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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Table S1. Search criteria used for targeted literature review

Parameter	Inclusion criteria	Exclusion criteria
Population	Patients of any age with Fabry disease Subgroups of interest will be based on: • Age (adults [≥18 years], adolescents, children) • Sex (male, female) • Patients with renal impairment • Patients with cardiomyopathy • Patients with angiokeratoma • Patients with acroparaesthesia • Amenable mutations	Other than diseases defined
Interventions	Migalastat, agalsidase alfa, agalsidase beta, pegunigalsidase alfa	–
Comparators	Agalsidase alfa, agalsidase beta, pegunigalsidase alfa, placebo	–
Study design	• Randomised controlled trials • Single-arm clinical studies • Observational studies/registries/survey (comparing ERT/no ERT or before and after ERT) • Treatment switch studies (eg OLE)	• Case studies • Studies with n<10 • Animal studies • Systematic reviews and meta-analyses*
Language	English	Other than English
Publication Dates	1 August 2022 – 9 January 2024	Before August 2022

Parameter	Inclusion criteria	Exclusion criteria
Outcomes	Number of people experiencing or time to occurrence of a FACE: • Renal events: end-stage renal disease requiring long-term dialysis or transplantation, doubling of serum creatinine levels from the start of baseline (where levels remained double or greater between two consecutive values) • Cardiac events: MI, NSTEMI, new symptomatic arrhythmia requiring medication, direct current cardioversion or an interventional procedure (eg ablation, pacemaker or defibrillator implantation), unstable angina defined by national practice guidelines and accompanied by electrocardiographic changes, congestive heart failure requiring hospitalisation, any major cardiac medical procedure (eg valve replacement, stent implantation, transplant or persistent atrial fibrillation) • Cerebrovascular events: Stroke, TIA • Composite event Other clinical outcomes: LVMi Kidney function: eGFR Mortality: Time to occurrence of death, number of deaths Safety: Any AE, serious AE, any TEAE, serious TEAE, fatal AE, infusion reactions, headache, gastrointestinal disruption, anti-drug neutralising antibodies	Other than specified in the inclusion criteria

*Used for background information and reference checking only

AE, adverse event; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FACE, Fabry-associated clinical event; LVMI, left ventricular mass index; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; OLE, open-label extension; TEAE, treatment-emergent adverse event; TIA, transient ischaemic attack; TLR, targeted literature review

Table S2. Indirect treatment comparison methods applied in this analysis

Method	Data/network requirements	Pros ✓ and cons X
Unanchored MAIC	Patient-level data required for ATTRACT Aggregated data required for the comparator study No network connection via a common comparator required (unanchored comparison)	✓ Works for disconnected networks or single-arm studies X Adjustment for prognostic factors required ✓ Adjusts for between-trial differences in baseline characteristics (treatment effect modifiers, and prognostic factors in case of unanchored comparison) X Adjusts only to the trial population of the comparator study X Increased uncertainty when there is little overlap in study populations (effective sample size becomes small) X Works only for pairwise comparisons
Anchored MAIC	Patient-level data required for ATTRACT Aggregated data required for the comparator study Connected network required (anchored comparison)	✓ Respects randomisation within studies ✓ No adjustment for prognostic factors required
NMA	Aggregated data only Connected network required	✓ Standard method accepted by the Health Technology Authority X No adjustment for between-trial differences in baseline characteristics

MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

Table S3. Matching for unanchored and anchored MAIC analyses of change from baseline in LVMi

Unanchored MAIC

Study	N	Mean age (years)	Males (%)	ACEi/ARB use (%)	Mean ERT duration (years)	Mean eGFR* (mL/min/1.73 m²)
Scenario 1†: ATTRACT matched with BALANCE (matching variables exclude ERT duration)						
ATTRACT (migalastat)	33	50.9	39	48	–	88.9
BALANCE[1] (pegunigalsidase alfa)	52	43.9	56	50	–	73.5
Adjusted ATTRACT	ESS: 7	43.9	56	50	–	73.5
Scenario 2‡: ATTRACT matched with BALANCE (matching variables exclude baseline eGFR)						
ATTRACT (migalastat)	24§	51.3	38	42	3.0	–
BALANCE[1] (pegunigalsidase alfa)	52	43.9	56	50	5.4	–
Adjusted ATTRACT	ESS: 3	43.3	57	48	5.3	–

Anchored MAIC

Study	N	Mean age (years)	Males (%)	ACEi/ARB use (%)	Mean ERT duration (years)	Mean eGFR* (mL/min/1.73 m²)
Scenario 1†: ATTRACT matched with BALANCE (matching variables exclude ERT duration)						
ATTRACT (migalastat)	49	48.7	43	51	–	91.1
BALANCE[1] (pegunigalsidase alfa)	77	44.3	61	55	–	73.7
Adjusted ATTRACT	ESS: 10	44.3	61	55	–	73.7
Scenario 2‡: ATTRACT matched with BALANCE (matching variables exclude baseline eGFR)						
ATTRACT (migalastat)	37‖	47.7	41	46	3.4	–
BALANCE[1] (pegunigalsidase alfa)	77	44.3	61	55	5.8	–
Adjusted ATTRACT	ESS: 14	44.3	61	55	5.8	–

Matching using all variables resulted in a low effective sample size (ESS), therefore scenarios including baseline eGFR (scenario 1) or previous ERT duration (scenario 2) were used to increase ESS

*The CKD-EPI equation 2009 version (as used in ATTRACT) was preferred when reported; †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; §Only 24 of 34 patients reported length of previous ERT duration; ‖Only 37 of 49 patients reported length of previous ERT duration

1. ClinicalTrials.gov. NCT02795676. Available at: https://clinicaltrials.gov/study/NCT02795676 (accessed 5 October 2025).

Table S4. Matching for unanchored and anchored MAIC analyses of eGFR slope

Unanchored MAIC

Study	N	Mean age (years)	Males (%)	ACEi/ARB use (%)	Mean ERT duration (years)	Mean eGFR* (mL/min/1.73 m²)
Scenario 1†: ATTRACT matched with BALANCE (matching variables exclude ERT duration)						
ATTRACT (migalastat)	34	51.2	41	47	–	88.7
BALANCE[1] (pegunigalsidase alfa)	52	43.9	56	50	–	73.5
Adjusted ATTRACT	ESS: 7	43.9	56	50	–	73.5
Scenario 2‡: ATTRACT matched with BALANCE (matching variables exclude baseline eGFR)						
ATTRACT (migalastat)	24 §	51.3	38	42	3.0	–
BALANCE[1] (pegunigalsidase alfa)	52	43.9	56	50	5.4	–
Adjusted ATTRACT	ESS: 3	43.3	57	48	5.3	–
ATTRACT matched with BRIGHT, BRIGHT51 and NCT01981720‖						
ATTRACT (migalastat)	34	51.2	41	–	–	88.7
BRIGHT[2] (pegunigalsidase alfa)	30	40.5	80	–	–	99.4
Adjusted ATTRACT	ESS: 13	40.5	80	–	–	99.4
BRIGHT51[3] (pegunigalsidase alfa)	29	40.9	79	–	–	99.4
Adjusted ATTRACT	ESS: 14	40.9	79	–	–	99.4
NCT01981720[4,5] (pegunigalsidase alfa)	15	33.4	53	–	–	111.7
Adjusted ATTRACT	ESS: 9	33.4	53	–	–	111.7

Anchored MAIC

Study	N	Mean age (years)	Males (%)	ACEi/ARB use (%)	Mean ERT duration (years)	Mean eGFR* (mL/min/1.73 m²)
Scenario 1†: ATTRACT matched with BALANCE (matching variables exclude ERT duration)						
ATTRACT (migalastat)	52	49.0	42	50	–	90.8
BALANCE[1] (pegunigalsidase alfa)	77	44.3	61	55	–	73.7
Adjusted ATTRACT	ESS: 10	44.3	61	55	–	73.7
Scenario 2‡: ATTRACT matched with BALANCE (matching variables exclude baseline eGFR)						
ATTRACT (migalastat)	39¶	47.9	38	46	3.4	–
BALANCE[1] (pegunigalsidase alfa)	77	44.3	61	55	5.8	–
Adjusted ATTRACT	ESS: 14	44.3	61	55	5.8	–

*The CKD-EPI equation 2009 version (as used in ATTRACT) was preferred when reported; †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; §Only 24 of 34 patients reported length of previous ERT duration; ‖Studies did not report ACEi/ARB use or previous ERT duration; ¶Only 39 of 52 patients reported length of previous ERT duration

1. Wallace EL *et al. J Med Genet* 2024;61:520–30; 2. Holida M *et al.* Presented at WORLD*Symposium*; 7–11 February 2022; San Diego, CA, USA. Poster LB-28; 3. Bernat J *et al. Genet Med Open* 2023;1:100016; 4. Atta M *et al.* Presented at 7th International Update on Fabry Disease; 29–31 May 2022; Würzburg, Germany. Poster T-1; 5. Gonzalez D *et al. Genet Med* 2022;24:S91

Table S5. Matching for unanchored MAIC analyses of FACE risk

Study	N	Mean age (years)	Males (%)	ACEi/ARB use (%)	Mean eGFR* (mL/min/1.73 m^2)
ATTRACT plus OLE (migalastat)	49	49.5	39	53	89.0
Fabry Outcome Survey registry, agalsidase alfa[1,†]	66	32.8	79	–	99.4
Adjusted ATTRACT	ESS: 12	32.8	79	–	99.4
International cohort study, agalsidase alfa[2]	248	46.0	47	36	89.0
Adjusted ATTRACT	ESS: 39	46.0	47	36	89.0
International cohort study, agalsidase beta[2]	139	46.0	56	37	86.0
Adjusted ATTRACT	ESS: 33	46.0	56	37	86.0
CFDI-NR, agalsidase alfa or beta – cohort 1a (ERT experienced)[3]	86	43.3	73	59	87.0
Adjusted ATTRACT	ESS: 22	43.3	73	59	87.0
CFDI-NR, agalsidase alfa or beta – cohort 1b (ERT naïve)[3]	92	47.6	40	56	79.1
Adjusted ATTRACT	ESS: 28	47.6	40	56	79.1
Placebo-controlled RCT, agalsidase beta arm[4]	51	46.9	88	35	53.0
Adjusted ATTRACT	ESS: 2[‡]	40.5	80	87	99.4

*The CKD-EPI equation 2009 version (as used in ATTRACT) was preferred when reported; †Matching variables were age, sex, ACEi/ARB use and eGFR (Giugliani *et al.*[1] did not report ACEi/ARB use; therefore, this variable was not included); ‡ESS deemed too low for meaningful analysis, therefore comparisons are not reported in the poster

CFDI-NR, Canadian Fabry Disease Initiative National Registry

1. Giugliani R *et al.* Presented at WORLD*Symposium*; 22–26 February 2023; Orlando, FL, USA. Poster 135; 2. Arends M *et al. J Med Genet* 2018;55:351–8. 3. Sirrs SM *et al. Mol Genet Metab* 2014;111:499–506; 4. Banikazemi M *et al. Ann Intern Med* 2007;146:77–86