. J Med Genet* 2023;60:722–31.
4. Sanofi BV. Fabrazyme SmPC, 2024 (accessed 5 October 2025).
5. Chiesi. Elfabrio SmPC, 2024 (accessed 5 October 2025).
6. Genzyme. Fabrazyme PI, 2024 (accessed 5 October 2025).
7. Chiesi. Elfabrio PI, 2023 (accessed 5 October 2025).
8. Takeda Pharmaceuticals. Replagal SmPC, 2025 (accessed 5 October 2025).
9. Amicus Therapeutics Europe Limited. Galafold SmPC, 2025 (accessed 5 October 2025).
10. Amicus Therapeutics Inc. Galafold PI, 2025 (accessed 5 October 2025).
11. Hughes DA *et al. J Med Genet* 2017;54:288–96.
12. Lyn N *et al.* Presented at ISPOR EU; 12–15 November 2023; Copenhagen, Denmark. Poster MSR50.
13. Wallace EL *et al. J Med Genet* 2024;61:520–30.
14. Holida M *et al.* Presented at WORLD*Symposium*; 7–11 February 2022; San Diego, CA, USA. Poster LB-28.
15. Bernat J *et al. Genet Med Open* 2023;1:100016.
16. Atta M *et al.* Presented at the 7th International Update on Fabry Disease; 29–31 May 2022; Würzburg, Germany. Poster T-1.
17. Gonzalez D *et al. Genet Med* 2022;24:S91.
18. Linhart A *et al. Orphanet J Rare Dis* 2023;18:332.
19. Giugliani R *et al.* Presented at WORLD*Symposium*; 22–26 February 2023; Orlando, FL, USA. Poster 135.
20. Arends M *et al. J Med Genet* 2018;55:351–8.
21. Sirrs SM *et al. Mol Genet Metab* 2014;111:499–506.
22. Banikazemi M *et al. Ann Intern Med* 2007;146:77–86.
23. ClinicalTrials.gov. NCT02795676. Available at: https://clinicaltrials.gov/study/NCT02795676 (accessed 5 October 2025).

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