Pegunigalsidase Alfa (ELFABRIO®) as a Long-term Enzyme Replacement Therapy in Adults with Fabry Disease: A Systematic Literature Review

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INTRODUCTION

- Fabry disease (FD) is a rare, progressive, multisystemic, and potentially fatal X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A[1]
- This leads to glycolipid accumulation, disrupted cellular metabolism, cell death, and progressive dysfunction of vital organs[1]
- Pegunigalsidase alfa, the first PEGylated α-galactosidase A, was developed to enhance stability, prolong half-life, improve bio-distribution, and reduce immunogenicity compared with existing enzyme replacement therapies (ERTs)[2]
- This systematic literature review (SLR) aimed to evaluate the efficacy and safety of pegunigalsidase alfa in adults with FD, including comparison against other ERTs

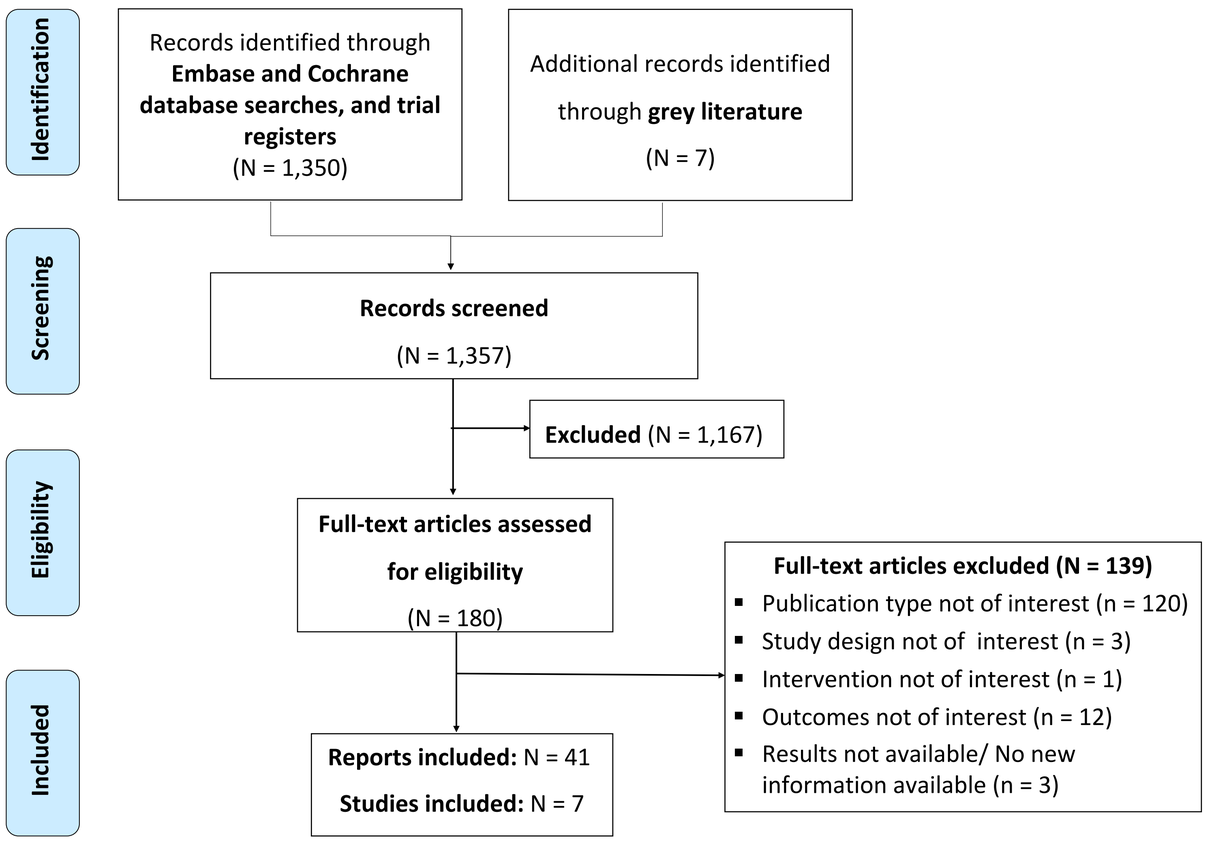
METHODS

- A comprehensive literature search was conducted in January 2025 across PubMed, the Cochrane Library, and clinical trial registries (ClinicalTrials.gov, WHO ICTRP, and ANZCTR)
- Randomised controlled trials (RCTs) and open-label extensions (OLEs) evaluating adult patients with FD treated with pegunigalsidase alfa and comparators, agalsidase alfa or agalsidase beta, were included
- Efficacy outcomes included changes in renal function (estimated glomerular filtration rate [eGFR], cardiac function (Left Ventricular Mass Index [LVMI]), and FD biomarker (plasma globotriaosylsphingosine [Lyso-Gb3])
- Safety outcomes included the incidence and severity of treatment-emergent adverse events (TEAEs)

RESULTS

- A total of 41 publications reporting seven trials (BALANCE, BRIDGE, BRIGHT, BRIGHT-51, PB-102-F01, PB-102-F02, and PB-102-F03) were included **(Figure 1)**
- Baseline demographics and clinical characteristics were largely comparable across studies **(Table 1)**
- Patients were predominantly male, with a mean age ranging from 33 to 44 years and baseline median eGFR between 73.7 [2.3] mL/min/1.73 m²/year (BALANCE) and 111.7 [5.5] mL/min/1.73 m²/year (PB-102-F03)
- No trials were identified that compared pegunigalsidase alfa with agalsidase alfa

Figure 1. PRISMA flow diagram depicting study selection and inclusion process



Abbreviations: PRISMA, Preferred reporting items for systematic reviews and meta-analyses.

Table 1. Baseline characteristics of the included studies

Trial	Study design	Intervention arm (N)	Gender, n	Age in years, mean (SD)	eGFR, mL/min/1.73 m²/year, mean (SD) or mean [SE]	LVMI, mean [SE]	Lyso-Gb3, mean (SD) or mean [SE]
BALANCE[3]	Phase III RCT	Peg alfa 1 mg/Kg: 52 Agal beta 1 mg/Kg: 25	Male: 47, Female: 30	44.3 (10.0)	73.7 [2.3]	NR	Peg alfa: 26.22 [3.78] nmol/L Agal beta: 32.14 [7.08] nmol/L
PB-102-F03[4]	Phase 1/2 OLE	Peg alfa 1mg/kg: 15	Male: 8, Female: 7	33.4 (NR)	111.7 [5.5]	52.7 [2.2] g/m²	Male: 124.4 [NR] ng/mL Female: 9.6 [NR] ng/mL
PB-102-F01 and PB-102-F02[5]	Phase 1/2 OLE	Peg alfa (0.2 mg/kg, 1.0 mg/kg, or 2.0 mg/kg): 18	NR	NR	111.2 (20.9)	NR	NR
BRIGHT[6]	Phase III OLE	Peg alfa 2mg/kg: 30	Male: 24, Female: 6	40.5 (11.3)	99.9 (22.1)	NR	19.4 (18.1) nmol/L
BRIDGE[7]	Phase III OLE	Peg alfa 1 mg/kg: 22	Male: 15, Female: 7	44.0 (11.0)	82.5 (23.4)	NR	38.3 (41.2) nmol/L
BRIGHT 51[8]	Phase III OLE	Peg alfa 2mg/Kg: 29	Male: 23, Female: 6	40.9 (NR)	NR	NR	19.36 [3.35] nmol/L

Abbreviations: Agal beta, Agalsidase beta; eGFR, estimated glomerular filtration rate; OLE, Open-label extension; Peg alfa, Pegunigalsidase alfa; RCT, Randomised controlled trial; SD, standard deviation; SE, standard error; LVMI, Left Ventricular Mass Index.

Efficacy Outcomes

Estimated Glomerular filtration rate (eGFR)

- In BALANCE trial, median eGFR decline was similar between pegunigalsidase alfa and agalsidase beta (−2.5 vs −2.2 mL/min/1.73 m²) **(Table 2)**
- PB-102-F01/F02 trials showed minimal decline (−0.8 mL/min/1.73 m² at Week 52), whereas longer follow-up (PB-102-F03, Week 260) demonstrated a larger decrease (−14.7 mL/min/1.73 m²), likely reflecting disease progression over time

Left Ventricular Mass Index (LVMI)

- In PB-102-F03 and BRIDGE trials, mean (SE) change from baseline in LVMI were 5.7 (2.2) and 2.4 (3.4) for males, and 13.6 (5.3) and 7.1 (5.0) g/m² for females, respectively
- Overall, cardiac function remained stable in patients switched from prior treatment with agalsidase alfa to pegunigalsidase alfa

Plasma-lyso Gb3

- Plasma lyso-Gb3 levels demonstrated overall biochemical improvement across studies
- In BALANCE trial, a slight increase (+3.3 nmol/L) was observed with pegunigalsidase alfa compared with a reduction (−8.7 nmol/L) for agalsidase beta at Week 104, whereas PB-102-F03 trial reported an 83% decrease at Week 260, confirming durable substrate clearance and biochemical response with prolonged therapy

Table 2. Change from baseline in efficacy outcomes

Trial name	Intervention	eGFR, mL/min/1.73 m²/year	LVMI, g/m²	Lyso-Gb3
BALANCE[3]	Peg alfa and agal beta	Week 104 (Peg alfa): -2.51 (-3.79, -1.24)[a] Week 104 (Agal beta): -2.16 (-3.81, -0.51)[a]	NR	Week 104 (Peg alfa): 3.30 (1.38)[b] nmol/L Week 104 (Agal beta): -8.74 (4.85)[b] nmol/L
PB-102-F03[4]	Peg alfa	Week 260: -14.7 (NR)[b]*	Week 260 (Male): 5.7 [2.2][b] Week 260 (Female): 13.6 [5.3][b]	Week 260: 83.3% reduction from baseline
PB-102-F01 & PB-102-F02[5]	Peg alfa	Week 52: -0.8 (7.7)[c]	NR	NR
BRIGHT[6]	Peg alfa	Week 52: 1.9 (5.9; 1.8)[d]	NR	Week 52: 5.1 (0.3; 7.9)[d] nmol/L
BRIDGE[7]	Peg alfa	NR	Week 52 (Male): 2.4 [3.4][b] Week 52 (Female): 7.1 [5.0][b]	Week 52: -14.3 (23.0)[c] nmol/L
BRIGHT 51[8]	Peg alfa	Week 108: -5.10 (1.96)[b]	NR	Week 108: 3.62 (NR)[b]* nmol/L

[a]median (range), [b]mean (SE), [c]mean (SD), [d]median (IQR), *calculated.
Abbreviations: Agal beta, Agalsidase beta; eGFR, IQR, inter-quartile range; Lyso-Gb3, LVMI, Peg alfa, Pegunigalsidase alfa; SD, standard deviation; SE, standard error.

Safety Outcomes

- In BALANCE trial, TEAEs occurred in 90% of patients receiving pegunigalsidase alfa and 96% with agalsidase beta, while serious TEAEs were infrequent (2% vs 0%) **(Table 3)**
- Among OLEs, the incidence of TEAEs ranged from 90% to 100%, with serious TEAEs reported in 6.7% of patients in BRIGHT and 18% in BRIDGE trials

Table 3. Safety outcomes (change from baseline)

Trial name	Intervention arm	TEAE (any), n (%)	TEAE (serious), n (%)	TEAE (withdrawal), n (%)	IRR (mild or moderate), n (%)
BALANCE[3]	Peg alfa agal beta	47 (90.0) 24 (96.0)	1 (2.0) 0 (0)	2 (4.0) 0 (0)	11 (21.0) 6 (24.0)
PB-102-F03[4]	Peg alfa	15 (100.0)	0	0	6 (40.0)
PB-102-F01 and PB-102-F02[5]	Peg alfa	NR	NR	NR	NR
BRIGHT[6]	Peg alfa	27 (90.0)	2 (6.7)	0 (0)	5 (16.7)
BRIDGE[7]	Peg alfa	21 (96.0)	4 (18.0)	2 (9.0)	5 (23.0)
BRIGHT 51[8]	Peg alfa	27 (93.1)	NR	NR	6 (20.7)

Abbreviations: Agal beta, Agalsidase beta; Peg alfa, Pegunigalsidase alfa; IRR, Infusion-related reactions; TEAE, treatment-emergent adverse event. Data presented in the table in the form of number of patients (n) and percentage (%).

CONCLUSIONS

In adults with Fabry disease, pegunigalsidase alfa demonstrated comparable efficacy and safety profile relative to agalsidase beta, supporting its long-term use. However, direct comparative data versus agalsidase alfa are lacking and further research is warranted

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