NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]
Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pegunigalsidase alfa for treating Fabry disease [ID3904]

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The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Chiesi Ltd:
   a. Full submission
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2. **Clarification questions and company responses**
   a. Clarification question
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3. **Patient group, professional group, and NHS organisation submission** from:
   a. Society for Mucopolysaccharide and Related Diseases (MPS Society)

4. **Expert personal perspectives** from:
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   b. Amicus Therapeutics UK
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9. **External Assessment Group critique of company response to technical engagement** prepared by BMJ Technology Assessment Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]

Document B

Company evidence submission

January 2023

File name	Version	Contains confidential information	Date
ID3904_PRX-102 NICE Document B FINAL_25Jan2023_redacted	**1**	**Yes**	**25 January 2023**

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Tables and figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
ACEi	Angiotensin converting enzyme inhibitor
ADAs	Anti-drug antibodies
ARB	Angiotensin II receptor blocker
BIMDG	British Inherited Metabolic Disease Group
BPI	Brief Pain Inventory
CFB	Change from baseline
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
E2W	Every 2 weeks
E4W	Every 4 weeks
eGFR	Estimated glomerular filtration rate
E2W	Every 2 weeks
E4W	Every 4 weeks
EMA	European Medicines Agency
ERT	Enzyme replacement therapy
FCE	Fabry clinical event
FD	Fabry disease
Gb3	Globotriaosylceramide
GI	Gastrointestinal
IgG	Immunoglobulin G
IRR	Infusion-related reaction
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
LSD	Lysosomal storage disorders
LVMI	Left ventricular mass index
Lyso-Gb3	Globotriaosylsphingosine
MRI	Magnetic resonance imaging
MSSI	Mainz Severity Score Index
OR	Odds ratio
PEG	Polyethylene glycol
PK	Pharmacokinetics
PP	Per-protocol
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
UPCR	Urine protein to creatinine ratio

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

Table 1 presents the decision problem for the submission. The population defined in the final scope is narrower than the proposed European Medicines Agency (EMA) indication for pegunigalsidase alfa (PRX–102, Elfabrio®): PRX-102 is indicated for long-term enzyme replacement therapy (ERT) in adult patients with a confirmed diagnosis of Fabry disease (FD) (deficiency of alpha-galactosidase).[1] In clinical practice, PRX-102 is anticipated to be used as a treatment option for patients with symptomatic FD who would usually be offered ERT in line with British Inherited Metabolic Disease Group (BIMDG) guidelines[2], including treatment-naïve patients and those previously treated with currently available therapies.

As such, this submission focuses on part of the technology's marketing authorisation: adults with FD who would usually be treated with an ERT. The proposed positioning is narrower than the marketing authorisation because this position is representative of how PRX-102 will be used in UK clinical practice.

The decision problem that this submission addresses is described in Table 1 below.

Table 1: The decision problem

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with FD	Adults with FD who would usually be treated with an ERT	Treatment choice in FD is individualised; however, in UK clinical practice it is anticipated that migalastat would continue to be used in patients with amenable mutations due its targeted nature and established use. The focused positioning of this submission is representative of how PRX-102 will be used in UK clinical practice.
Intervention	Pegunigalsidase alfa, Elfabrio®	Pegunigalsidase alfa (PRX-102), Elfabrio®	As per NICE scope
Comparator(s)	• Agalsidase alfa • Agalsidase beta • Migalastat (for those aged over 16 years with an amenable mutation)	• Agalsidase alfa • Agalsidase beta	Treatment choice in FD is individualised; however, in UK clinical practice it is anticipated that migalastat would continue to be used in patients with amenable mutation due its targeted nature and established use. As such, PRX-102 would only be considered in those patients eligible for migalastat if ERT was being considered as a treatment option instead because they are unsuitable for treatment with migalastat for any reason (such as tolerance or issues with compliance or patient choice or any other reason). This updated positioning means that migalastat is no longer considered a relevant comparator for this submission.
Outcomes	The outcome measures to be considered include: • Symptoms of FD (including pain, and gastrointestinal issues such as diarrhoea, nausea and abdominal pain) • Gb3 levels in kidney • Plasma lyso-Gb3 levels	The outcome measures to be considered include: • Symptoms of FD (including pain, and gastrointestinal issues such as diarrhoea, nausea and abdominal pain) • Gb3 levels in kidney • Plasma lyso-Gb3 levels • Kidney function	Carer utilities were not expected to be influential for the value case for PRX-102 or a key driver in the model – therefore, carer utilities have not been considered in the model. Use of infusion premedication is required with current ERTs, and in some cases can cause the patient to stop treatment. Therefore, use of infusion premedication has been included as an outcome of interest within the submission.

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Kidney function • Cardiac function and disease measurements (such as left ventricular mass index) • Event-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events) • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Cardiac function and disease measurements (such as left ventricular mass index) • Event-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events) • Mortality • Adverse effects of treatment (including ADAs) • Health-related quality of life (for patients) • Use of infusion premedication	
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	Given the non-inferiority of PRX-102 E2W compared with agalsidase beta E2W, and the conclusion of clinical equivalence between the ERTs accepted in the NICE submission for migalastat (HST4), we assume that PRX-102 E2W demonstrates equivalent efficacy to both ERTs. As such, the base case analysis is a cost comparison of ERTs, which establishes the difference between drug cost and resource costs for all considered treatments. A cost–utility analysis is presented as a scenario analysis as per the NICE reference case.	N/A

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective		
Subgroups to be considered	Patients who have an amenable mutation and are on migalastat.	Please note that we will not address this subgroup in the appraisal due to a lack of available evidence. PRX-102 will be positioned as a treatment option for all adults with FD who would usually be treated with ERTs in line with clinical guidelines.	BALANCE was not designed to examine outcomes in patients with amenable mutations. BRIDGE and BRIGHT demonstrated efficacy in a broader patient population (not just patients that were renally impaired). Clinicians from the advisory board also indicated that there was no reason to assume that mutation status is a treatment modifier (see advisory board summary report in Appendix P). However, in an integrated analysis of 112 patients from the PRX-102 trials, of which 17 had amenable mutations and 64 did not, results demonstrated that the presence of an amenable mutation [redacted] (Appendix M5).
Key: BIMDG, British Inherited Metabolic Disease Group; FD, Fabry disease; Gb3, globotriaosylceramide; Lyso-Gb3, globotriaosylsphingosine; NICE, National Institute for Health and Care Excellence; PRX-102, pegunigalsidase alfa; TBC, to be confirmed.			

B.1.2. Description of the technology being appraised

Table 2 presents a description of PRX-102. The draft summary of product characteristics (SmPC) is presented in Appendix C1.

Table 2: Technology being evaluated

UK approved name and brand name	Pegunigalsidase alfa (PRX-102); Elfabrio®
Mechanism of action	PRX-102 is the first PEGylated alpha-galactosidase A, with studies showing superior stability, a longer half-life (~80 hours), improved biodistribution and reduced risk of immunogenicity compared with existing ERTs.[3-6] PRX-102 comprises 2 enzyme subunits covalently cross-linked with a PEG moiety and additional PEG molecules, preserving catalytic activity and translocation to the lysosome.[6] The PRX-102 molecule is more stable than other commercially-available ERTs, and can remain active in lysosomal-like conditions for 5 times as long.[6] In in vitro assays with rabbit polyclonal antibodies, PRX-102 demonstrated a lower antibody recognition compared with plant-expressed recombinant human α-Galactosidase-A (prh-α-Gal-A),[3] attributed to the additional PEG moieties of PRX-102, which is believed to mask the antibody binding sites.
Marketing authorisation/CE mark status	Marketing authorisation has been applied for via the EC decision reliance procedure. Committee for Medicinal Products for Human Use approval is expected in [redacted], and MAA approval is expected on [redacted].[7]
Indications and any restriction(s) as described in the proposed summary of product characteristics (SmPC)	**Proposed indication:** PRX-102 is indicated for long-term ERT in adult patients with a confirmed diagnosis of FD (deficiency of alpha-galactosidase)[7] **Restrictions:** • Safety and efficacy of PRX-102 in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients • The safety and efficacy of PRX-102 in children and adolescents aged 0–17 years have not yet been established as no data are available • There are no data on the potential effect of PRX-102 on fertility in humans, although animal studies show no evidence of impaired fertility • It is preferable to avoid the use of PRX-102 during pregnancy unless clearly necessary, given the limited PRX-102 data that exist in pregnant females. However, animal studies do not indicate harmful effects regarding reproductive toxicity • For females who are breastfeeding, a risk to newborns/infants cannot be excluded as animal studies have shown excretion of PRX-102 in milk. As such, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from PRX-102 therapy, balancing the benefits of breast feeding for the child and PRX-102 therapy for the woman • For patients who have life-threatening hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients listed in section 6.1 of the SmPC, PRX-102 is contraindicated • Patients that have already experienced IRRs (including severe hypersensitivity reactions), should receive pre-treatment with antihistamines and/or corticosteroids to help prevent subsequent

	reactions in cases where symptomatic treatment was required, although IRRs may occur in some patients after receiving pre-treatment • Appropriate medical support should be readily available when PRX-102 is administered given that allergic-type hypersensitivity IRRs can be severe • In case of a severe allergic or anaphylactic-type reaction, PRX-102 should be immediately discontinued and current medical standards for emergency treatment should be followed • In patients who have previously experienced severe hypersensitivity reactions during PRX-102 infusion, caution should be exercised upon re-challenge • Patients who develop infusion or immune reactions with PRX-102 treatment should be monitored for ADAs to PRX-102. It is treatment-physician responsibility to decide the appropriate action upon results of the monitoring for ADAs • Patients who are ADA-positive to other ERTs, who have experienced hypersensitivity reactions to PRX-102 and patients who are switching to PRX-102 should be monitored for ADAs to PRX-102. Moreover, physicians should put in place all minimisation measures in patients who have experienced severe hypersensitivity reactions to other ERTs and be ready in case a severe reaction should re-occur
Method of administration and dosage	• PRX-102 is supplied as a sterile, clear solution in single-use 10 ml vials containing 20 mg of active product at a concentration of 2 mg/ml. A 5 mg vial is anticipated to be commercially available in [redacted] • The recommended dose of PRX-102 is 1 mg/kg of body weight administered once E2W by intravenous infusion or 2 mg/kg of body weight administered once E4W by intravenous infusion. The choice between the 2 posology options is based on the clinical judgement, patients' compliance, and response to treatment • For maintenance treatment, the target infusion duration is dependent on the patient's tolerability. The increase in the infusion rate should be achieved gradually starting from the initial infusion rate • For patients switching from agalsidase alfa or agalsidase beta, the pre-treatment regimen should be preserved for the initial 3 months (6 infusions) of PRX-102 treatment, with stepwise discontinuation of pre-treatment based on tolerability • PRX-102 treatment should be managed by a physician experienced in the treatment of patients with FD[1] • Appropriate medical support measures should be readily available when PRX-102 is administered to patients who have not had treatment before, or who have experienced severe hypersensitivity reactions to PRX-102 in the past[1] • Infusion of PRX-102 at home and administration by the patient in presence of a responsible adult or administration by the patient's caregiver (self-administration) may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion and/or self-administration should be made after evaluation and recommendation by the treating physician[1] • Appropriate training should be given by the treating physician and/or nurse to the patient and/or caregiver prior to initiation of home infusion and/or self-administration.[1] The dose and infusion rate used in the home setting should remain the same as was used in the hospital setting; they should be changed only under the supervision of a healthcare professional and the treating physician. Self-administration should be closely followed by the treating physician

	• Patients experiencing IRRs, including hypersensitivity reactions or anaphylactic reactions during the home infusion/self-administration need to immediately reduce the infusion rate or stop the infusion process considering the severity of the reaction and seek the attention of a healthcare professional[1]
Additional tests or investigations	• Patients should be observed for IRRs for 2 hours after the infusion[1] • Patients who develop infusion or immune reactions with PRX-102 treatment should be monitored for ADAs to PRX-102[1] • Patients who are ADA-positive to other ERTs, who have experienced hypersensitivity reactions to PRX-102 and patients who are switching to PRX-102 should be monitored for ADAs to PRX-102. Physicians should also put in place all minimisation measures in patients who have experienced severe hypersensitivity reactions to other ERTs and be ready in case a severe reaction should re-occur[1]
List price and average cost of a course of treatment	• List price per 20 mg vial is £1,255.19. • As FD is a chronic disease and patients require life-long treatment, it is challenging to provide a comprehensible average cost of course of treatment. For an average UK patient (72.2 kg)[8], the average cost at list price of 4 weeks of treatment for the E2W posology is £9,062.25 or £9,060.40 for the E4W posology, assuming vials are rounded up or down in line with NHS clinical practice.
Patient access scheme (if applicable)	A simple PAS discount of [redacted]% has been submitted to NHS England. This results in a PAS price per 20 mg vial of £[redacted].

Key: ADA, anti-drug antibodies; ERT, enzyme replacement therapy; E2W, every 2 weeks; E4W, every 4 weeks; EC, European Commission; FD, Fabry disease; Gb3, globotriaosylceramide; lyso-Gb3, globotriaosylsphingosine; IRR, infusion-related reaction; MAA, Market Authorisation Application; NHS, National Health Service; PAS, patient access scheme; PEG, polyethylene glycol.
Source: Chiesi, PRX-102 draft SmPC. 2022.[1]

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease background

FD is a rare (Orphanet: ORPHA:324; International Classification of Diseases Tenth Revision [ICD-10]: E75.2; Online Mendelian Inheritance in Man® [OMIM]: 301500)[9], progressive, X-linked lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-galactosidase A, due to a mutation in the galactosidase alpha (*GLA*) gene. This deficiency leads to progressive accumulation of glycolipids (mainly globotriaosylceramide [Gb3] and globotriaosylsphingosine [lyso-Gb3]) in the plasma and lysosomes of a wide range of cells.[10-13] This accumulation leads to dysfunction of metabolic processes, cell death and eventually progressive vital organ dysfunction and a reduced life expectancy. Patients with FD experience a variety of clinical signs and symptoms that commonly include renal dysfunction, cardiovascular (CV) problems, neuropathic pain, cerebrovascular disease, gastrointestinal (GI) problems, angiokeratomas and hypohidrosis.[11-13] Patients with FD experience a wide range of symptoms, so diagnosis can be challenging, and clinical management requires a multidisciplinary approach.[12] Most patients with FD are first diagnosed in adulthood; a cohort study of 535 patients in England reported a mean (standard deviation [SD]) age at diagnosis of 37 (20.4) years.[8]

The severity of FD depends on the extent of the α-galactosidase A deficiency. The classic form involves early symptoms that manifest in childhood in multiple organs. The later-onset non-classic form is milder, and is characterised by slower progression, delayed symptom onset and more limited organ involvement.[12, 14] As the *GLA* gene is located on the X chromosome, all males carrying the mutation (i.e. hemizygous males) are affected. Females may carry the mutation on both X chromosomes (homozygous) and be affected, or only on 1 X chromosome (heterozygous), and clinical characteristics range from asymptomatic to severely symptomatic.[12] Because of the X-linked nature of FD, the classic phenotype tends to present more often in males than in females.[11, 12, 14]

B.1.3.2. Epidemiology

Published evidence on the prevalence and incidence of patients with FD in the UK is very limited and estimates are uncertain. A UK/Ireland registry of males with FD conducted between 1985–2000 showed a total prevalence of 1 in 366,000 males, with an incident birth rate of 1 in 100,000.[15] A 2014 survey in the north of England found that 1 in 49,000 males have symptomatic FD[16], while 2017 estimates from the National Institute for Health and Care Excellence (NICE) highly specialised technology (HST4) for migalastat reported 855 people with FD in England, equating to 0.002% of the population.[17] A recent real-world cohort study in England from the Clinical Practice Research Datalink (CPRD) reported a 2019 point prevalence of 3.69 per 100,000, and an incidence of 0.152 per 100,000.[8] This gives a prevalent population in England of approximately 2,100 patients, with approximately 90 incident patients per year.

Company estimates indicate that of all FD patients, approximately 50% are diagnosed (~1050 patients); of those approximately 50% are treated (~525 patients), and approximately 50% of treated patients receive an ERT.[18] This equates to ~262 patients with diagnosed symptomatic FD treated with an ERT in England. Assuming the same proportions for incident patients, there are expected to be approximately 11 new patients per year.

B.1.3.3. Burden of Fabry disease and impact of enzyme replacement therapy

B.1.3.3.1. Mortality

There are limited UK data on the mortality of FD. Studies evaluating the UK Anderson-Fabry disease (AFD) register data between 1996–2001 reported that median survival in patients with FD is lower than the general population, particularly for males (50 vs. 70 years), but also for females (70 vs. 85 years).[15, 19] More recent data from the 2022 Fabry Outcome Survey (26 countries) show the estimated median survival for males with FD treated with ERT for 5 years is now longer at 77.5 years, compared with 60 years for untreated males.[20] A real-world cohort study in England using CPRD data between January 2000–December 2019 (n = 535) reported a 5-year survival rate of 95.3% and a 10-year survival rate of 87.8%.[8] These

results echo a separate multinational study (including 39 countries) from 2009, in which the life expectancy at birth for patients with FD (regardless of treatment status) was lower than for the general US population in males (58.2 vs. 74.7 years) and females (75.4 vs. 80.0 years) with FD.[21] The shorter survival for males vs. females in this study is unsurprising as males usually have a greater α-galactosidase deficiency, as discussed in Section B.1.3.1.

While the cause of death in patients with FD varies, the most common cause is CV related, which accounts for 38–40% of all deaths.[21] CV death from FD is caused by Gb3 accumulating in the vascular endothelium and cardiomyocytes, which then leads to CV disease.[22] Approximately a quarter of deaths are of unknown cause or not reported (24.1%).[21] Additionally, death due to renal complications in FD range from 7%–19%. Pre-2001 data report that the principal cause of death was renal failure in males (42%), suggesting that a renal cause of death is less frequent than previously, possibly reflecting a benefit of ERTs.[23]

B.1.3.3.2. Symptomatic burden

Patients with FD experience a broad range of symptoms as glycolipids accumulate in cells throughout the body. Common symptoms include neuropathic pain, GI symptoms, fatigue, chest pains and angiokeratoma.[15, 24] Serious complications such as CV, renal and cerebrovascular events are also common.[25, 26]

Table 3 summarises the frequency of key complications in adults with classic and non-classic FD from 2017 recruited from 3 centres in Germany, the UK and the Netherlands.[25] Males with non-classic FD were more likely to have any event (40.9%) than males with classic FD (30.4%) or females with either phenotype, while females with classic FD were more likely to have a history of any event than females with non-classic FD (19.0% vs. 10.8%). These findings were driven by the frequency of CV events, which seemed to be most common in males with non-classic FD (28.8%). However, males with classic FD were more likely to have a renal event (8.7%) than any other group, although impaired renal function was common in males of both phenotypes (classic: 29.0%; non-classic: 27.7%) but less common in females (classic: 5.6%; non-classic: 9.5%).

Table 3: Symptoms presenting in adults with classic and non-classic FD in a multinational retrospective cohort study

	Males		Females	
	Classic FD (n = 138)	**Non-classic FD (n = 66)**	**Classic FD (n = 147)**	**Non-classic FD (n = 148)**
Any event	42 (30.4%)	27 (40.9%)	28 (19.0%)	16 (10.8%)
Cardiac event	16 (11.6%)	19 (28.8%)	11 (7.5%)	9 (6.1%)
Renal event	12 (8.7%)	2 (3%)	2 (1.4%)	1 (0.7%)
Cerebral events	15 (10.9%)	6 (7%)	16 (10.9%)	6 (4.1%)
Other symptoms				
Impaired renal function[a]	38/131 (29.0%)	18/65 (27.7%)	8/142 (5.6%)	14/147 (9.5%)
Left ventricular hypertrophy[b]	66/105 (62.9%)	33/49 (67.3%)	59/132 (44.7%)	40/128 (31.2%)
Concentric hypertrophy	57/105 (54.3%)	28/49 (57.1%)	47/132 (35.6)	32/128 (25.0%)

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FD, Fabry disease; ICD, implantable cardiac defibrillator; PM, pacemaker; TIA, transient ischemic attack.
Notes: Impaired kidney function is eGFR < 60 mL/min per 1.73 m^2; b, left ventricular hypertrophy is left ventricular mass ≥ 49 g/m^2 in males and ≥ 45 g/m^2 in females; clinical events were defined as follows:

- Renal events: CKD stage G5 eGFR < 15 ml/min/1.73m^2), renal transplantation or dialysis
- Cardiac events: atrial fibrillation, admission for any rhythm disturbance, admission for congestive heart failure, implantation of an ICD or PM, myocardial infarction, coronary artery bypass graft surgery or a percutaneous transluminal angioplasty intervention
- Cerebral events: stroke or TIA diagnosed by a neurologist

Source: Arends et al. 2017.[25]

Results from the Fabry Outcome Survey, carried out in 19 countries from 2001–2007 (n = 1,453), further support the multisystemic nature of the disease.[26] The most frequent signs and symptoms were neurological (68%), followed by CV (55%), ocular involvement (53%) and GI (51%). The most common manifestations in males were neurological (75%), dermatological (66%) and CV (60%); in females, the most common manifestations were neurological (61%), CV (50%) and ocular (49%). These findings suggest that females also have a significant risk of organ involvement, which is similar to males. The real-world CPRD study in England (n = 535) found that pain (49%), respiratory symptoms (32.5%), mental health symptoms (23.0%) and GI symptoms (22.1%) were the most frequently reported in patients with FD.[8]

Although females with FD have a lower incidence and narrower range of symptoms than males, they still experience debilitating symptoms that should not be dismissed.[15] A Dutch study that included 63 female patients with FD and 52 age-matched controls showed that fatigue (89.0% vs. 57.0%), loss of libido (60% vs. 23%), dizziness (60% vs. 19%), joint paint (58% vs. 25%), pain in hands (58% vs. 11%), palpitations (48% vs. 13%), pain in feet (39% vs. 9%) and proteinuria during pregnancy (34% vs. 0.0%) are more prevalent in females with FD than controls.[27]

The introduction of ERTs, which are currently used as gold-standard treatment, have shown beneficial effects on symptomatic burden in FD. In a Dutch prospective study of 75 patients with FD treated with ERT between 1999–2010, renal function and left ventricular mass index (LVMI) remained stable in females, whereas renal function declined and LVMI increased in males.[28] The odds for developing a first complication increased with age (odds ratio [OR] 1.05; 95% confidence interval [CI]: 1.0–1.1 per year; p = 0.012), but declined with longer treatment duration (OR 0.81; 95% CI: 0.68–0.96 per year of ERT; p = 0.015) independent of sex. In summary, long-term ERT combined with optimal supportive care did not prevent disease progression, but longer treatment duration reduced the risk of developing additional complications. Although the introduction of ERTs have shown beneficial effects on symptomatic burden, patients continue to experience a significant clinical burden that impacts their quality of life (QoL).[21, 26]

B.1.3.3.3. Quality of life burden

As a result of their symptomatic burden, patients with FD experience a poorer QoL compared with the general population, particularly in terms of physical functioning.[24]

Patients with FD more frequently experience limitations in activities of daily life compared with age-matched healthy people, particularly for females and males aged under 50 years.[29] QoL has been found to decrease with increasing age and disease severity.[24] A 2015 systematic review found that patients with CV complications, stroke or transient ischemic attacks and multiple Fabry complications had a significantly reduced QoL compared with patients who had no organ involvement (cerebrovascular accident, p = 0.037; CV complications, p = 0.026; multiple complications, p < 0.001).[24]

Although there are limited data linking FD and mental health QoL, FD may be associated with cognitive deficits and a high prevalence of psychological disorders such as depression.[30] A real-world CPRD study in England between January 2000–December 2019 (n = 535) reported that 23% of patients with FD had mental health issues.[8] In a separate study, Achenbach's adult questionnaire results showed that patients with FD exhibit social-adaptive functioning deficits that are significantly correlated with anxiety ($p = 0.05$) and depression ($p < 0.01$).[31]

The introduction of ERTs have shown beneficial effects on QoL in FD. A 2006 UK economic study reported improvement in overall utility values for patients treated with ERT compared with untreated patients (0.94 vs. 0.6).[32] A Polish prospective study (n = 33) reported a higher EQ-5D index score for patients treated with ERT vs. no ERT (0.80 vs. 0.58).[33] A European study in patients with FD with GI symptoms (n = 714) reported improved EQ-5D scores after 12 months of treatment with agalsidase alfa (mean [SD]: 0.69 [0.31] vs. 0.65 [0.35]).[34] Despite the introduction of ERTs, patients continue to experience symptoms, as well as a corresponding significant burden and impact on their QoL.[24]

B.1.3.3.4. Socioeconomic burden

FD incurs a substantial economic burden, which is largely driven by direct medical costs. Costs increase with the symptomatic burden of FD; patients with multiple complications incur a cost burden that is approximately 3 times higher than patients with a single complication.[35] In untreated patients, the cost of hospitalisation is the main cost driver, accounting for approximately 70% of direct medical costs in the UK.[35, 36] In a 2017 UK cost-of-illness study, the total annual direct medical costs of managing FD was £3,300 per adult and £1,300 per child.[35, 36] Of these, hospital costs accounted for £2,300 (69.7%) and £630 (48.5%), respectively.[36]

The real-world CPRD study in England from 2000–2019 (n = 535) showed that FD patients had a mean of 5.6 GP appointments (associated cost: £185), 9.3 consultations (associated cost: £203) and 33.1 primary care prescriptions (associated cost: £296) per patient-year, with cardiology being the most frequent referral.[8] 55.3% of patients with ≥ 1 year follow-up post-diagnosis have ≥ 1 outpatient

visit, and 41.1% have ≥ 1 admission in the same time period.[8] Additionally, one-third of patients during the observation period attended accident and emergency (A&E).

As a disease that affects adults of working age, FD also affects productivity of patients. Indirect costs are associated with productivity loss in untreated patients, accounting for approximately 66% of the overall economic burden in these patients.[37] Economic burden increases with the symptomatic burden of FD, as patients with multiple complications incur a cost burden that is almost 3 times that of patients with a single complication.[35] Results from a US survey from 2016–2017 found that, of 90 patients with moderate Fabry-related pain, approximately 66% reported a moderate or severe interference with work, and of the 99 patients with severe Fabry-related pain, approximately 85% reported a moderate or severe interference with work activities.[38] In a UK cohort study of males with FD, of the 46 questioned on employment status, 8 (17%) stated they had never worked because of their diagnosis, and only 56.8% were currently employed.[15] Approximately, 70% of patients stated that the pain associated with FD required taking time off work, while 68.5% of patients reported that other consequences of the disease, such as diarrhoea and fatigue, interfered with their ability to carry out a job.

B.1.3.4. Clinical care pathway and proposed positioning of the technology

The following sections provide an overview of the UK clinical guidelines for managing FD, the current treatment options and unmet need, and justification for the proposed use of PRX-102 in treating adults with FD who would usually receive ERT.

B.1.3.4.1. UK clinical guidelines

The clinical manifestations of FD are highly heterogeneous and are influenced by age, sex and genetics. As a result of this heterogeneity and the number of organ systems involved, there is no specific, clinically defined treatment pathway for FD, and patients are therefore treated on an individual basis.[39, 40]

In the NHS in England, clinical management of adults with FD is delivered through the lysosomal storage disorders (LSD) highly specialised service, provided by Highly Specialised LSD Centres, including outreach when delivered as part of a provider network.[41] Patients with FD are treated with intravenous (IV) infusions of ERTs (agalsidase alfa or agalsidase beta). For patients with an amenable mutation, oral chaperone therapy with migalastat can be used.[42]

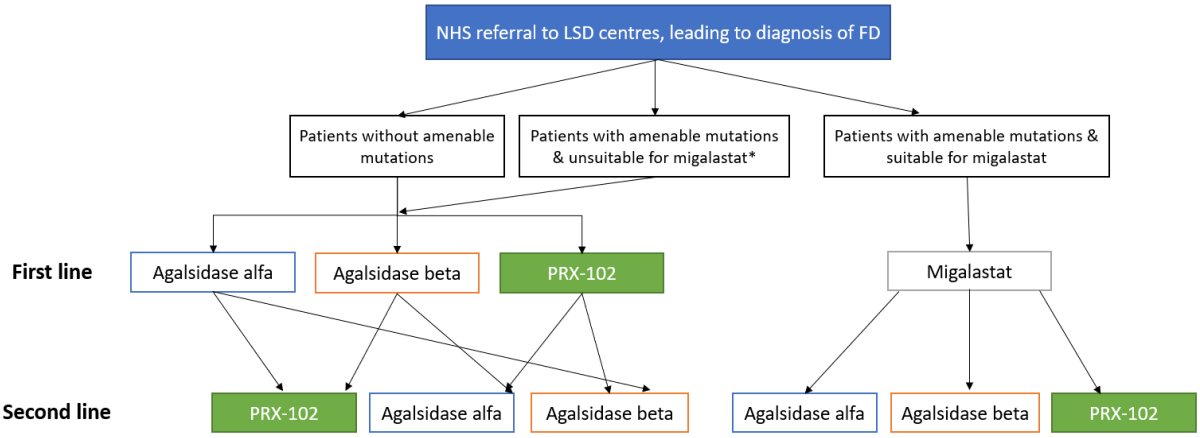
UK clinical guidelines for the treatment of adults with FD were published by the BIMDG in 2020.[2] These include specific criteria for starting ERT, based on early clinical signs of renal, cardiac or neurological involvement. Most males and approximately half of females meet these criteria when diagnosed. For patients whose FD does not meet criteria at diagnosis, approximately 10% each year will progress to needing ERT.[17] The BIMDG guidelines recommend IV infusions of ERT for adult patients (≥ 16 years) with a confirmed diagnosis of FD and meeting treatment initiation criteria[2], specifically agalsidase beta 1 mg/kg every 2 weeks (E2W) (in some circumstance 0.3 mg/kg E2W) or agalsidase alfa 0.2 mg/kg E2W. For patients with a confirmed diagnosis of FD and meeting treatment initiation criteria with an amenable mutation, migalastat is also recommended (123 mg tablets every other day). In 2017, NICE recommended migalastat as an option for treating FD in people over 16 years of age with an amenable mutation, only if migalastat is provided with the discount agreed in the patient access scheme, and only if ERT would otherwise be offered.[43]

B.1.3.4.2. Place of PRX-102 in the treatment pathway

PRX-102 is positioned as an additional treatment option for adults with FD who would be treated with an ERT. This would include patients who are treatment-naïve who would usually be treated with agalsidase alfa or agalsidase beta, and those previously treated with currently available therapies, such as agalsidase alfa, agalsidase beta or migalastat. The eligible patient population would only include patients with an amenable mutation, in those who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). The decision about which ERT to use in these patients (PRX-102, agalsidase alfa or agalsidase beta) would be made by the

clinician and the patient. The current clinical pathway of care and proposed positioning of PRX-102 is shown in Figure 1.

Figure 1: Proposed place of PRX-102 in the treatment pathway



Key: FD, Fabry disease; LSD, lysosomal storage disorder.
Notes: *, unsuitable due to issues with adherence, tolerance, patient/clinician choice, or any other reason.

B.1.3.4.3. Unmet need

The need for additional options for patients with FD who are usually treated with ERTs is apparent when considering the limitations of the current therapies, agalsidase alfa and agalsidase beta.

Current ERTs have short circulatory half-lives (agalsidase alfa: 108 ± 17 minutes in males, 89 ± 28 minutes in females; agalsidase beta: 80–120 minutes)[44, 45], which means that patients require frequent infusions E2W. Despite treatment, patients continue to experience symptoms and long-term complications of FD.[6] Both agalsidase alfa and agalsidase beta can also induce the production of neutralising anti-drug antibodies (ADAs), which limit the efficacy of ERT and reduces their long-term benefit.[46, 47]

Current ERTs are given via IV infusion E2W, which can take place at home or in hospital. Infusion times vary between agalsidase alfa and agalsidase beta, but both require a substantial administration time every fortnight for the patient (and homecare professional if patient is unable to self-administer at home). These therapies may also be associated with infusion-related reactions (IRRs), defined as hypersensitivity or anaphylactoid reactions occurring during IV administration.

Delayed infusion reactions (DIR) can also occur, which present once an infusion has been administered.[48] DIRs may require the use of pre-medication and prolongation of infusion times to reduce their occurrence. Examples of pre-medication for FD include antihistamines and/or low-dose corticosteroids.

Clinicians can advise patients to switch to an alternative treatment for a number of reasons, including the patient's response to the initial infusion or any changes in renal, cardiac or central nervous system symptoms observed during annual monitoring.[49] At a UK advisory board, clinicians stated that they would most often switch patients from agalsidase alfa to agalsidase beta. Treatment is usually initiated with agalsidase alfa as it has a shorter infusion time, and if there is evidence of organ damage progression, patients would be switched to agalsidase beta due to its higher dose of ERT.[49]

Migalastat provides an additional treatment option for patients with FD who have an amenable mutation. As such, it is only eligible for use in approximately 50% of the global FD population.[36] In addition, not all eligible patients will be suitable for treatment because of issues with tolerance or adherence, as migalastat requires a 4-hour fasting window to be effective (2 hours before and after administration).[50]

Given the limitations of current treatments for FD, there is an unmet need for a new therapy that provides improved and sustained efficacy without inducing an immune response or IRRs, and with a more convenient administration regimen that relieves the ERT infusion burden.

B.1.4. Equality considerations

No equality considerations were identified in relation to the treatment of adult patients with FD.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

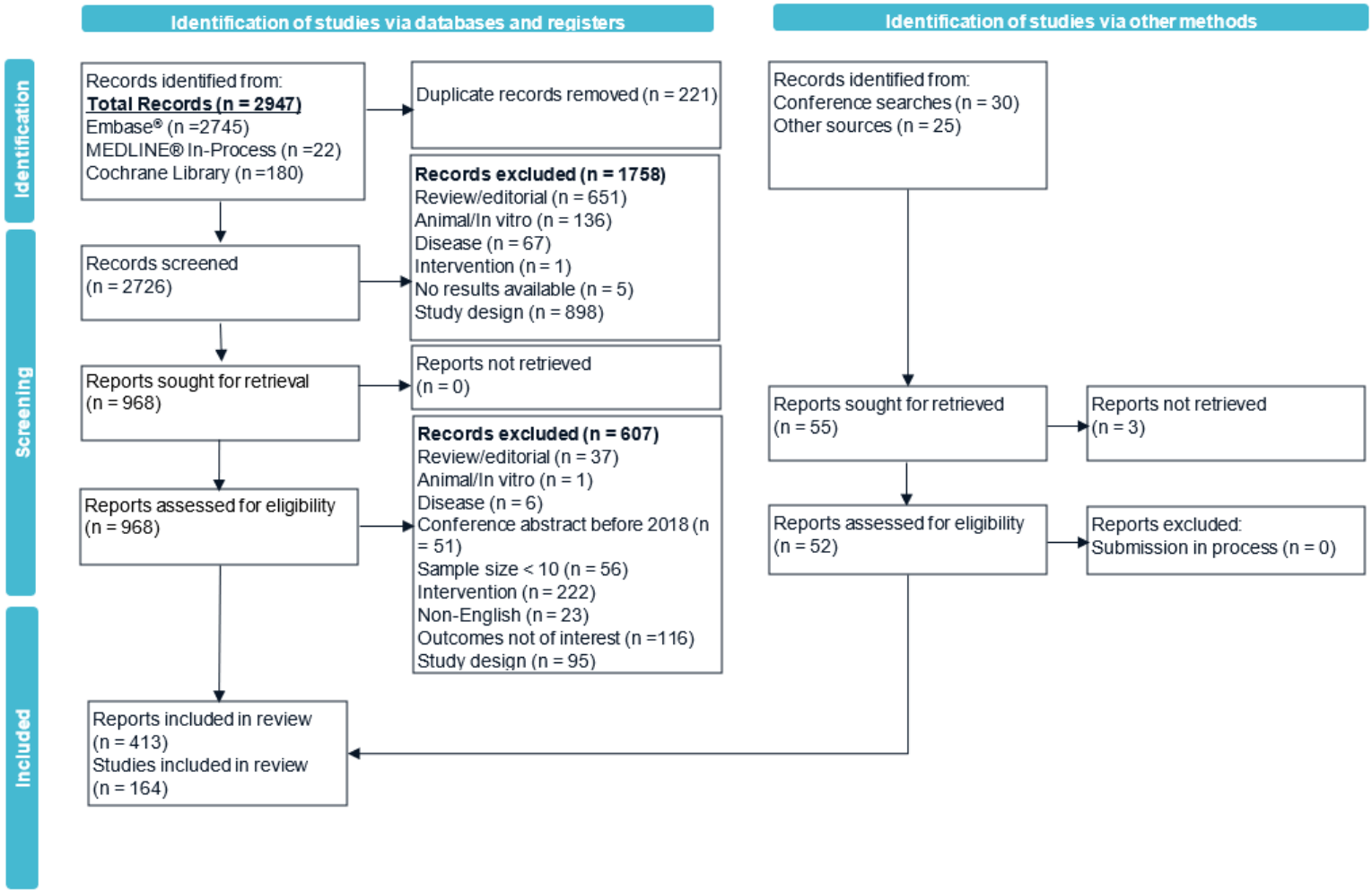
A clinical systematic literature review (SLR) was conducted to identify relevant clinical evidence for this submission for adult patients with FD. Database searches were conducted on 18 May 2021, with an update conducted on 28 September 2022.

A total of 164 studies were included in the clinical SLR. These included 156 studies from the original SLR (15 randomised control trials [RCTs] and 141 non-RCTs/observational studies) and 8 studies from the updated SLR (1 RCT and 7 non-RCTs/observational studies).

Of the 16 included RCTs, 13 were relevant to the scope of this appraisal as they investigated PRX-102 (n = 1), agalsidase alfa (n = 6) or agalsidase beta (n = 6). Of the 141 non-RCTs/observational studies identified in the original SLR, 5 investigated PRX-102, and these studies have also been included in the submission.

The overall Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is presented in Figure 2. Full details of the SLR process and methods used to identify and select the relevant clinical evidence are presented in Appendix D.1.

Figure 2: Overall PRISMA for both the original (18 May 2021) and updated (28 September 2022) SLR



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

B.2.2. List of relevant clinical effectiveness evidence

A total of 6 studies that included PRX-102 were identified in the clinical SLR (1 RCT and 5 non-RCTs). Of these, 3 studies (summarised in Table 4) included the key relevant primary and secondary efficacy outcomes from Phase III studies, and are as follows:

- BALANCE (NCT02795676): a Phase III randomised, double-blind, active controlled study comparing the safety and efficacy of PRX-102 1 mg/kg E2W with agalsidase beta 1 mg/kg E2W in patients with FD with impaired renal function who were previously treated with agalsidase beta[4]
- BRIGHT (NCT03180840): a Phase III open-label switch study assessing the safety, efficacy, and pharmacokinetics (PK) of PRX-102 2 mg/kg administered every 4 weeks (E4W) in patients with FD who were switched from either agalsidase alfa or agalsidase beta E2W after receiving either treatment for at least 3 years, and on a stable dose for at least 6 months[51]
- BRIDGE (NCT03018730): a Phase III open-label switch study assessing the safety and efficacy of PRX-102 1 mg/kg E2W in patients with FD who were switched from agalsidase alfa E2W after receiving this treatment for at least 2 years[52]

Further supporting evidence identified in the SLR included the following Phase I/II studies (summarised in Table 5 and detailed in Appendix M.4):

- PB-102-F01 (NCT01678898): a Phase I/II open-label, dose-ranging study of PRX-102 in treatment-naïve adults with FD to assess the safety, tolerability, PK, immunogenicity and exploratory efficacy of PRX-102 administered E2W at 0.2 mg/kg, 1.0 mg/kg or 2.0 mg/kg for 12 weeks[7]
- PB-102-F02 (NCT01678898): an extension of PB-102-F01 to evaluate the safety, tolerability, PK and exploratory efficacy parameters of PRX-102 administered E2W for 38 weeks (9 months, at the same dose that patients received in study PB-102-F01) in adults with FD[7]

- PB-102-F03 (NCT01981720): a multi-centre extension study (for patients who completed PB-102-F02) of PRX-102 administered E2W (gradually adjusted to receive 1 mg/kg) for up to 60 months in adults with FD[7]

One additional study, PEOPLE, was identified as a PRX-102 study known to the manufacturer. This study was not captured in the original SLR as this study was completed in August 2022, after the original SLR was conducted. PEOPLE (NCT05186324) was a qualitative concept elicitation interview-based study to collect evidence on the patient experience of PRX-102 administered E4W in the BRIGHT clinical study and results will be available in Q2 2023.

Table 4: Phase III clinical effectiveness evidence

Study	BALANCE[5, 53, 54]	BRIGHT[55, 56]	BRIDGE[57, 58]
Study design	Phase III, randomised, double-blind, active-controlled study Follow up: 2-year blinded treatment period, with 4 year open-label extension	Phase III, open-label, switch over study Follow up: 1-year treatment period, with 4-year open-label extension	Phase III, open-label, switch over study Follow up: 1-year treatment period, with 5-year open-label extension
Population	Adults with FD experiencing kidney function deterioration while on ERT (agalsidase beta for ≥ 1 year and on a stable dose for ≥ 6 months) (n = 78)	Adults with FD previously treated with agalsidase alfa E2W or agalsidase beta E2W for ≥ 3 years and on a stable dose for ≥ 6 months (n = 30)	Adults with FD previously treated with agalsidase alfa E2W for ≥ 2 years and on a stable dose for ≥ 6 months (n = 22)
Intervention(s)	PRX-102, 1 mg/kg E2W	PRX-102, 2 mg/kg E4W	PRX-102, 1 mg/kg E2W
Comparator(s)	Agalsidase beta, 1 mg/kg E2W	From baseline	From baseline
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	No
Rationale if study not used in the model	N/A	N/A	BRIDGE is a single-arm study, and we already have the data for PRX-102 at the same dose from the BALANCE trial
Reported outcomes specified in the decision problem	• Plasma lyso-Gb3 concentration • Urine lyso-Gb3 concentration • Plasma Gb3 concentration • Cardiac MRI • Cardiac stress test • Echocardiogram • eGFR slope (primary endpoint)	• Plasma lyso-Gb3 • Plasma Gb3 • Urine lyso-Gb3 • ECG • Left ventricular mass index (g/m2) by echocardiogram • eGFR slope • UPCR spot urine test	• Plasma lyso-Gb3 • Plasma Gb3 • Urine lyso-Gb3 • Change from baseline in ECG • Change in eGFR • Frequency of pain medication use • Exercise tolerance (stress test)

Study	BALANCE[5, 53, 54]	BRIGHT[55, 56]	BRIDGE[57, 58]
	• eGFR as determined by serum creatinine • UPCR • MSSI • Short Form BPI • Use of pain medication • Quality of life questionnaire (EQ-5D-5L) • Serious renal events, cardiac events, cerebrovascular events, and non-cardiac-related death • Achievement of Fabry Kidney Disease therapeutic goals as per the European Expert Consensus Statement on Therapeutic Goals in FD • Adverse effects of treatment (including ADAs)	• Usage of pain medication • Stress test • Short Form BPI • MSSI • Quality of life (EQ-5D-5L) • FCEs • Adverse effects of treatment (including IRRs, Infusion premedication, treatment-induced anti-PRX-102 antibodies, injection site reactions)	• Short form BPI • MSSI • Quality of life (EQ-5D-5L) • FCEs • Adverse effects of treatment (including assessment of injection site reactions, assessment of infusion related reactions, and treatment-emergent anti-PRX-102 antibodies)
Key publications	Protocol: • Warnock et al. 2020 (ASN 2020) • Warnock et al. 2020 (WORLD 2020) Efficacy and safety: • Wallace et al. 2022 (7th update on Fabry Disease, 2022)	Efficacy and safety: • Longo et al. 2022 (SSIEM 2022) • Bernat et al. 2022 (ACMG 2022)	Efficacy and safety: • Linhart et al. 2020 (WORLD 2020) • Jovanovic et al. 2022 (SSIEM 2020)
Key: ADA, anti-drug antibody; CSR, clinical study report; BPI, Brief Pain Inventory; E2W, every 2 weeks; E4W, every 4 weeks; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FCEs, Fabry clinical events; FD, Fabry disease; Gb3, globotriaosylsphingosine (lyso-Gb3); IRR, infusion-related reaction; MRI, magnetic resonance imaging; MSSI, Mainz Severity Score Index; PRX-102, pegunigalsidase alfa; UPCR, urine protein to creatinine ratio. **Source:** Chiesi, BALANCE CSR[4]; Chiesi, BRIDGE CSR[52]; Chiesi, BRIGHT CSR[51]; Warnock et al. 2020[53]; Wallace et al. 2022[5]; Longo et al. 2022 (SSIEM22)[56]; Bernat et al. 2022 (ACMG, eP149)[55]; Linhart et al. 2020 (WORLD)[57]; Jovanovic et al. 2022 (SSIEM).[58]			

Table 5: Phase I/II clinical effectiveness evidence

Study	PB-102-F01	PB-102-F02	PB-102-F03
Study design	**PB-102-F01/PB-102-F02** Phase I/II, open-label, dose ranging study Study period: 5 November 2012–6 March 2012 Follow up: 3-month treatment period (PB-102-F01), with a 9-month open-label extension (PB-102-F02) **PB-F02-F03** Phase I/II, multi-centre extension study Study period: 4 December 2012–5 August 2019 Follow up: An additional 60-month treatment period for patients who completed PB-102-F01 and PB-102-F02		
Population	• Symptomatic adults with FD (≥ 18 years, males and females): • PB-102-F01: n = 18 • PB-102-F02: n = 16 • PB-102-F03: n = 15		
Intervention(s)	• PRX-102 0.2 mg/kg E2W • PRX-102 1 mg/kg E2W • PRX-102 2 mg/kg E2W		• PRX-102 1 mg/kg E2W
Comparator(s)	None		
Indicate if study supports application for marketing authorisation	Yes		
Indicate if study used in the economic model	No		
Rationale if study not used in the model	Although the respective studies are small, non-comparative, and not included in the economic model, results of all 3 Phase I/II trials provide further evidence of safety and efficacy of PRX-102 within the treatment naïve population, including pharmacokinetic data.		

Study	PB-102-F01	PB-102-F02	PB-102-F03
Reported outcomes	• Gb3 concentrations in plasma and urine sediment • Lyso-Gb3 concentration in plasma • Kidney function, as assessed by eGFR and proteinuria • Proteinuria as determined from a spot urine sample and expressed UPCR (mg/g) • Assessment of pain using the short-form BPI questionnaire • Gb3 concentration in kidney, assessed histologically in kidney biopsy samples (at baseline) • Gb3 concentration in skin, assessed histologically in skin punch biopsy (at baseline) • LVM and cardiac fibrosis, assessed by cardiac MRI (at baseline) • Cerebrovascular disease, as assessed by clinical and MRI evaluation • Cardiac function, as assessed by echocardiography and stress test (at baseline) • MSSI (at baseline) • Gastrointestinal symptoms questionnaire • Emergence of treatment-induced anti-PRX-102 IgG antibodies		• FCEs • The following were evaluated every 3 months up to 24 months, and then every 6 months up to study end: – Gb3 concentrations in plasma – Lyso-Gb3 concentration in plasma – Kidney function, as assessed by eGFR and proteinuria – Proteinuria was determined from a spot urine sample and expressed UPCR (mg/g) – Assessment of pain using the short-form BPI questionnaire • The following was evaluated every 6 months: – MSSI – TEAEs – Emergence of treatment-induced anti-PRX-102 antibodies

Key: BPI, Brief Pain Inventory; CSR, clinical study report; E2W, every 2 weeks; eGFR, estimated glomerular filtration rate; FCE, Fabry clinical event; FD, Fabry disease; Gb3, globotriaosylceramide; LVM, left ventricular mass; Lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging; MSSI, Mainz Severity Score Index; PRX-102, pegunigalsidase alfa; TEAEs, treatment emergent adverse events; UPCR, urine protein to creatinine ratio.
Source: Hughes et al. 2020[59]; Atta et al. 2022[60]; Bernat et al. 2022[61]; Chiesi, PB-102-F01 CSR[62]; PB-102-F02 CSR[63]; PB-102-F03 CSR[64]

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

The following sections (Sections B.2.3–B.2.7) focus on the BALANCE RCT, given that it provides a direct head-to-head comparison of clinical effectiveness and safety between PRX-102 E2W and agalsidase beta E2W in patients with declining renal function, and is used to inform the economic model. BRIDGE provides supporting evidence for clinical effectiveness and safety of PRX-102 E2W compared with agalsidase alfa E2W in patients with stable renal function, with BRIGHT providing supportive evidence for the effectiveness and safety of the E4W posology. Evidence for efficacy of PRX-102 in treatment-naïve patients and long-term safety data over 60 months is provided by the Phase I/II studies; a short summary of these studies is provided in Section B.2.3.4 and additional details are provided in Appendix M.4.

The summarised methodology for the Phase III PRX-102 trials is provided in Table 6.

Table 6: Summary of study methodology for the Phase III PRX-102 trials

Trial name	BALANCE[5, 53, 54]	BRIGHT[55, 56]	BRIDGE[57, 58]
Location	29 centres in 12 countries: USA, the UK, the Netherlands, Spain, France, Italy, Norway, Slovenia, Switzerland, Finland, Hungary and the Czech Republic	14 centres in 7 countries: Belgium, the Czech Republic, Denmark, Italy, Norway, the UK and the US	10 study centres in 8 countries: (the UK, Norway, the Netherlands, the Czech Republic, Slovenia, Spain[a], Australia and Canada)
Follow-up	24 months	12 months	12 months
Trial design	Phase III randomised, double-blind, active controlled study comparing PRX-102 E2W with agalsidase beta E2W	Phase III, open-label, switch-over study from agalsidase alfa or beta E2W with PRX-102 E4W	Phase III, open-label, switch-over study from agalsidase alfa E2W to PRX-102 E2W
Key eligibility criteria for patients	• Symptomatic adults with FD, age 18–60 years • Screening eGFR by CKD-EPI equation 40 to 120 mL/min/1.73 m^2	• Male and female patients aged ≥ 18 and ≤ 60 years with documented diagnosis of FD • Previous treatment with agalsidase alfa or agalsidase beta for at least 3 years before inclusion • eGFR ≥ 30 mL/min/1.73 m^2	• Male and female patients aged 18–60 years with documented diagnosis of FD, previous treatment with agalsidase alfa for at least 2 years and on a stable dose (> 80% labelled dose/kg EOW) for at least 6 months • eGFR ≥ 40 mL/min/1.73 m^2 by CKD-EPI equation
Settings and locations	Received infusions were conducted on site and in home settings	Received infusions were conducted on site and in home settings	Received infusions were conducted on site and in home settings
Trial drugs	• PRX-102 1 mg/kg E2W (n = 53) • Agalsidase beta 1 mg/kg E2W (n = 25)	PRX-102 2.0 mg/kg E4W (n = 30)	PRX-102 1.0 mg/kg E2W (n = 22)
Permitted and disallowed concomitant medication	• The use of agalsidase alfa or any other approved or investigational drug for treating FD was strictly prohibited throughout the trial, as such drugs had the potential to interfere with the evaluation of efficacy • If before study entry a patient had been using a premedication to diminish the side effects of agalsidase beta (such as corticosteroids, antihistamines, or paracetamol) • Patients who had been on stable doses of ACEi or ARB for 4 weeks or more before	The following medications were strictly prohibited during the study: • Agalsidase beta • Agalsidase alfa • Any other investigational or approved drug for treating FD Once the patient entered the study, initiation of ACEi or ARB therapy was only permitted after discussion with,	The following medications were strictly prohibited during the study: • Agalsidase beta • Agalsidase alfa • Any other investigational or approved drug for treating FD Once the patient entered the study, initiation of ACEi or ARB therapy was only permitted after discussion with, and the approval of, the Sponsor's Medical Director

Trial name	BALANCE[5, 53, 54]	BRIGHT[55, 56]	BRIDGE[57, 58]
	study entry were permitted to remain on them; however, following randomisation, initiation or discontinuation of ACEi or ARB therapy was permitted only after discussion with the Medical Monitor	and the approval of, the Sponsor's Medical Director The use of premedication to prevent infusion reactions associated with previous ERT before entry into the study was continued during the first infusion of PRX-102, but then titrated down/removed gradually during subsequent infusions depending on the patients' tolerability	The use of premedication to prevent infusion reactions associated with previous ERT before entry into the study was continued during the first infusion of PRX-102, but then titrated down/removed gradually during subsequent infusions depending on the patients' tolerability
Primary outcomes (including scoring methods and timings of assessments)	Annualised change (slope) in $eGFR_{CKD-EPI}$	Number of participants with treatment-related adverse events as assessed by CTCAE v4.03	Number of participants with treatment-related adverse events as assessed by CTCAE v4.03
Other outcomes used in the economic model/specified in the scope	Change from baseline to all timepoints in the following measures: • $eGFR_{CKD-EPI}$ • Protein/creatinine ratio spot urine test; UPCR categories: (≤ 0.5 gr/gr; 0.5 < and < 1 gr/gr; ≥1 gr/gr) • LVMI (g/m^2) based on cardiac MRI • Exercise tolerance (stress test) • Plasma lyso-Gb3 • Urine lyso-Gb3 • Plasma Gb3 • MSSI • Frequency of pain medication use • Short form BPI	• $eGFR_{CKD-EPI}$; • eGFR slope • Plasma lyso-Gb3 • Plasma Gb3 • Urine lyso-Gb3 • UPCR spot urine test • LVMI (g/m^2) by echocardiogram • Usage of pain medication • Stress test • Short Form BPI • MSSI • QoL (EQ-5D-5L) • FCEs	• LVMI (g/m^2) by MRI • Change in $eGFR_{CKD-EPI}$ • Plasma lyso-Gb3 • Plasma Gb3 • Urine lyso-Gb3 • UPCR spot urine test • Frequency of pain medication use • Exercise tolerance (stress test) • Short form BPI • MSSI • QoL (EQ-5D-5L) • FCEs

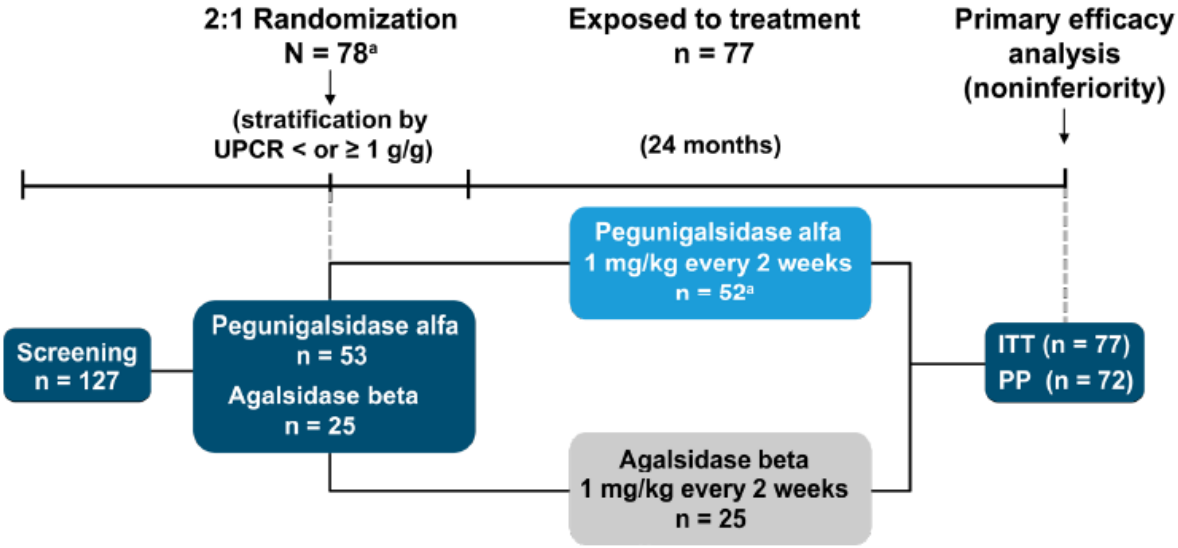
Trial name	BALANCE[5, 53, 54]	BRIGHT[55, 56]	BRIDGE[57, 58]
	• QoL (EQ-5D-5L) • Incidence of FCEs • Achievement of Fabry Kidney Disease therapeutic goals		
Pre-planned subgroups	The subgroups included the following variables: • Sex (male or female) • ADA status at baseline (negative or positive), • FD classification (classic/non-classic) • Baseline eGFR category (≤ 60; 60 < and ≤ 90; > 90 mL/min/1.73m^2), baseline eGFR slope category (≤ -5; > -5 mL/min/ 1.73m^2/year) • Use of ACEi/ARB at baseline (Yes/No), UPCR category at baseline (≤ 0.5 gr/gr; 0.5 < and < 1 gr/gr; ≥1 gr/gr), and region (US/ex-US)	Subgroup analyses were conducted based on baseline characteristics and demographics for selected efficacy and safety endpoints, chosen from the following list: • Sex (male or female) • ADA status (negative or positive), • FD classification, (classic/non-classic) • eGFR, • Previous ERT treatment, • Use of ACEi or ARB • Hyperfiltration status (this last subgroup was added as a post-hoc analysis)	Analyses of efficacy and safety endpoints were performed overall and partly for the following subgroups: • Sex (male or female) (all endpoints) • Treatment-emergent immunogenicity status (ADA-positive/ADA-negative) • Disease manifestation at baseline: classic/non-classic
Key: ACEi, angiotensin converting enzyme inhibitor; ADA, anti-drug antibodies; ARB, angiotensin II receptor blocker; BPI, Brief Pain Inventory; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; E2W, every 2 weeks; E4W, every 4 weeks; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; FD, Fabry disease; FCE, Fabry clinical event; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; MSSI, Mainz Severity Score Index; QoL, quality of life; UPCR, urine protein to creatinine ratio. **Notes:** [a] The single centre in Spain screened patients but no patients were treated. **Source:** Chiesi. BALANCE CSR[4]; Chiesi. BRIDGE CSR[52]; Chiesi. BRIGHT CSR[51]; Jovanovic et al. 2022[58]; Linhart et al. 2020[57]; Bernat et al. 2022[55]; Longo et al. 2022[56]; Warnock et al. 2020 ASN[54], Warnock et al. 2020 WORLD[53], Wallace et al. 2022[5]			

B.2.3.1. BALANCE trial

B.2.3.1.1. Study design

BALANCE was a 24-month Phase III, randomised, double-blind, multinational, active controlled study of PRX-102 1 mg/kg E2W in 78 patients with FD with impaired renal function (Figure 3). The primary objective of this study was to evaluate the safety, efficacy and PK of PRX-102 E2W compared with agalsidase beta E2W in patients with deteriorating renal function.[4] The open-label extension phase is ongoing (NCT03566017 [PB-102-F60]; Section B.2.10.4), where patients will continue to receive PRX-102 E2W for up to 4 years.

Figure 3: BALANCE study design schematic



Key: ITT, intention to treat; PP, per protocol; UPCR, urinary protein-to-creatinine ratio.
Notes: [a], Patient withdrew consent before the first dose.
Source: Wallace et al. 2022.[5]

Following screening, eligible patients were randomised in a 2:1 ratio to either switch to PRX-102 E2W or continue treatment with agalsidase beta E2W. Randomisation was stratified by urine protein-to-creatinine ratio (UPCR), a measure of kidney function. Both treatments were administered as an IV infusion E2W at 1 mg/kg, for up to 24 months. Patients and study staff were blinded as to which treatment was being given. The first few infusions were administered at the site, and patients could

thereafter receive treatment at home if the investigator and the sponsor's Medical Monitor agreed that it was safe to do so.[4]

B.2.3.1.2. Eligibility criteria

Table 7 summarises the inclusion and exclusion criteria for the BALANCE trial.

Table 7: Inclusion/exclusion criteria for the BALANCE trial

Inclusion criteria	Exclusion criteria
• Symptomatic adult FD patients aged 18–60 years • Males: plasma and/or leukocyte α-galactosidase activity (by activity assay) < 30% mean normal levels and 1 or more of the characteristic features of FD: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations a first-degree male relative with FD, and 1 or more of the characteristic features of FD: – Neuropathic pain – Cornea verticillata – Clustered angiokeratoma • eGFR at screening of ≥ 40 – ≤ 120 ml/min/1.73 m^2 by CKD-EPI equation • Linear negative slope of eGFR of ≥ 2 mL/min/1.73 m^2/year based on at least 3 serum creatinine values over approximately 1 year (range of 9–18 months including the value obtained at the screening visit) • Treatment with a dose of 1 mg/kg agalsidase beta per infusion E2W for at least 1 year and at least 80% of 13 (10.4) mg/kg total dose over the last 6 months • Patients whose partners are of child-bearing potential who agree to use medically accepted methods of contraception – not including the rhythm method	• History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa • Known non-pathogenic Fabry mutations (polymorphism) • History of renal dialysis or transplantation • History of acute kidney injury in the 12 months before screening, including specific kidney diseases (e.g. acute interstitial nephritis, acute glomerular and vasculitis renal diseases); non-specific conditions (e.g. ischaemia, toxic injury); as well as extrarenal pathology (e.g. prerenal azotaemia, and acute postrenal obstructive nephropathy) • ACEi or ARB therapy initiated, or dose changed in the 4 weeks before screening • eGFR at screening of ≥ 91 – ≤ 120 ml/min/1.73 m^2, having a historical eGFR value of > 120 ml/min/1.73 m^2 (during 9–18 months before screening) • UPCR > 0.5 g/g and not treated with an ACEi or ARB • Known history of hypersensitivity to gadolinium-based contrast agent that is not managed by the use of premedication • Females who are pregnant, planning to become pregnant during the study, or are breastfeeding • Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before screening • Congestive heart failure NYHA Class IV • Cerebrovascular event (stroke, transient ischaemic attack) in the 6-month period before screening • Patients with any medical, emotional, behavioural, or psychological condition that may interfere with the patient's compliance to adhere to study requirements (as determined by the investigator and/or medical director)
Key: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; E2W, every 2 weeks; FD, Fabry disease; NYHA, New York Heart Association; UPCR, urine protein to creatinine ratio. **Source**: Chiesi. BALANCE CSR[4]; Warnock et al. ASN 2020[54]; Warnock et al. WORLD 2020[53]	

B.2.3.1.3. Baseline characteristics

Table 8 presents the baseline characteristics; baseline characteristics by sex are presented in Appendix M.1. Patient disposition data for BALANCE are presented in Appendix D.2.[4]

In BALANCE, age was similar across treatment arms, with a mean age of 44.3 years (range, 18–60 years). This is similar to the mean age at first diagnosis of FD in England (37 years), according an analysis of UK CPRD data.[8] Additionally, clinical experts considered the age across treatment arms to be representative of FD patients in the UK.[49]

Males outnumbered females in both arms, with a greater proportion of males in the agalsidase beta E2W arm vs. PRX-102 E2W arm (72% vs. 56%). As mandated in the protocol, enrolment of females could not exceed 50%. As randomisation was not stratified by sex, by chance a higher percentage of females were randomised to the PRX-102 E2W arm (44% vs. 28%).[4]

Treatment arms were comparable on all baseline estimated glomerular filtration rate (eGFR) data (see Table 8). Similarly, the overall mean eGFR slope was similar at screening and baseline (at screening; [redacted] vs. at baseline; -8.1 mL/min/1.73 m^2/year) and was similar between the arms at both timepoints.[4]

At baseline, [redacted]% of patients had proteinuria (see Appendix M.1 for a summary of medical history conditions). Overall, more than half the patients ([redacted]%) were taking angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) at baseline, with a greater proportion taking them in the agalsidase beta E2W arm compared with the PRX-102 E2W arm ([redacted]% vs. [redacted]%).[4]

Table 8: BALANCE: baseline characteristics, ITT population

	PRX-102 1 mg/kg E2W (n = 52)	Agalsidase beta 1 mg/kg E2W (n = 25)	Overall (n = 77)
Mean age, years ± SE	43.9 ± 1.4	45.2 ± 1.9	44.3 ± 1.1
Sex, n (%)			
Male	29 (55.8)	18 (72.0)	47 (61.0)
Female	23 (44.2)	7 (28.0)	30 (39.0)
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black or African American	1 (1.9)	2 (8.0)	3 (3.9)
White	49 (94.2)	23 (92.0)	72 (93.5)
Type of FD, n (%)			
Classic	27 (51.9%)	14 (56.0%)	41 (53.2%)
Non-classic	25 (48.1%)	11 (44.0%)	36 (46.8%)
eGFR (mL/min/1.73 m^2) at baseline			
Mean ± SE, years	73.3 ± 2.8	73.5 ± 4.0	73.3 ± 2.3
Range: min, max	30.2, 125.9	34.1, 107.6	30.2, 125.9
eGFR category (mL/min/1.73 m^2), n (%) at baseline			
≤ 60	13 (25.0%)	8 (32.0%)	21 (27.3%)
60 < and ≤90	28 (53.8%)	11 (44.0%)	39 (50.6%)
> 90	11 (21.2%)	6 (24.0%)	17 (22.1%)
eGFR slope (mL/min/1.73 m^2/year) at baseline			
Mean ± SE, years	-8.07 ± 0.91	-8.48 ± 0.83	-8.21 ± 0.67
Range: min, max	-30.5, 6.3	-20.3, -2.8	-30.5, 6.3
eGFR slope categories (mL/min/1.73 m^2/year), n (%) at baseline			
≤ -5	[redacted]	[redacted]	[redacted]
> -5	[redacted]	[redacted]	[redacted]
UPCR categories at baseline, n (%)			
UPCR ≤ 0.5 gr/gr	36 (69.2%)	20 (80.0%)	56 (72.7%)
0.5 < UPCR < 1 gr/gr	9 (17.3%)	2 (8.0%)	11 (14.3%)
1 ≤ UPCR gr/gr	7 (13.5%)	3 (12.0%)	10 (13.0%)
Treatment with ACEIs or ARBs, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Duration of the last continuous agalsidase-beta treatment (months)[a]			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]
ADA positive	[redacted]	[redacted]	-
ADA negative	[redacted]	[redacted]	-

Key: ACEis, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CSR, clinical study report; eGFR, estimated glomerular filtration rate; E2W, every 2 weeks; FD, Fabry disease; Gb3, globotriaosylceramide; ITT, intention-to -treat; Lyso-Gb3, globotriaosylsphingosine; NR, not reported; PRX-102, Pegunigalsidase alfa; SD, standard deviation; SE, standard error; UPCR, urine protein creatinine ratio.
Notes: [a], Defined as the value in plasma × 100/12.95, where 12.95 nmol/hr/mL is the mean of the lab normal reference range; [b], eGFR slope at screening was based on historical serum creatinine and screening serum creatinine. [c], eGFR slope at baseline was based on historical, screening, and baseline serum creatinine; [d], "Last" treatment refers to patients who had several periods of treatment with agalsidase beta in the past.
Source: Wallace et al. 2022[5]; Chiesi, BALANCE CSR.[4]

B.2.3.2. BRIGHT trial

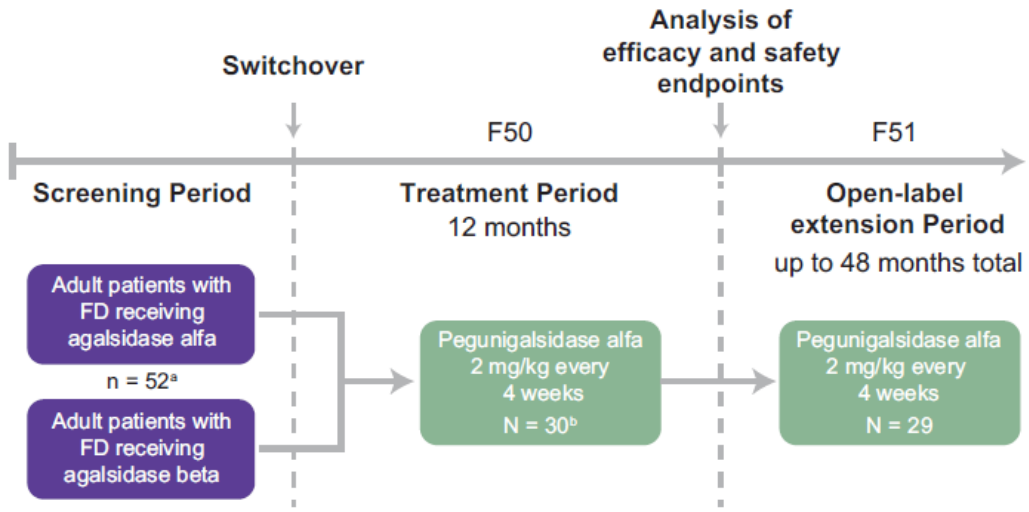
B.2.3.2.1. Study design

BRIGHT (PB-102-F50; NCT03180840) was a Phase III, open-label, multinational, switchover study designed to assess PK, safety and efficacy of PRX-102 E4W in adults with FD previously treated with either agalsidase alfa or agalsidase beta ≥ 3 years, and on a stable dose (> 80% labelled dose/kg) for ≥ 6 months. Following screening, eligible patients were switched from their current ERT to PRX-102 2 mg/kg E4W for 12 months (or 14 infusions) (Figure 4).[51]

For PK analyses, blood samples were taken from all patients on Day 1 and at the end of the study (Infusion 14 at 12 months).[51] PK parameters were derived from the plasma concentration vs. time profiles to determine the PK of the study drug.

The BRIGHT extension study (PB-102-F51; NCT03614234) is an ongoing Phase III open-label, multinational extension study to evaluate the long-term safety and efficacy of PRX-102 2 mg/kg E4W for up to 48 months, in patients who complete BRIGHT (PB-102-F50).[51]

Figure 4: BRIGHT trial design schematic



Key: eGFR, estimated glomerular filtration rate; FD, Fabry disease.
Notes: [a], Patients with a linear negative eGFR slope of ≥ 2 mL/min/1.73 m2/year were excluded. [b], The patient who did not complete the study withdrew because of a major traffic accident unrelated to FD.
Source: Bernat et al. 2022.[61]

B.2.3.2.2. Eligibility criteria

Table 9 summarises the inclusion and exclusion criteria for the BRIGHT trial.

Table 9: Inclusion/exclusion criteria for the BRIGHT study

Inclusion criteria	Exclusion criteria
• Patients aged 18–60 years with a documented diagnosis of FD • Males: plasma and/or leukocyte α-galactosidase A activity (by activity assay) less than lower limit of normal per laboratory reference range and 1 or more of the characteristic features of FD: – Neuropathic pain – Cornea verticillata – Clustered angiokeratoma • Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations a first-degree male relative with FD, and 1 or more of the characteristic features of FD: – Neuropathic pain – Cornea verticillata – Clustered angiokeratoma • Treatment with agalsidase alfa or agalsidase beta for at least 3 years and on a stable dose (> 80% labelled dose/kg) for at least the last 6 months • eGFR ≥ 30 mL/min/1.73 m^2 by CKD-EPI equation at screening visit • Availability of at least 3 historical serum creatinine evaluations since starting agalsidase alfa or agalsidase beta treatment and not more than 2 years • Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically accepted, highly effective method of contraception, including: combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence • Patients whose clinical condition, in the opinion of the Investigator, that are suitable for treatment with ERT every 4 weeks	• History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa or agalsidase beta • History of renal dialysis or transplantation • Linear negative slope of eGFR of ≥ 2 mL/min/1.73 m^2 based on at least 4 serum creatinine values over approximately 2 years (including the value obtained at the screening visit) • History of acute kidney injury in the 12 months before screening, including specific kidney diseases (e.g. acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g. ischaemia, toxic injury); as well as extrarenal pathology (e.g. prerenal azotaemia, and acute post renal obstructive nephropathy) • ACE inhibitor or ARB therapy initiated, or dose changed in the 4 weeks before screening • UPCR at screening > 0.5 g/g or mg/mg or 500 mg/g and not treated with an ACE inhibitor or ARB • Females who are pregnant, planning to become pregnant during the study, or are breastfeeding • Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before screening • Cerebrovascular event (stroke, transient ischaemic attack) in the 6-month period before screening • Presence of any medical, emotional, behavioural, or psychological condition that, in the judgment of the Investigator and/or Medical Director, would interfere with the patient's compliance with the requirements of the study
Key: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FD, Fabry disease; UPCR, urine protein to creatinine ratio. **Source:** Bernat et al. 2022[55]; Longo et al. 2022[56]; Chiesi, BRIGHT CSR[51]	

B.2.3.2.3. Baseline characteristics

Baseline characteristics of the safety population from the BRIGHT trial are summarised in Appendix M.2. Patient disposition data for BRIGHT are presented in Appendix D.2.

All 30 patients were white, with a mean (SD) age of 40.5 (11.3) years, and a median age of [redacted] years, ranging from [redacted] years of age. The mean (SD) age at the start of FD therapy was [redacted] years: [redacted] years for males and [redacted] years for females. Twenty-four (80.0%) patients were male, and 6 (20.0%) patients were female, in line with the plan to include ~20% female patients in the study. Classic FD was reported for 16 (72.7%) male patients; 6 (27.3%) male and 6 (100.0%) female patients had non-classic FD.

Mean (SD) eGFR at baseline was [redacted] mL/min/1.73 m^2 overall and was slightly higher in male patients ([redacted] mL/min/1.73 m^2) than female patients ([redacted] mL/min/1.73 m^2). Mean eGFR values ranged from [redacted] mL/min/1.73 m^2 in male patients and from [redacted] mL/min/1.73 m^2 in female patients.

B.2.3.3. BRIDGE trial

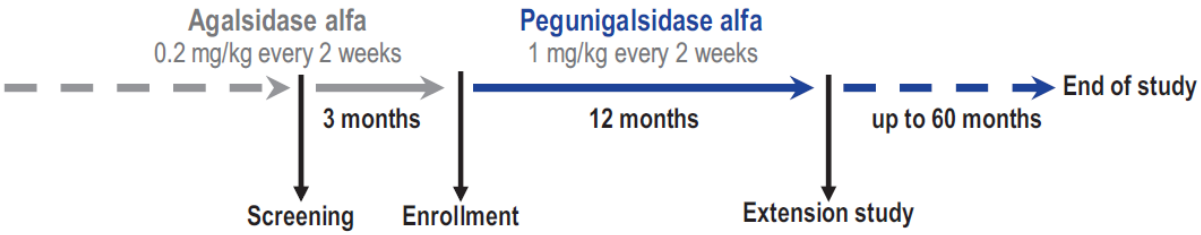
B.2.3.3.1. Study design

BRIDGE was a Phase III, open-label switchover study that assessed the safety and efficacy of PRX-102 1 mg/kg E2W in symptomatic patients with FD currently treated with agalsidase alfa E2W (Figure 5). The objectives were to evaluate the safety (primary objective) and efficacy (secondary objective) of PRX-102.[52]

Patient eligibility was checked after the 3-month screening period. For the enrolled patients, pre-medication, if used for the patients' agalsidase alfa infusions before study entry, was continued for the first infusions with PRX-102 treatment, and was then gradually tapered at the investigator's discretion during the first 2 months after switching to PRX-102. At Visit 1, the first PRX-102 infusion was administered under controlled conditions at the study centre. Patients received subsequent PRX-102

infusions E2W. Patients were allowed to receive the PRX-102 infusions at home if the Investigator and Sponsor Medical Monitor agreed that it was safe to do so, based on the patient's clinical condition and local practices and regulations. In the event of premature study discontinuation, a premature withdrawal visit was planned, during which all the tests planned at the last visit (i.e. Visit 27) were performed.[52]

Figure 5: BRIDGE trial design



Source: Jovanovic et al. 2022.[58]

B.2.3.3.2. Eligibility criteria

Table 10 summarises the inclusion and exclusion criteria for the BRIDGE trial.

Table 10: Inclusion/exclusion criteria for the BRIDGE trial

Inclusion criteria	Exclusion criteria
• Symptomatic adult FD patients aged 18–60 years • Males: plasma and/or leukocyte α-galactosidase activity (by activity assay) < LLN according to laboratory range and 1 or more of the characteristic features of FD: – Neuropathic pain – Cornea verticillata – Clustered angiokeratoma • Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations a first-degree male relative with FD, and 1 or more of the characteristic features of FD: – Neuropathic pain – Cornea verticillata – Clustered angiokeratoma • Treatment with agalsidase alfa for at least 2 years and on a stable dose (> 80% labelled dose/kg) for at least 6 months	• History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa • History of renal dialysis or transplantation • History of acute kidney injury in the 12 months before screening, including specific kidney diseases (e.g. acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g. ischaemia, toxic injury); as well as extrarenal pathology (e.g. prerenal azotaemia, and acute postrenal obstructive nephropathy) • ACE inhibitor or ARB therapy initiated, or dose changed in the 4 weeks before screening • UPCR > 0.5 g/g and not treated with an ACE inhibitor or ARB • Known history of hypersensitivity to gadolinium-based contrast agent that is not managed by the use of premedication

Inclusion criteria	Exclusion criteria
• eGFR ≥ 40 ml/min/1.73 m^2 by CKD-EPI equation • Availability of at least 2 historical serum creatinine evaluations since starting agalsidase alfa treatment and not more than 2 years • Patients whose partners are of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method	• Females who are pregnant, planning to become pregnant during the study, or are breastfeeding • Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before screening • Congestive heart failure NYHA Class IV • Cerebrovascular event (stroke, transient ischaemic attack) in the 6-month period before screening
Key: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FD, Fabry disease; LLN, lower limit of normal; NYHA, New York Heart Association; UPCR, urine protein to creatinine ratio. **Source:** Jovanovic et al. 2022[58]; Linhart et al. 2020[57]; BRIDGE CSR, 2020.[52]	

B.2.3.3.3. Baseline characteristics

Baseline demographics of the efficacy and safety populations from the BRIDGE trial are presented in Appendix M.3, and patient disposition characteristics are presented in Appendix D.2.

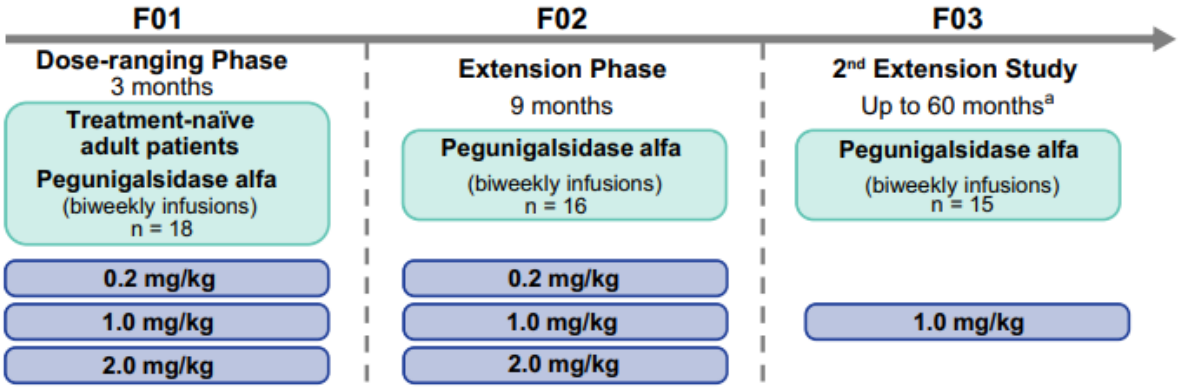
All 20 patients in the efficacy population were white, with a median age of 45.0 years, ranging from 26–60 years of age.[52] The median age at the start of FD therapy was 38.0 years, ranging from 17–53 years.

Overall, in the efficacy population, the mean (SD) baseline eGFR was 79.5 mL/min/1.73 m^2.[52] The mean (SD) annualised eGFR slope was -5.9 mL/min/1.73 m^2 /year. No major differences in these parameters were observed between males and females.

B.2.3.4. Phase I/II studies

Figure 6 presents an overview of the PB-102-F01, PB-102-F02 and PB-102-F03 studies.

Figure 6: Study design for the Phase I/II studies PB-102-F0, PB-102-F02 and PB-102-F03



Notes: [a] The maximum overall duration of treatment with PRX-102 was 72 months: 3 months in F01, 9 months in F02, and up to 60 months in F03. Planned evaluation visits occurred ±6 days at Months 2 and 3, every 3 months to Month 24, then every 6 months to Month 60. A final visit occurred at 3 months after the last infusion (± 6 days).
Source: Atta et al. 2022[60]

Study PB-102-F01 was a Phase I/II, open-label, multinational, dose-ranging study designed to assess the safety, tolerability, PK, immunogenicity and exploratory efficacy parameters of PRX-102 E2W in adult patients with FD.[62] Patients were enrolled into 1 of 3 treatment groups in a stepwise manner to receive increasing doses of PRX-102: 0.2 mg/kg (n = 6), 1.0 mg/kg (n = 8), or 2.0 mg/kg (n = 4) via IV infusion E2W for 3 months.

On successful completion of the 3-month study period (n = 16), patients were enrolled into the open-label extension study, PB-102-F02.[63] Enrolled patients continued to receive the same dose of PRX-102 E2W that they received in study PB-102-F01, as an IV infusion E2W for 9 months. PB-102-F02 was designed to further assess the safety, tolerability, PK and exploratory efficacy parameters of PRX-102. Following completion of both the PB-102-F01 and PB-102-F02 studies (12 months of treatment of PRX-102), patients were eligible to enter the PB-102-F03 extension study.

In PB-102-F03, 15 of the 16 patients who completed study PB-102-F02 were enrolled, and they were gradually adjusted (for the 0.2 mg/kg and 2.0 mg/kg groups) to receive the 1.0 mg/kg PRX-102 E2W for up to 60 months and no less than 36 months.[64] The screening visit (Day 1) of study PB-102-F03 corresponded to the last

infusion visit of study PB-102-F02. The baseline in the PB-102-F03 study corresponded to the baseline in study PB-102-F01. PB-102-F03 was designed to further assess the safety, tolerability, and exploratory efficacy parameters of PRX-102.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses conducted in the BALANCE study are outlined in Table 11. BALANCE consisted of 3 study populations:

- Intention-to-treat (ITT) population: all randomly assigned patients who received at least 1 dose of treatment (n = 77)
- Per-protocol (PP) population: all patients who completed at least 24 months of treatment (n = 72)
- Safety population: all patients who received at least 1 dose (partial or complete) of treatment (n = 77)

A summary of the statistical analyses conducted for BRIGHT, BRIDGE and the Phase I/II studies can be found in Appendix M.2, M.3, and M.4, respectively. Additionally, patient flows for each of the Phase III clinical trials can be found in Appendix D.2.

Table 11: Summary of statistical analyses in BALANCE

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The SAP for a previous interim analysis, signed 15 April 2021, included testing for non-inferiority of PRX-102 compared with agalsidase beta for the interim analysis and testing for superiority of PRX-102 compared with agalsidase beta for the final analysis. However, following the conversion of agalsidase beta's marketing authorisation to full approval in March 2021, it was agreed with FDA (End-of-Review Meeting, 9 September 2021) that it is not necessary anymore to demonstrate superiority over agalsidase beta. A Type C meeting to reach agreement with the FDA on the proposed primary model to assess non-inferiority took place on 21 January 2022 and the SAP reflects this discussion. **Primary** The primary efficacy endpoint is the annualised change (slope) in eGFR. The eGFR is not measured directly but is derived from the value of the serum creatinine and from patient characteristics, with 30 planned visits over 2 years in which serum creatinine is evaluated.	• The ITT population consisted of all randomised patients who received ≥ 1 dose of study medication, based on the assigned treatment arm in the randomisation. This was the main set for the efficacy analyses • The PP population included all ITT patients who completed ≥ 24 months of treatment, with study drug compliance of ≥ 80%, and with no major protocol deviations that could have impacted the primary endpoint and those were pre-specified in the SAP. This analysis set was used for sensitivity analyses for the primary endpoint. In a non-inferiority study, the PP and the ITT should be considered together in the interpretation of the study. In light of that the PP population is used, in addition to the ITT, for the primary analysis as well as for all sensitivity and supportive analyses for the primary efficacy analysis in the SAP • The safety population consisted of all patients who were randomised and who received ≥ 1 partial dose of study medication. Assignment was by actual treatment received. All safety analyses were performed on this population • Descriptive statistics, namely sample size (n), mean and its standard error, standard deviation, median, minimum	• Originally, the study sample size was planned to demonstrate non-inferiority after 1 year of treatment (interim analysis) and superiority after 2 years of treatment (final analysis) • Subsequent to the FDA granting full approval of agalsidase beta, it was no longer necessary to demonstrate treatment superiority of PRX-102 over agalsidase beta. A trial amendment determined that a non-inferiority analysis of the 24-month data was performed, as per agreement with the FDA. The pre-planned non-inferiority margin from the interim analysis was used for the final analysis. • The initial sample size of approximately 66 patients in a 2:1 randomisation ratio was kept, which results in at least 90% power to demonstrate the non-inferiority of PRX-102 vs. agalsidase beta in terms of annualised change (slope) in eGFR. The power was	• A Data Management Plan was created to define data management procedures for the study. The clinical database is being held and managed by Target Health for the lifetime of the study • Target e*CRF® was used for online edit checks, batch edit checks, and query management. Target e*CRF® application requirements for the study are documented in the Application Specification Documentation

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
• All analyses described in this section were conducted on the ITT set. In addition, some of the analyses were conducted also on the PP set • For all of the analyses discussed in this section, time was measured relative to the day of 1st infusion **Secondary** • All the analyses of secondary endpoints were performed only on the ITT set for the following endpoints: – UPCR – Stress test – Echocardiogram – Plasma lyso-Gb3 – Plasma Gb3 and Urine lyso-Gb3 – Concentrations – MSSI – Use of pain medication – Short Form BPI – Quality of Life (EQ-5D-5L) – FCEs	and maximum are provided for all continuous variables and 25th and 75th percentile for some of the continuous variables. Counts and percentages are provided for categorical variables • Unless otherwise specified, baseline values were defined as the last assessment before the first treatment infusion. • Subgroup analyses were conducted for the primary endpoint and for selected additional efficacy and safety endpoints. The subgroups included the following variables: – Sex (male or female) – ADA status at baseline (negative or positive) – FD classification (classic/non-classic) – Baseline eGFR category (≤ 60; 60 < and ≤ 90; > 90 mL/min/1.73m^2) – Baseline eGFR slope category (≤-5; >-5 mL/min/ 1.73m^2/year) – Use of ACEi/ARB at baseline (Yes/No) – UPCR category at baseline (≤ 0.5 gr/gr; 0.5 < and < 1 gr/gr; ≥1 gr/gr), and region (US/ex-US)	computed assuming a one-sided two-sample t-test with a one-sided alpha level of 0.025 and a non-inferiority margin of -3.0 mL/min/1.73 m^2/year. The true difference in slopes was assumed to be 1.1 mL/min/1.73 m^2/year in favour of PRX-102, and the standard deviation of the slopes was assumed to be 1.5 mL/min/1.73 m^2/year in each arm. To allow for a drop-out rate of 15%, 78 patients were planned to be randomised • With these assumptions, the power for showing superiority would be approximately 80%.	

Key: ACEi, angiotensin converting enzyme inhibitor; ADA, anti-drug antibodies; ARB, angiotensin II receptor blocker; BPI, Brief Pain Inventory; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FCE, Fabry clinical events; FDA, US Food and Drug Administration; ITT, intention-to-treat; PP, per protocol; MSSI, Mainz Severity Score Index; SAP, statistical analysis plan; UPCR, urine protein to creatinine ratio.
Source: Chiesi, BALANCE CSR.[4]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for BALANCE is presented in Table 12. Quality assessments for BRIGHT, BRIDGE and the Phase I/II trials are presented in Appendix D.3.

Table 12: Quality assessment results for the BALANCE trial

Question	Answer	Rationale
Was randomisation carried out appropriately?	Yes	Following screening, eligible patients were randomised in a 2:1 ratio to either switch to PRX-102 or continue treatment with agalsidase beta, with randomisation stratified according to whether the UPCR, a measure of kidney function, was above or below a specified threshold (1 gr/gr protein/ creatinine).
Was the concealment of treatment allocation adequate?	Yes	Patients were blinded as to which product they were receiving.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Prognostic variables such as age, sex, baseline eGFR, proteinuria, baseline cardiac measurements (including LVMI and LVMmri), baseline lysoGb3, and use of ARB/ACE-inhibitors were similar between study arms.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Patients and study staff were blinded as to which treatment was being given.
Were there any unexpected imbalances in drop-outs between groups?	No	There were no unexpected dropouts between groups as reported from the clinical study report
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	There was no evidence of any additional outcomes being measured, other than those which were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The ITT analysis set included all treated patients in the study.
Key: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CSR, clinical study report; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; LVMI, left ventricular mass index; LVMmri, left ventricular mass magnetic resonance imaging; lysoGb3, plasma lysoglobotriaosylsphingosine; UPCR, urine protein-to-creatinine ratio. **Source:** Chiesi, BALANCE CSR.[4]		

B.2.6. Clinical effectiveness results of the relevant trials

This section provides clinical efficacy data for the Phase III trials, with a main focus on BALANCE (Section B.2.3.1); summaries have been provided for the results of the BRIGHT (Section B.2.6.2.1) and BRIDGE trials (Section B.2.6.3.1) with full details in Appendix M2 and M.3, respectively. A summary of Phase I/II trials is provided in Section B.2.6.4, with full details in Appendix M.4.

B.2.6.1. BALANCE trial

B.2.6.1.1. Summary of key trial endpoints and results

An overview of the key efficacy endpoints reported from the BALANCE trial are summarised in Table 13. PRX-102 E2W showed comparable efficacy to that of agalsidase beta E2W, with both ERTs leading to improvements in kidney function and a stabilisation of the general disease status[5]:

- When compared with agalsidase beta E2W, PRX-102 E2W was shown to be non-inferior for the eGFR slope (primary endpoint). Estimated median slopes were -2.514 for the PRX-102 E2W arm and -2.155 for the agalsidase beta E2W arm, with a difference in median slopes (95% CI) of -0.359 between the 2 arms. The 95% CI for the difference in slopes was -2.444 to 1.726, which met the prespecified non-inferiority margin of -3.0
- In the PRX-102 E2W and agalsidase beta E2W arms, stability was seen for secondary efficacy endpoints including LVMI, UPCR and plasma lyso-Gb3. For patients who had hypertrophy at baseline, mean LVMI values slightly decreased over 2 years of treatment with PRX-102 E2W ([redacted] overall; [redacted] in males and [redacted] in females). There was a modest overall increase in mean LVMI for patients who received agalsidase beta E2W ([redacted] overall; [redacted] in males and [redacted] in females)
- The Mainz Severity Score Index (MSSI) and the Brief Pain Inventory (BPI) showed stability in the PRX-102 E2W and agalsidase beta E2W arms, and most patients reported improvement or no change on the QoL measure. Most patients did not change categories for the number of pain medications being taken

Table 13: Summarised efficacy results for BALANCE, ITT population

	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)	Difference (95% CI)[a], p-value
Primary efficacy endpoint			
Estimated median annual eGFR slopes (mL/min/1.73 m^2/year)			
Median (95% CI)	-2.514 (-3.788. -1.240)	-2.155 (-3.805; -0.505)	-0.359 (-2.444; 1.726)[b] NR
Secondary efficacy endpoints			
Kidney function			
Change in UPCR			
UPCR ≥ 1 gr/gr (severe proteinuria) at baseline, n (%)	[redacted]	[redacted]	[redacted]
UPCR ≥ 1 gr/gr (severe proteinuria) at Week 104, n (%)	[redacted]	[redacted]	[redacted]
Achievement of kidney function therapeutic goals			
Yes, n (%)	[redacted]	[redacted]	[redacted]
Cardiac function			
LVMI for patients with hypertrophy at baseline			
Mean (SE) change from baseline at Week 104	[redacted]	[redacted]	[redacted]
LVMI for patients without hypertrophy at baseline			
Mean (SE) change from baseline at Week 104	[redacted]	[redacted]	[redacted]
Exercise tolerance (stress test)			
Normal stress test at baseline, n (%)	[redacted]	[redacted]	[redacted]
Normal stress test at Week 104, n (%)	[redacted]	[redacted]	[redacted]
Echocardiogram			
Normal aortic at Week 104, n (%)	[redacted]	[redacted]	[redacted]
Normal mitral at Week 104, n (%)	[redacted]	[redacted]	[redacted]
Normal pulmonic at Week 104, n (%)	[redacted]	[redacted]	[redacted]
Normal tricuspid at Week 104, n (%)	[redacted]	[redacted]	[redacted]
Biomarkers of FD			
Plasma lyso-Gb3			
Mean (SE) change from baseline to Week 104	[redacted]	[redacted]	[redacted]
Adjusted means in change of log at Week 104, mean (95% CI)	[redacted]	[redacted]	[redacted]

	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)	Difference (95% CI)[a], p-value
Urine lyso-Gb3			
Mean (SE) change from baseline to Week 104	[redacted]	[redacted]	[redacted]
Plasma Gb3			
Mean (SE) change from baseline to Week 104	[redacted]	[redacted]	[redacted]
Symptoms of FD			
Pain severity (measured on BPI)			
Mean (SE) change from baseline to Week 104 in pain severity	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline to Week 104 in pain interference	[redacted]	[redacted]	[redacted]
Frequency of pain medication use			
Pain medication used at any point during the study, n (%)	[redacted]	[redacted]	[redacted]
MSSI			
Mean (SE) change from baseline at Week 104	[redacted]	[redacted]	[redacted]
Occurrence of FCEs			
Overall FCEs, n (%)	[redacted]	[redacted]	[redacted]
Number of events (rate)	[redacted]	[redacted]	[redacted]
Quality of life			
EQ-5D-5L			
Mean (SE) change from baseline to Week 104 in overall health score	[redacted]	[redacted]	[redacted]

Key: BPI, Brief Pain Inventory; CI, confidence interval; CSR, clinical study report; E2W, every 2 weeks; eGFR; estimated glomerular filtration rate; FD, Fabry disease; FCEs, Fabry clinical events; Gb3, globotriaosylceramide; ITT, intention-to-treat; LVMI, left ventricular mass index; NS, not significant; SE, standard error; UPCR, urine protein to creatinine ratio.
Notes: a, Pegunigalsidase alfa -agalsidase beta; b, For non-inferiority to be indicated, the lower limit of the 95% CI had to be greater than the prespecified non-inferiority margin of -3.0. With -2.444, this criterion was met; hence, non-inferiority was shown for the ITT set.
Source: Wallace et al. 2022[5]; Chiesi, BALANCE CSR.[4]

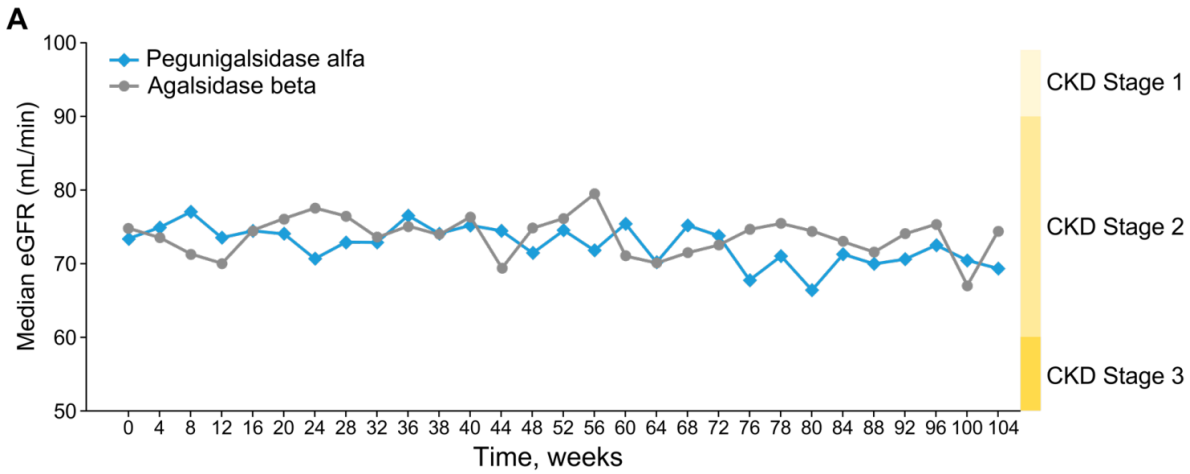
B.2.6.1.2. Primary efficacy endpoint: eGFR slope

The primary endpoint was the annualised change in eGFR (slope), derived from the eGFR assessments over time.[4, 5] The primary objective was to assess whether PRX-102 E2W was non-inferior to agalsidase beta E2W for this endpoint after 24 months of treatment.

Primary efficacy analysis

Results of the primary efficacy analysis (change in eGFR slope) for the ITT population are presented in Figure 7. At 24 months, the difference in median eGFR slope between PRX-102 E2W and agalsidase beta E2W was -0.36 mL/min/1.73 m^2/year (95% CI: -2.444, 1.726; Figure 7).[5] The lower CI met the prespecified non-inferiority margin and the 95% CI included 0, indicating no significant difference between treatment groups.

Figure 7: Median eGFR values over time in the BALANCE trial: ITT population



Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{CKD-EPI}$, chronic kidney disease-epidemiology collaboration equation; ITT, intention-to-treat.
Source: Wallace et al. 2022.[5]

In summary, the results indicate that PRX-102 E2W is not inferior to agalsidase beta E2W, meaning that the primary endpoint was met.[4, 5] The robustness of the finding that PRX-102 E2W was non-inferior to agalsidase beta E2W was confirmed in a wide variety of sensitivity and supportive analyses, as presented in Appendix M.1.3.1. More details of eGFR results by subgroup (sex, ADA status, FD classification, baseline eGFR category, baseline eGFR slope category, use of ACEi/ARB and UPCR category at baseline) are presented in Section B.2.7.1 and in Appendix E.

B.2.6.1.3. Secondary efficacy endpoints: Kidney function

B.2.6.1.3.1. Urine protein/creatinine ratio

Table 14 presents the proportion of patients by UPCR category at baseline and Week 104.[4] In the PRX-102 E2W arm, the proportion of patients categorised as having severe proteinuria (UPCR ≥ 1 g/g) remained stable with [redacted] at baseline and [redacted] at Week 104, while in the agalsidase beta E2W arm, the proportion increased slightly from [redacted] to [redacted].[4] In the PRX-102 E2W arm, a deterioration in category was seen in [redacted] patients ([redacted]); 1 from moderate to severe, and another from mild to moderate between baseline and Week 104. In the same timeframe, an improvement in UPCR was observed in 4 patients ([redacted]). In the agalsidase beta E2W arm, a deterioration in category was seen in 2 patients ([redacted]) and none of the patients improved their UPCR category.

Table 14: Number and proportion of patients in UPCR categories at baseline and Week 104 – ITT population

		PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)
		n (%)	n (%)
Baseline	n	[redacted]	[redacted]
	Mild proteinuria (UPCR ≤ 0.5 gr/gr)	[redacted]	[redacted]
	Moderate proteinuria (0.5 < UPCR < 1 gr/gr)	[redacted]	[redacted]
	Severe proteinuria (UPCR ≥ 1 gr/gr)	[redacted]	[redacted]
Week 104	n	[redacted]	[redacted]
	Mild proteinuria (UPCR ≤ 0.5 gr/gr)	[redacted]	[redacted]
	Moderate proteinuria (0.5 < UPCR < 1 gr/gr)	[redacted]	[redacted]
	Severe proteinuria (UPCR ≥ 1 gr/gr)	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; ITT, intention-to-treat; UPCR, urine protein creatinine ratio
Source: Chiesi, BALANCE CSR.[4]

B.2.6.1.3.2. Achievement of kidney function therapeutic goals

At Week 104, the defined kidney function therapeutic goals were achieved by a similar proportion of patients receiving PRX-102 E2W compared with agalsidase beta E2W ([redacted] vs. [redacted]); this minor difference was not statistically significant.[4]

B.2.6.1.4. Secondary efficacy endpoints: Cardiac function

B.2.6.1.4.1. Left ventricular mass index (g/m^2) by magnetic resonance imaging

Cardiac complications of FD may include a thickening of the left ventricular wall, or hypertrophy.[4] In male patients aged 20–60 years, normal LVMI is 57–91 g/m^2, and for female patients aged 20–60 years, normal LVMI is 47–77 g/m^2.[65] Hypertrophy, as defined by cardiac magnetic resonance imaging (MRI), is an LVMI greater than 91 g/m^2 for males or greater than 77 g/m^2 for females.[4]

LVMI results are shown in Table 15. In most cases, for the PRX-102 and agalsidase beta arms, the hypertrophy status remained the same over the study, which indicates radiological stability. In patients who had hypertrophy at baseline, mean LVMI values slightly decreased over 2 years of treatment in the PRX-102 E2W arm, while a modest overall increase in mean LVMI was observed in the agalsidase beta E2W arm.[4] In patients without hypertrophy, both sexes showed very little change from baseline. Data were missing for some patients as cardiac MRI could not be performed because of COVID-19 restrictions at the hospital.

Table 15: Summary of LVMI (g/m^2) by sex and hypertrophy status – ITT population

	PRX-102 E2W			Agalsidase beta E2W		
	Males (n = 29)	**Females (n = 23)**	**Overall (n = 52)**	**Males (n = 18)**	**Females (n = 7)**	**Overall (n = 25)**
LVMI for patients with hypertrophy at baseline						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 104						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRX-102 – agalsidase beta: difference in means (95% CI), males:	[redacted]					
PRX-102 – agalsidase beta: difference in means (95% CI), females:	[redacted]					
PRX-102 – agalsidase beta: difference in means (95% CI), overall:	[redacted]					

	PRX-102 E2W			Agalsidase beta E2W		
	Males (n = 29)	**Females (n = 23)**	**Overall (n = 52)**	**Males (n = 18)**	**Females (n = 7)**	**Overall (n = 25)**
LVMI for patients without hypertrophy at baseline						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 104						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRX-102 – agalsidase beta: difference in means (95% CI), males: [redacted]						
PRX-102 – agalsidase beta: difference in means (95% CI), females: [redacted]						
PRX-102 – agalsidase beta: difference in means (95% CI), overall: [redacted]						

Key: CI, confidence interval; CSR, clinical study report; E2W, every 2 weeks; ITT, intention-to-treat; LVMI left ventricular mass index; SE, standard error.
Source: Chiesi, BALANCE CSR.[4]

When interpreting the data, variability was high as indicated by the large CIs and sample sizes in the subgroups were low.[4] All CIs contained 0, which suggests no statistically significant differences between treatments for both sexes. Additional cardiac efficacy outcome information for BALANCE can be found in Appendix M.1.3.2.

B.2.6.1.5. Secondary efficacy endpoints: FD biomarkers

The underlying pathophysiology in FD is progressive accumulation of Gb3 due to the absence or insufficiency of the GAL-A enzyme.[4] Accordingly, the change from baseline in levels of Gb3 and its metabolite, lyso-Gb3, are important biomarkers of the extent and progression of FD. Three Gb3 measures were investigated in BALANCE: plasma lyso-Gb3, urine lyso-Gb3 and plasma Gb3.

B.2.6.1.5.1. Plasma lyso-Gb3

Changes in plasma lyso-Gb3 concentrations from baseline to Week 104 in the ITT population are presented in Figure 8.

Figure 8: Mean plasma lyso-Gb3 over time in BALANCE – ITT population

Key: CSR, clinical study report; ITT, intention-to-treat; Lyso-Gb3, globotriaosylsphingosine.
Source: Chiesi, BALANCE CSR.[4]

Median values for plasma lyso-Gb3 levels at baseline were [redacted] nM in the PRX-102 E2W arm and [redacted] nM in the agalsidase beta E2W arm.[4] At Week 104, the change from baseline in median values was 1.15 nM in the PRX-102 E2W arm and [redacted] nM in the agalsidase beta E2W arm. In mean values, the mean plasma lyso-Gb3 concentration was similar between the PRX-102 E2W and agalsidase beta E2W arms ([redacted] nM and [redacted] nM, respectively). At Week 104, the concentration of lyso-Gb3 had increased slightly ([redacted] nM) in the PRX-102 E2W arm and had decreased slightly ([redacted] nM) in the agalsidase beta E2W arm. These results indicate stability in both arms, and these changes were not reflected in the eGFR slopes of each treatment arm (Section B.2.6.1.2).

B.2.6.1.5.2. Urine lyso-Gb3 concentrations

The mean urine lyso-Gb3 concentrations at baseline were similar in the PRX-102 and agalsidase beta arms (48.1 and 44.5 pM/mM creatinine, respectively).[4] At Week 104, the concentration had increased slightly (by 7.0 pM/mM creatinine) in the PRX-102 alfa arm and decreased (-11.2 pM/mM creatinine) in the agalsidase beta arm.

Since the CIs contained 0, this suggests no difference between the 2 arms, and changes in both treatment arms for both variables were not considered clinically significant.

B.2.6.1.5.3. Plasma Gb3 concentrations

At baseline, the mean Gb3 plasma concentration was higher in the PRX-102 arm than in the agalsidase beta arm (5087.7 nM vs. 4695.4 nM, respectively). In the PRX-102 arm, there was a mean increase from baseline of 138.0 nM, while in the agalsidase beta arm, there was a mean decrease of -81.8 nM. Since the CIs contained 0, this suggests no difference between the 2 arms, and changes in both treatment arms for both variables were not considered clinically significant.

B.2.6.1.6. Secondary efficacy endpoints: Symptoms of FD

B.2.6.1.6.1. Change in pain severity

Table 16 shows the change from baseline at Week 104 for 'Pain at Its Worst in Last 24 Hours' and 'Pain on Average'. For both these measures, the mean scores for both arms were in the mild range at baseline and did not change markedly over the treatment period.[4] The CIs contained 0, which suggests no statistically significant difference between the arms. The results were similar for the other measures, 'Pain at Its Least in Last 24 Hours' and 'Pain Right Now At Week 104' (data not shown). Improvement or no change in pain severity was more often reported in the PRX-102 arm ([redacted]%) than the agalsidase beta arm ([redacted]%). Worsening in pain severity was reported by a [redacted] proportion of patients in the PRX-102 E2W compared with the agalsidase beta E2W arm ([redacted]% vs. [redacted]%).

Table 16: Change in scores in the Brief Pain Inventory Short Form at Week 104 – ITT population

Pain severity	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)
Pain at its worst in last 24 hours		
Baseline		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Change from baseline at Week 104		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
95% CI for the change from baseline	[redacted]	[redacted]
PRX-102 – agalsidase beta: Difference in means (95% CI)	[redacted]	
Pain on average		
Baseline		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Change from baseline at Week 104		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
95% CI for the change from baseline	[redacted]	[redacted]
PRX-102 – agalsidase beta: Difference in means (95% CI)	[redacted]	

Key: CI, confidence interval; CSR, clinical study report; E2W, every 2 weeks; ITT, intention-to-treat; SE, standard error.
Source: Chiesi, BALANCE CSR.[4]

B.2.6.1.6.2. Frequency of pain medication use

A total of 38 patients ([redacted]%) in the PRX-102 E2W arm and 22 patients ([redacted]%) in the agalsidase beta E2W arm used pain medication during the study.[4] The most common medications were oral paracetamol and ibuprofen. For most patients, there was no change in the frequency of pain medication use over the study period.

B.2.6.1.6.3. Mainz Severity Score Index

The MSSI[66] yields scores for general, neurological, cardiovascular, renal, and overall assessments. An overall score of less than 20 points is considered mild, 20–40 is considered moderate, and greater than 40 is considered to reflect severe signs and symptoms of FD.[4] Table 17 shows the change from baseline in overall MSSI score at Week 104.

Table 17: Change in overall score on the Mainz Severity Score Index at Week 104 – ITT population

	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)
Baseline		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Week 104		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Change from baseline at Week 104		
Mean (SE)	[redacted]	[redacted]
95% CI for the change from baseline	[redacted]	[redacted]
Difference in means for PRX-102 – agalsidase beta (95% CI)	[redacted]	

Key: CI, confidence interval; CSR, clinical study report; E2W, every 2 weeks; ITT, intention-to-treat; SE, standard error.
Source: Chiesi, BALANCE CSR.[4]

At baseline, the overall mean score in both groups were at the low end of the moderate range ([redacted] for PRX-102 E2W and [redacted] for agalsidase beta E2W). Scores remained stable during the study, with a minor mean decrease (improvement by [redacted] points) seen in the PRX-102 E2W arm and a minor increase in the agalsidase beta E2W arm ([redacted] points).[4] The CIs of the difference in mean changes did not contain 0, which suggests a difference between the 2 arms in favour of PRX-102 E2W. The findings for the scores on the individual scales (neurological scores, cardiovascular scores and renal scores) were similar to the overall score (see Appendix M.1.3.3).

B.2.6.1.6.4. Incidence of Fabry clinical events

A summary of the patients who experienced Fabry clinical events (FCEs; as defined by Hopkin et al.[67]) is shown in Table 18.

Table 18: Number of patients with Fabry clinical events – ITT population

FCE categories	PRX-102 E2W		Agalsidase beta E2W	
	Number (%) of patients (n = 52)	Number of events (rate)[a]	Number (%) of patients (n = 25)	Number of events (rate)[a]
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac events	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular events	[redacted]	[redacted]	[redacted]	[redacted]
Renal events	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac related death	[redacted]	[redacted]	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; FCE, Fabry clinical events; ITT, intention-to-treat.
Notes: [a] Rate is calculated as the adjusted number of events per 100 years of exposure.
Source: Chiesi, BALANCE CSR.[4]

In the PRX-102 E2W arm, [redacted] patients ([redacted]) experienced a total of 11 FCEs during the study: 7 were cardiac, 3 cerebrovascular, and 1 renal. In the agalsidase alfa E2W arm, [redacted] ([redacted]) patients experienced 2 events: both were cardiac.[4] Of note, all patients reporting FCEs had either experienced a similar event when untreated or receiving treatment with agalsidase beta E2W before the study, or had signs/symptoms of organ damage when the study started. These results reflect pre-existing organ involvement in ERT-experienced patients and do not allow any conclusions to be drawn on the effect of changing to a new ERT.

Time to first event by treatment group is presented by the Kaplan–Meier curve in Figure 9. The time is measured from the date of randomisation, and patients with no FCEs are censored at the time of last assessment.[4]

Figure 9: Kaplan–Meier of time to first Fabry clinical event – ITT population

Key: CSR, clinical study report; FCE, Fabry clinical event; ITT, intention-to-treat.
Source: Chiesi, BALANCE CSR.[4]

B.2.6.1.7. HRQL endpoint: Change in EQ-5D-5L scores

A QoL questionnaire (EQ-5D-5L) was conducted in both PRX-102 E2W and agalsidase beta E2W arms for each domain (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Most patients reported [redacted] or [redacted] in QoL on all domains by Week 104 (Table 19).[4]

Table 19: Proportion of patients with changes in quality of life assessments at Week 104 – ITT population

		PRX-102 E2W (n = 52)		Agalsidase beta E2W (n = 25)	
Number of patients with data at Week 104		**n = 46**		**n = 22**	
Mobility	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Self-care	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Pain/discomfort	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/depression	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; ITT, intention-to-treat.
Source: Chiesi, BALANCE CSR.[4]

Results were [redacted] between treatment arms for the mobility and self-care domains. For 'pain/discomfort', a [redacted] proportion of patients receiving PRX-102 E2W experienced [redacted] compared with agalsidase beta E2W. For the 'usual activities' domain, a [redacted] proportion of patients receiving PRX-102 E2W experienced [redacted] compared with agalsidase beta E2W.[4]

The overall health score is presented in Table 20 by key timepoints. Mean (standard error [SE]) scores at baseline were similar, with 74.6 (3.1) points in the PRX-102 E2W arm and [redacted] points in the agalsidase beta E2W arm.[4] Mean (SE) changes in overall health score between baseline and Week 104 were small, with increases of [redacted] points in the PRX-102 E2W arm and [redacted] points in the agalsidase beta E2W arm.

Table 20: Summary of quality of life EQ-5D-5L overall health score – ITT population

	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)
Baseline		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Visit 53 (week 104)		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline		
n	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; ITT, intent-to-treat; SD, standard deviation; SE, standard error.
Source: Chiesi, BALANCE CSR.[4]

Table 21 shows these percentage of patients with changes in QoL assessments at Week 104. In both arms, for each domain, the majority of patients reported improvement or no change. The rate of worsening was higher in the PRX-102 arm for 'usual activities' with [redacted]% of patients compared with [redacted]% in the agalsidase beta arm, but it was higher in the agalsidase beta arm for 'pain/discomfort' with [redacted]% compared with [redacted]% compared with the PRX-102 arm.

Table 21: Proportion of patients with changes in quality of life assessments at Week 104 – ITT set

		PRX-102 n = 52		Agalsidase beta n = 25	
Number of patients with data at Week 104		**n = 46**		**n = 22**	
Mobility	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Self-care	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Pain/discomfort	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/depression	Improvement or no change	[redacted]	[redacted]	[redacted]	[redacted]
	Worsening	[redacted]	[redacted]	[redacted]	[redacted]

Key: CSR, clinical study report; ITT- intent-to-treat.
Source: Chiesi, BALANCE CSR.[4]

B.2.6.2. BRIGHT trial

B.2.6.2.1. Summary of key trial endpoints and results

An overview of the key efficacy endpoints and results from BRIGHT relevant to the submission are presented below in Table 22. In BRIGHT, safety was the primary outcome (see Section B.2.10.2). As such, no primary efficacy variable was defined. Further details of efficacy variables in BRIGHT are presented in Appendix M.2.[51]

In summary, patients showed stability in renal function and in plasma lyso-Gb3 levels, and improved or stable cardiac function after switching to PRX-102 E4W for 52 weeks following at least 3 years of treatment with agalsidase alfa E2W or agalsidase beta E2W. Results showed that over the 52-week treatment period:

Absolute eGFR values remained stable, with a mean (SE) change from baseline of −1.3 (1.4) mL/min/1.73 m^2 (Figure 10).[61] Mean (SE) annualised eGFR slope remained in the overall stability range (changed from [redacted] to -2.9 [1.1] mL/min/1.73 m^2/year).[51, 55] Stabilisation of function is achieved if a patient has a GFR slope loss ≤ 1–3 mL/min/1.73 m^2/year, as a loss of up to 1 mL/min/1.73 m^2/year is considered normal for individuals over the age of 40 years[39] Mean (SE) plasma

lyso-Gb3 concentrations were stable, with a negligible change from 19.4 (3.4) nM to 22.2 (3.6) nM (mean increase of [redacted] nM (Figure 11)[51, 55]

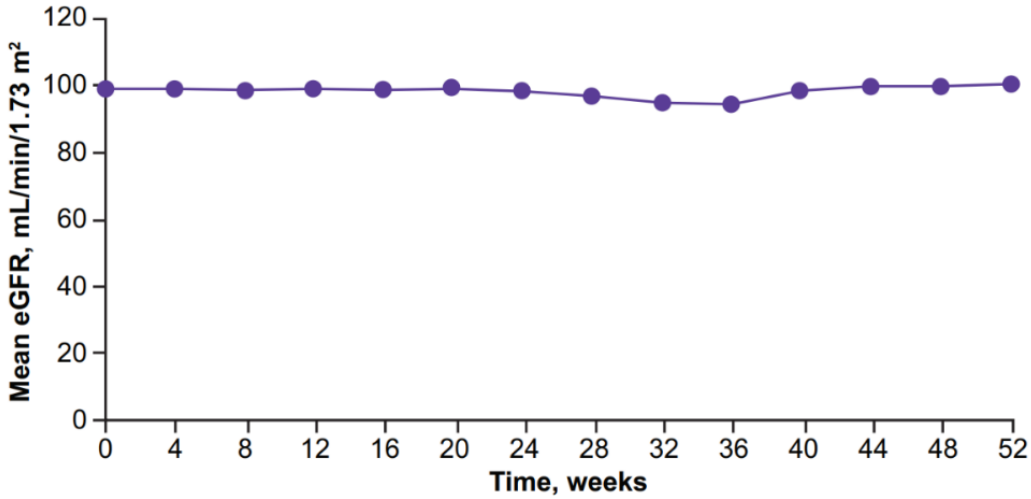
Table 22: Key efficacy results from BRIGHT

Endpoint	Baseline (n = 29)	Week 52 (n = 28)	Change from baseline
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2/year), mean (SE)	[redacted]	[redacted]	−1.3 (1.4)
eGFR slope (mL/min/1.73 m^2/year), mean (SE)	[redacted]	-2.92 (1.05)	NR
Biomarkers of FD			
Plasma lyso-Gb3 (nM), mean (SE)	19.4 (3.4)	22.2 (3.6)	[redacted]
Urine lyso-Gb3 (pM/mM), mean (SE)	[redacted]	[redacted]	[redacted]
Plasma Gb3 (nM), mean (SE)	[redacted]	[redacted]	[redacted]
Cardiac function			
Exercise tolerance (stress test)			
Normal stress test, n (%)	[redacted]	[redacted]	NR
Echocardiogram			
Normal aortic, n (%)	[redacted]	[redacted]	NR
Normal mitral, n (%)	[redacted]	[redacted]	NR
Normal pulmonic, n (%)	[redacted]	[redacted]	NR
Normal tricuspid, n (%)	[redacted]	[redacted]	NR
Kidney function			
UPCR category, n (%)	Normal to mildly increased: [redacted] Moderately increased: [redacted] Severely increased: [redacted]	Normal to mildly increased: [redacted] Moderately increased: [redacted] Severely increased: [redacted]	NR
Symptoms of FD			
Short form BPI			
Pain severity, mean (SE)	[redacted]	[redacted]	[redacted]
Pain interference, mean (SE)	[redacted]	[redacted]	[redacted]
MSSI			
Mean (SE) overall MSSI scores	[redacted]	[redacted]	[redacted]
Frequency of pain medication use			
Pain medication used at any point during the study, n (%)	[redacted]		
Occurrence of FCEs			
Overall FCEs, n (%)	[redacted]	[redacted]	[redacted]
Quality of life, assessed by EQ-5D-5L			
Mean (SE) overall health score	[redacted]	[redacted]	[redacted]

Key: BPI, Brief Pain Inventory; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FCEs, Fabry clinical events; Gb3, globotriaosylceramide; Lyso-Gb3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; SE, standard error; UPCR, urine protein to creatinine ratio.

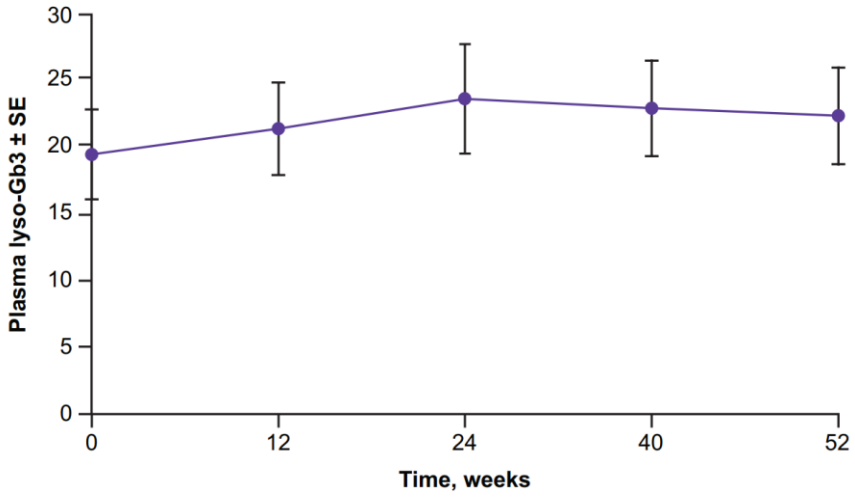
Endpoint	Baseline (n = 29)	Week 52 (n = 28)	Change from baseline
Notes: [a] data presented for pain medication use is for any point during the study. **Source:** Bernat et al. 2022[61]; Longo et al. 2022[56]; Chiesi, BRIGHT CSR.[51]			

Figure 10: Mean eGFR over time in the BRIGHT study



Key: eGFR, estimated glomerular filtration rate
Source: Bernat et al. 2022.[61]

Figure 11: Mean change from baseline in plasma lyso-Gb3 levels over time in BRIGHT study



Key: Lyso-Gb3, globotriaosylsphingosine; SE, standard error.
Source: Bernat et al. 2022.[55]

B.2.6.3. BRIDGE trial

B.2.6.3.1. Summary of efficacy results

An overview of the key endpoints and results relevant to the submission are presented below in Table 23.[52] Safety was the primary outcome of BRIDGE (see Section B.2.3.3). As such, no primary efficacy variable was defined. Further details of efficacy variables analysed in this study are presented in Appendix M.3.

In summary, patients showed improvements in renal function, sustained reductions in plasma lyso-Gb3 and stable cardiac function after switching to PRX-102 E2W following at least 2 years of treatment with agalsidase alfa E2W. Results showed that after 12 months of treatment with PRX-102 E2W:

- Mean annualised eGFR slope improved by 4.7 mL/min/1.73 m^2, from -5.9 to -1.2 mL/min/1.73 m^2/year (see Figure 12)[58]
- Fewer patients had progressing or fast progressing kidney disease (decreases of 5% and 25%, respectively), and most patients achieved stable renal function (an increase of 25%) (Figure 13)[58]
- Continuous reductions in plasma lyso-Gb3 concentrations were observed over 9 months and maintained up to 12 months, with a total mean decrease of 31.5% from 38.5 nmol/L at baseline to 24.2 nmol/L at Month 12 (Figure 14)[58]

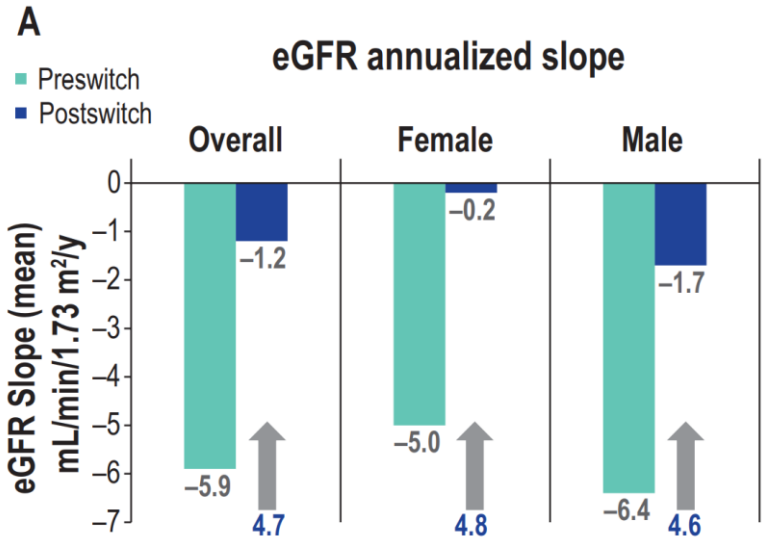
Table 23: Key results from BRIDGE

Endpoint	Baseline (n = 20)	Week 52 (n = 20)	Change from baseline
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2/year), mean (SE)	[redacted]	[redacted]	[redacted]
eGFR slope (mL/min/1.73 m^2/year), mean (SE)	-5.90 (1.34)	-1.19 (1.77)	4.7 (2.3) p = [redacted]
Biomarkers of FD			
Plasma lyso-Gb3 (nM), mean (SE)	38.5 [redacted]	24.2 [redacted]	[redacted]
Urine lyso-Gb3 (pM/mM), mean (SE)	[redacted]	[redacted]	[redacted]
Plasma Gb3 (nM), mean (SE)	[redacted]	[redacted]	[redacted]

Endpoint	Baseline (n = 20)	Week 52 (n = 20)	Change from baseline
Cardiac function			
LVMI			
LVMI (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]
Exercise tolerance (stress test)			
Normal stress test, n (%)	[redacted]	[redacted]	[redacted]
Echocardiogram			
Normal aortic, n (%)	[redacted]	[redacted]	[redacted]
Normal mitral, n (%)	[redacted]	[redacted]	[redacted]
Normal pulmonic, n (%)	[redacted]	[redacted]	[redacted]
Normal tricuspid, n (%)	[redacted]	[redacted]	[redacted]
Kidney function			
UPCR category, n (%)	Normal to mildly increased: [redacted] Moderately increased: [redacted] Severely increased: [redacted]	Normal to mildly increased: [redacted] Moderately increased: [redacted] Severely increased: [redacted]	[redacted]
Symptoms of FD			
Short form BPI			
Pain severity, mean (SE)	[redacted]	[redacted]	[redacted]
Pain interference, mean (SE)	[redacted]	[redacted]	[redacted]
MSSI			
Mean (SE) overall MSSI scores	[redacted]	[redacted]	[redacted]
Frequency of pain medication use			
Pain medication used at any point during the study, n (%)			[redacted]
Occurrence of FCEs			
Overall FCEs, n (%)			[redacted]
Quality of life, assessed by EQ-5D-5L			
Mean (SE) overall health score	[redacted]	[redacted]	[redacted]

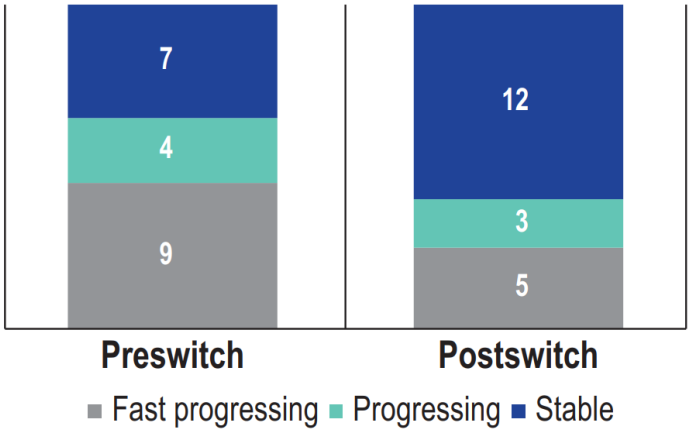
Key: BPI, Brief Pain Inventory; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FCEs, Fabry clinical events; FD, Fabry disease; Gb3, globotriaosylceramide; Lyso-Gb3, globotriaosylsphingosine; LVMI, left ventricular mass index; MSSI, Mainz Severity Score Index; SE, standard error; UPCR, urine protein to creatinine ratio.
Notes: [a] data presented for pain medication use and FCEs are for any point during the study.
Source: Jovanovic et al. 2022[58]; Chiesi, BRIGHT CSR.[51]

Figure 12: Changes in eGFR slope after 12 months in BRIDGE



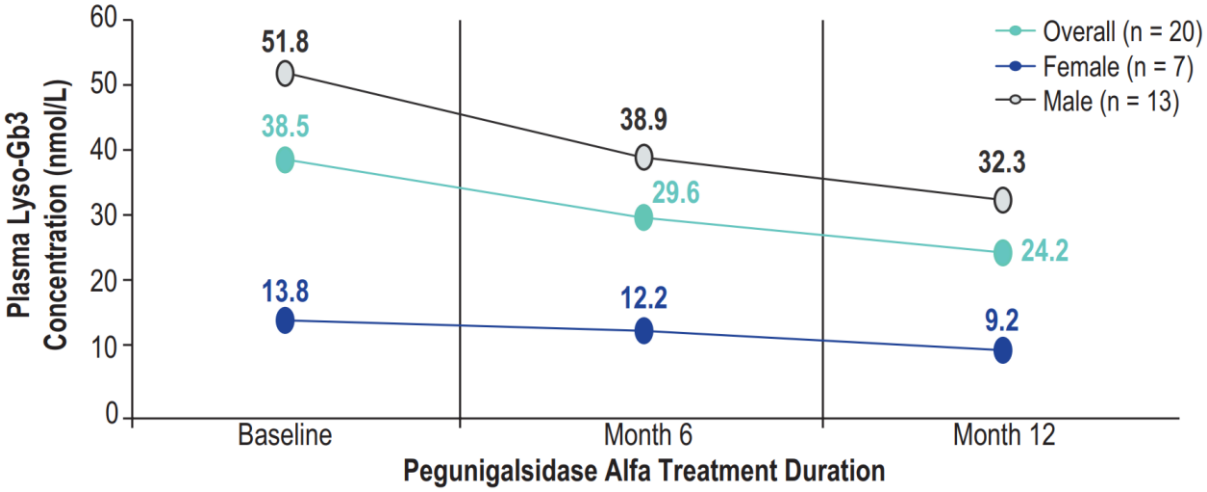
Key: eGFR, estimated glomerular filtration rate.
Source: Jovanovic et al. 2022.[58]

Figure 13: Change in kidney disease category according to eGFR slope after 12 months of PRX-102 treatment in BRIDGE



Key: eGFR, estimated glomerular filtration rate.
Source: Jovanovic et al. 2022.[58]

Figure 14: Plasma lyso-Gb3 concentration over 12 months of treatment with PRX-102 in BRIDGE



Key: Lyso-Gb3, globotriaosylsphingosine.
Source: Jovanovic et al. 2022.[58]

B.2.6.4. Phase I/II studies

A summary of efficacy data from the Phase I/II studies of PRX-102 E2W in treatment-naïve patients and long-term extension can be found in Appendix M.4, along with further details on key outcomes. A brief summary is provided below.

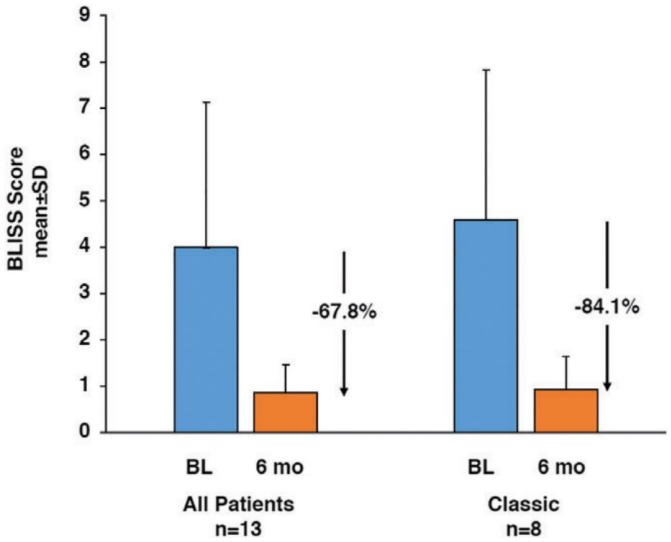
B.2.6.4.1. PB-102-F01 and PB-102-F02

The PB-102-F01 and PB-102-F02 studies demonstrated that treatment-naïve patients treated with PRX-102 E2W for 12 months exhibited stable renal and cardiac function.[35] eGFR results indicated stability in kidney function after 12 months of treatment with PRX-102. Mean eGFR increased from 111.2 mL/min/1.73 m^2 at baseline to 110.5 mL/min/1.73 m^2 at 12 months, showing a mean change of -0.8 mL/min/1.73 m^2 over the 12 months.[35] In particular, these studies provided data on outcomes that were not assessed in the Phase III trials; Gb3 levels in the kidney and the half-life of PRX-102.

B.2.6.4.1.1. Gb3 deposition in the kidney

Patients were evaluated for kidney Gb3 levels and for plasma lyso-Gb3 concentration. Kidney Gb3 inclusions were assessed by the quantitative Barisoni Lipid Inclusion Scoring System (BLISS) methodology. For all 3 dose levels combined, an overall mean reduction of Gb3 inclusions in kidney peritubular capillaries was observed after 6 months of treatment with PRX-102 E2W (67.8% reduction in patients with available data (n = 13), and 84.1% in patients with classic FD (n = 8); Figure 15).[35] Male patients exhibited higher baseline levels and higher reductions (85.0% reduction), although pronounced reduction was also detected in female patients (47.7% reduction).[59]

Figure 15: Reduction of Gb3 deposition in kidney peritubular capillaries following 6 months of PRX-102 treatment



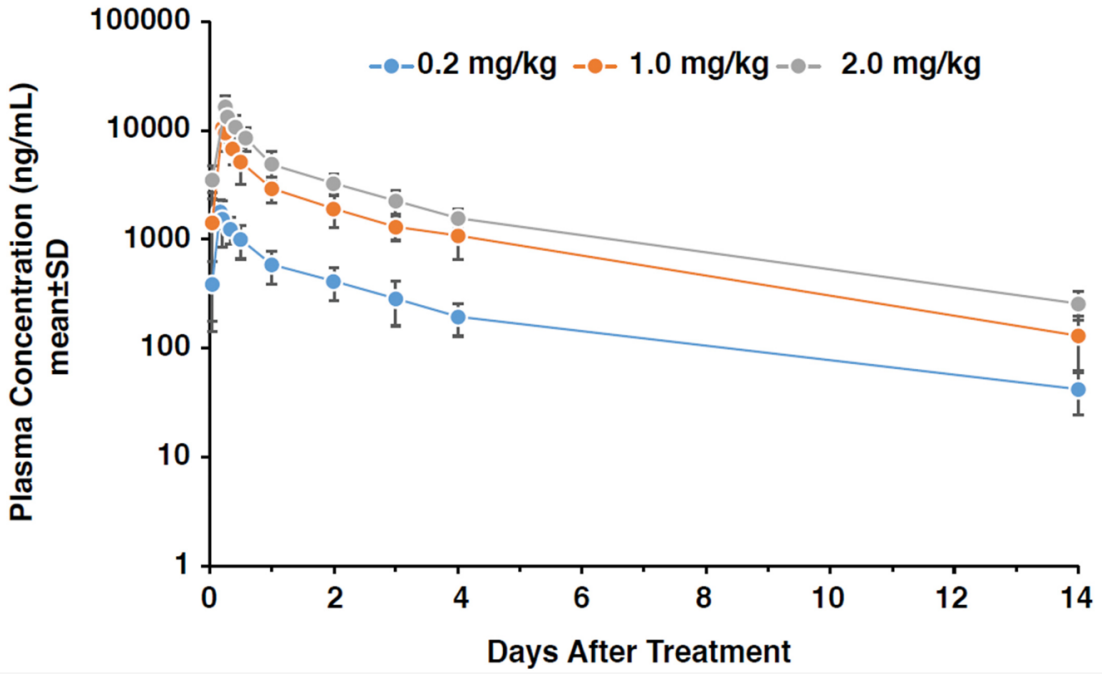
Key: BL, baseline; BLISS, Barisoni Lipid Inclusion Scoring System; Gb3, globotriaosylceramide; SD, standard deviation.
Source: Schiffman et al. 2019.[35]

The outcome of ≥ 50% reduction in the average number of Gb3 inclusions per kidney peritubular capillary (PTC) from baseline to Month 6 was shown in 11 of 14 (78.6%) of patients who received PRX-102. Results show that PRX-102 reaches the affected tissue and reduces kidney Gb3 inclusions and reduces levels of circulating lyso-Gb3. The high correlation found between the 2 FD biomarkers, the reduction of kidney Gb3 inclusions and the reduction of plasma lyso-Gb3 over 6 months of treatment supports the effectiveness of PRX-102 in treating FD.[59]

B.2.6.4.1.2. Pharmacokinetic analyses

PK results for all 3 dose levels combined showed measurable concentrations of PRX-102 present throughout the entire 14-day dosing interval, with a plasma half-life of approximately 80 hours (Figure 16).[35] This is significantly longer than the half-lives of current ERTs (agalsidase alfa: 108 ± 17 minutes in males, and 89 ± 28 minutes in females; agalsidase beta: 80–120 minutes).[44, 45] Additionally, the eGFR results indicated stability in kidney function after 12 months of treatment with PRX-102. Mean eGFR increased from 111.2 mL/min/1.73 m^2 at baseline to 110.5 mL/min/1.73 m^2 at 12 months, showing a mean change of −0.8 mL/min/1.73 m^2 over 12 months.[35]

Figure 16: PRX-102 plasma levels following dosing on Day 1



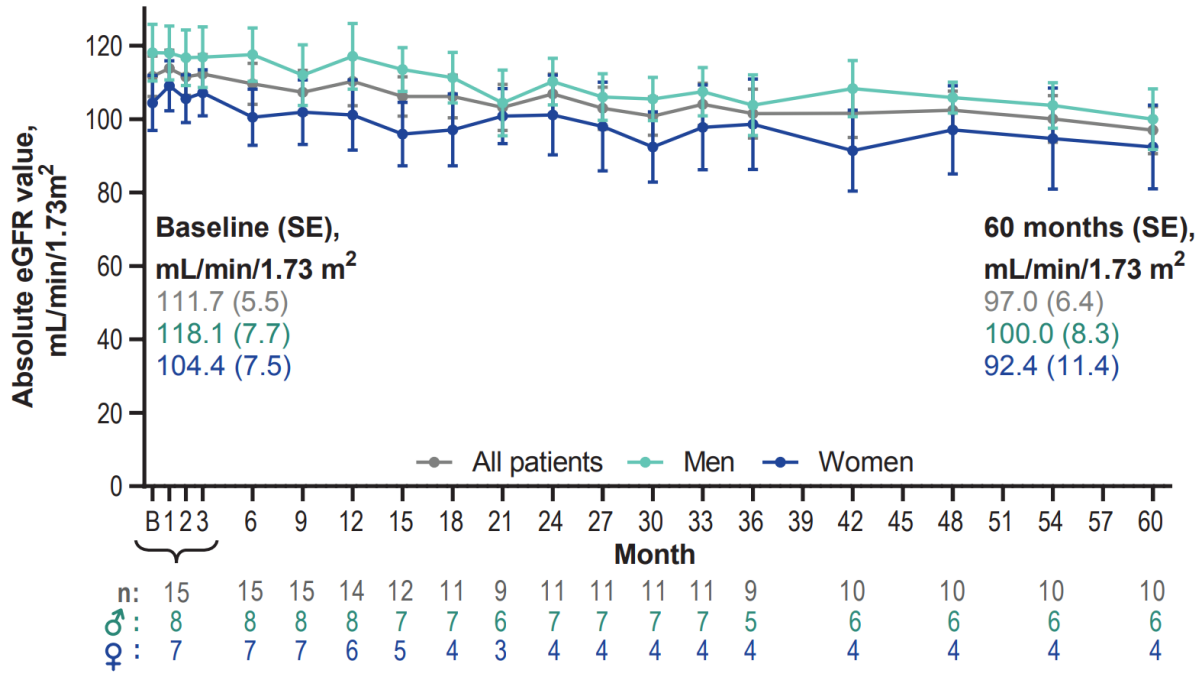
Key: SD, standard deviation.
Source: Schiffman et al. 2019.[35]

B.2.6.4.1.3. PB-102-F03 open-label extension

Long-term efficacy has been demonstrated for PRX-102 E2W in the PB-102-F03 study, which enrolled patients who completed Phase I/II studies into an open-label extension. In PB-102-F03, patients received PRX-102 E2W for up to 60 months (n = 15 for > 1 year; n = 10 for ≥ 5 years, maximum duration of 72 months).[68] Results showed that long-term treatment with PRX-102 E2W provides continued benefits in patients with FD.

At 60 months, renal function remained relatively stable according to Kidney Disease: Improving Global Outcomes (KDIGO) classification[13], with a mean (SE) annualised eGFR slope of -1.6 (0.8) mL/min/1.73 m^2 overall, -2.4 (0.9) mL/min/1.73 m^2 for males and -0.7 (1.3) mL/min/1.73 m^2 for females (Figure 17).[60, 61]

Figure 17: Mean (± SE) absolute eGFR over time



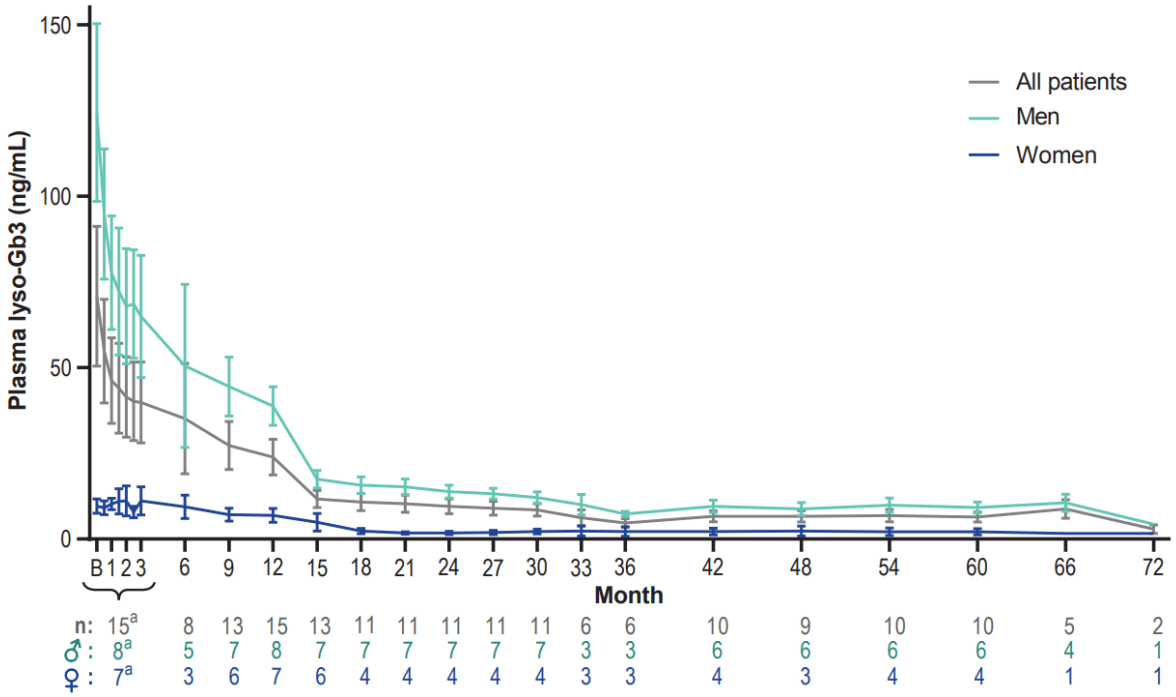
Key: eGFR, estimated glomerular filtration rate; SE, standard error.
Notes: Baseline values are from either Visit 1 or screening if Visit 1 is not available. A small number of patients (n = 2) had values at 72 months and are not included in the graph.
Source: Atta et al. 2022.[60]

Cardiac function also remained stable throughout the 60 months of treatment.[60, 61] Based on cardiac MRI, no cardiac fibrosis developed over the 60 months of treatment. After 60 months, mean LVMI (SE) had increased in females by 13.6 g/m^2

(5.3) compared with 5.7 g/m^2 (2.2) in males, with mean values for both groups within normal ranges. Additionally, echocardiography parameters (pulmonary regurgitation [PR], QRS complexes, and QT interval durations) and stress test measurements (chest pain, dizziness, palpitations, shortness of breath, other), most remained stable and within normal ranges.

Plasma lyso-Gb3 concentrations decreased steadily from baseline and remained low throughout the 60 month follow-up period (Figure 18), with a mean (SE) reduction from baseline of 68.4 (25.0) ng/mL.[60, 61]

Figure 18: Mean (± SE) plasma lyso-Gb3 over time



Key: Lyso-Gb3, globotriaosylsphingosine; SE, standard error.
Source: Atta et al. 2022.[60]

A high correlation (R = 0.963) was observed between the absolute change from baseline to Month 6 in kidney Gb3 deposition, as evaluated by BLISS methodology, and in the absolute change from baseline to Month 24 in plasma lyso-Gb3. This further supports PRX-102 efficacy using 2 different Fabry-related biomarkers.[60, 61]

B.2.7. Subgroup analysis

B.2.7.1. BALANCE

Subgroup analyses were conducted for the primary endpoint in BALANCE (change in eGFR slope), and for selected additional efficacy and safety endpoints. The subgroups included the following variables[4]:

- Sex (male or female)
- ADA status at baseline (negative or positive)
- FD classification (classic or non-classic)
- Baseline eGFR category (≤ 60; 60 < and ≤ 90; > 90 mL/min/1.73m^2)
- Baseline eGFR slope category (≤ -5; > -5 mL/min/ 1.73m^2/year)
- Use of ACEi/ARB at baseline (yes/no)
- UPCR category at baseline (≤ 0.5 gr/gr; 0.5 < and < 1 gr/gr; ≥ 1 gr/gr)
- Region (US/ex-US)

Figure 19 summarises the results of the pre-defined subgroup analysis in a forest plot. All CIs crossed zero, but due to the smaller sample sizes in these subgroups, the CIs are much wider than the CIs in the primary efficacy analysis. The analysis suggested that the treatment effect of PRX-102 was consistent across a range of subgroups tested. Subgroup analyses data for change in eGFR slope, and for selected additional efficacy and safety endpoints, are presented in Appendix E.

Figure 19: Forest plot for subgroup analysis on the primary endpoint, change in eGFR slope in the BALANCE trial – ITT population

Key: ACEi, angiotensin-converting enzyme inhibitor; ADA, anti-drug antibody; ARB, angiotensin II receptor blocker; CI, confidence interval; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FD, Fabry disease; ITT, intention-to-treat; UPCR, urine protein to creatinine ratio.
Source: Chiesi, BALANCE CSR.[4]

B.2.7.2. BRIGHT

Subgroup analyses were conducted according to baseline characteristics and demographics for selected efficacy and safety endpoints. For the safety and efficacy endpoints, subgroups included[51]:

- Sex: male or female
- ADA status at baseline: negative or positive for anti-PRX-102 immunoglobulin G (IgG) antibodies
- FD classification: classic or non-classic
- Baseline eGFR: ≤ or > 60 mL/minute/1.73 m^2
- ERT treatment at screening: agalsidase alfa or agalsidase beta
- Use of ACEi or ARB treatment at baseline: yes or no

Details of the subgroup analyses conducted for BRIGHT can be found in Appendix E. Results were consistent among the subgroups of interest.

B.2.7.3. BRIDGE

Analyses of efficacy and safety endpoints were performed overall and partly for the following subgroups[52]:

- Sex: male/female (all endpoints)
- Treatment-emergent immunogenicity status (ADA-positive/ADA-negative)
- FD classification: classic or non-classic

Details of the subgroup analysis conducted for BRIDGE are summarised in Appendix E. Results were consistent among the subgroups of interest.

B.2.8. Meta-analysis

No meta-analysis of the PRX-102 studies was performed to evaluate efficacy as only 1 head-to-head trial was conducted. A pooled analysis of safety from 5 PRX-102 clinical studies has been published as a conference abstract and poster (Mehta et al. 2022).[69]

B.2.9. Indirect and mixed treatment comparisons

The relevant comparators of PRX-102 for this appraisal are the other ERTs, agalsidase alfa and agalsidase beta. As the only head-to-head data for PRX-102 E2W are compared with agalsidase beta E2W from the BALANCE trial, the feasibility of an indirect treatment comparison (ITC) of PRX-102 E2W vs. agalsidase alfa E2W was assessed. Supportive evidence for the efficacy of PRX-102 vs. agalsidase alfa is also available from the 2 additional PRX-102 studies, BRIDGE and BRIGHT, in which patients were switched to PRX-102 E2W and E4W, respectively, after previous treatment with agalsidase alfa or beta, as well as the accepted equivalent efficacy of agalsidase alfa and agalsidase beta as evidenced by several SLRs and meta-analyses[70-72] and a large international retrospective cohort study.[73]

The ITC feasibility assessment demonstrated that any statistical analysis would lead to substantial uncertainty because of the significant limitations and heterogenous nature of the identified evidence base (see section B.2.9.2). As such, a naïve comparison between the Phase III PRX-102 trials (BALANCE, BRIGHT, and BRIDGE) was also attempted (see Appendix D.1.3.1), but again, the analyses are very limited due to small patient populations and differing baseline characteristics between trials such as sex and age. However, despite the limitations of the analyses, results of the naïve comparisons suggest that there are [redacted] in efficacy of PRX-102 for key outcomes of interest between BALANCE (PRX-102 E2W in renally impaired population) and BRIGHT (PRX-102 E4W in non-renally impaired population), and between BALANCE (PRX-102 E2W in renally impaired population) and BRIDGE (PRX-102 E2W in non-renally impaired population).

B.2.9.1. Evidence included in the ITC feasibility assessment

As described in Section B.2.1, an SLR was conducted to identify relevant clinical evidence for the relevant treatments of interest for this appraisal (PRX-102, agalsidase alfa and agalsidase beta). Of the 13 RCTs identified, 5 were dose-ranging studies (3 agalsidase alfa studies, 2 agalsidase beta studies), and were therefore not included for consideration in formal statistical analysis. As such, a total of 8 RCTs were included for consideration in a feasibility assessment for an ITC (1

PRX-102 study, 3 agalsidase alfa studies and 4 agalsidase beta studies; Table 24). See Appendix D1 for full details of these studies.

Table 24: Randomised studies (multiple treatments) from the SLR

Study name	ITT N	Intervention	Intervention dose
BALANCE[4]	52	PRX-102	1.0 mg/kg E2W
	25	Agalsidase beta	**1.0 mg/kg E2W**
Vedder 2007[74]	18	Agalsidase alfa	**0.2 mg/kg E2W**
	16	Agalsidase beta	0.2 mg/kg E2W
Hughes 2008[75]	7	Agalsidase alfa	**0.2 mg/kg E2W**
	8	Placebo	NA
Banikazemi 2007[76]	51	Agalsidase beta	**1.0 mg/kg E2W**
	31	Placebo	0.25 mg/min
Schiffmann 2001[77]	14	Agalsidase alfa	**0.2 mg/kg E2W**
	12	Placebo	0.2 mg/kg E2W
Sirrs 2014[78]	62	Agalsidase alfa	**0.2 mg/kg E2W**
	30	Agalsidase beta	**1.0 mg/kg E2W**
Eng 2001[79]	29	Agalsidase beta	**1.0 mg/kg E2W**
	29	Placebo	0.25 mg/min
Hajioff 2003[80]	8	Agalsidase alfa	**0.2 mg/kg E2W**
	7	Placebo	NR

Key: E2W, every 2 weeks; ERT, enzyme replacement therapy; ITT, intention-to-treat; IV, intravenously; N, number of patients; NA, not applicable; NR, not reported; SLR, systematic literature review; SmPC, summary of product characteristics.
Notes: Bolded doses are the indicated dose in the SmPC.

A summary of the design and methodology of each of the 8 RCTs included in the feasibility study is shown in Table 25, and a summary of patient characteristics for studies with PRX-102, agalsidase alfa and agalsidase beta of each trial is included in Table 26.

Table 25: Summary of trial design of the included RCTs

Study name	Intervention(s)	FD type	Study type	Blinding	Phase	Crossover	Centre	Region	Study duration
BALANCE[4]	PRX-102 (n = 53) Agalsidase beta (n = 25)	Mixed	RCT	Double-blinded	Phase III	Yes	Multicentre international	US, UK, Netherlands, Spain, France, Italy, Norway, Slovenia, Switzerland, Finland, Hungary, and the Czech Republic	The total duration of treatment for each patient was to be up to 104 weeks (24 months)
Vedder 2007[74]	Agalsidase alfa (n = 18) Agalsidase beta (n = 16)	Unclear	RCT	Open-label	NR	Yes	Multicentre international	The Netherlands, Norway	Study duration: 96 weeks (24 months)
Hughes 2008[75]	Agalsidase alfa (n = 7) Placebo (n = 8)	Unclear	RCT	Double-blinded	NR	No	NR	NR	RCT phase: 6 months (24 weeks) Open-label extension: 24 months (96 weeks)
Banikazemi 2007[76]	Agalsidase beta (n = 51) Placebo (n = 31)	Unclear	RCT	Double-blinded	Phase IV	Yes	Multicentre international	North America and Europe (9 countries)	Up to 140 weeks (up to 35 months)
Schiffmann 2001[77]	Agalsidase alfa (n = 14) Placebo (n = 12)	Unclear	RCT	Double-blinded	NR	No	Single-centre	USA	24 weeks (6 months)
Sirrs 2014[78]	Agalsidase alfa (n = 62) Agalsidase beta (n = 30)	Unclear	RCT	NR	NR	Yes	Multicentre	Canada	Overall 240 weeks (5 years) follow-up

Study name	Intervention(s)	FD type	Study type	Blinding	Phase	Crossover	Centre	Region	Study duration
Eng 2001[79]	Agalsidase beta (n = 29) Placebo (n = 29)	Classical	RCT	Double-blinded	Phase III	Yes	Multicentre international	France, Netherlands, Puerto Rico, United Kingdom, United States	RCT phase: 20 weeks Follow-up time (years), mean (SD): 8.6 (2.5);
Hajioff 2003[80]	Agalsidase alfa (n = 8) Placebo (n = 7)	Classical	RCT	Double-blinded	NR	No	NR	NR	RCT phase: 24 weeks

Key: ERT, enzyme replacement therapy; FD, Fabry disease; N, number of patients; NR, not reported; RCT, randomised controlled trial; SD, standard deviation.

Table 26: Summary of baseline characteristics in the included RCTs

Study name	ITT N	Intervention	Intervention dose	Age: Mean (SD)	Age: Median (min, max)	Males % (n/N)
BALANCE[4]	52	PRX-102	1 mg/kg E2W	43.9 (10.2)	44 (20, 60)	55.8 (29/52)
	25	Agalsidase beta	1 mg/kg E2W	45.2 (9.6)	48 (18, 58)	72.0 (18/25)
Vedder 2007[74]	18	Agalsidase alfa	0.2 mg/kg E2W	NR (13)	44 (19, 60)	50.0 (9/18)
	16	Agalsidase beta	0.2 mg/kg E2W	NR (14)	47 (24, 76)	56.2 (9/16)
Hughes 2008[75]	7	Agalsidase alfa	0.2 mg/kg E2W	37.1 (NR)	40.3 (23.1, 50.8)	100.0 (7/7)
	8	Placebo	NA	37.3 (NR)	36.2 (26.1, 49.8)	100.0 (8/8)
Banikazemi 2007[76]	51	Agalsidase beta	1.0 mg/kg E2W	46.9 (9.8)	NR (NR, NR)	88.0 (45/51)
	31	Placebo	0.25 mg/min E2W	44.3 (9.2)	NR (NR, NR)	87.0 (27/31)
Schiffmann 2001[77]	14	Agalsidase alfa	0.2 mg/kg E2W	34 (NR)	NR (NR, NR)	100.0 (14/14)
	12	Placebo	0.2 mg/kg E2W	34.4 (NR)	NR (NR, NR)	100.0 (12/12)
Sirrs 2014[78]	62	Agalsidase alfa	0.2 mg/kg E2W	47.6 (15.6)	NR (NR, NR)	40.2 (37/92)
	30	Agalsidase beta	1.0 mg/kg E2W			

Study name	ITT N	Intervention	Intervention dose	Age: Mean (SD)	Age: Median (min, max)	Males % (n/N)
Eng 2001[79]	29	Agalsidase beta	1.0 mg/kg E2W	32 (9.4)	NR (16, 48)	93.1 (27/29)
	29	Placebo	0.25 mg/min E2W	28.4 (11.4)	NR (17, 61)	100.0 (29/29)
Hajioff 2003[80]	8	Agalsidase alfa	0.2 mg/kg E2W	NR (NR)	NR (NR, NR)	100.0 (8/8)
	7	Placebo	NA	NR (NR)	NR (NR, NR)	100.0 (7/7)

Key: E2W, every 2 weeks; ERT, enzyme replacement therapy; ITT, intention-to-treat; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SD, standard deviation.

The outcomes that were well reported across the studies and considered for use in an ITC were: eGFR; LVMI by MRI; plasma Gb3; urine GB3; and pain as assessed by the BPI. All outcomes were considered as change from baseline (CFB) endpoints. The availability of these outcomes across the studies is provided in Appendix D.1.3.

Regarding eGFR, 6 of the 8 studies reported some form of eGFR endpoint, and of these, the following 4 studies at the following timepoints and definitions could be used in an analysis on the CFB in eGFR (Appendix D.1.3):

- BALANCE:[4] 12 months; CFB in eGFR, determined by using the CKD Epidemiology Collaboration equation
- Vedder 2007:[74] 12 months; CFB in measured GFR
- Hughes 2008:[75] 6 months; no definition reported
- Schiffmann:[77] 6 months; CFB in GFR measured by creatinine clearance

Regarding LVMI, only 2 studies reported this (BALANCE and Hughes 2008), yet definitions were consistent (Appendix D.1.3). It is not possible to perform an analysis on the LVMI endpoint due to limited reporting, leading to a disconnected network.

Six of the 8 studies reported a plasma Gb3 endpoint, with the timepoint ranging from 3–24 months (Appendix D.1.3). Any analysis on this endpoint would have high levels of uncertainty because the timepoints need to be assumed to have equal efficacy. The following studies, timepoints and definitions could be used in an analysis on the CFB in plasma GB3 endpoint:

- BALANCE:[4] 6 months; CFB in levels of Gb3 in plasma
- Vedder 2007:[74] 12 months; CFB in levels of Gb3 in plasma
- Hughes 2008:[75] 6 months; CFB in Gb3 plasma levels
- Schiffmann 2001:[77] 6 months; CFB in Gb3 plasma levels
- Eng 2001:[79] 5 months; CFB in Gb3 plasma levels

Regarding urine Gb3, this was reported in 5 of the 8 studies, with 4 of these studies reporting urine Gb3 but BALANCE reporting lyso-Gb3 in urine; as such, BALANCE is not comparable to the other studies (Appendix D.1.3). No analysis was possible on the urine Gb3 endpoint.

Regarding pain assessed by the BPI, this was reported in 5 studies although the timepoint varied across the studies from 2–24 months (Appendix D.1.3). As such, any analysis performed on this endpoint would be associated with high levels of uncertainty, because the timepoints need to be assumed to have equal efficacy. The following studies, timepoints and definitions could be used in an analysis on the CFB in pain assessed by the BPI endpoint:

- BALANCE:[4] 24 months; BPI (short form), pain score
- Vedder 2007:[74] 12 months; BPI-3 pain score (short form)
- Banikazemi 2007:[76] 24 months; neuropathic pain as assessed by Question 12 of the BPI long form
- Schiffmann 2001:[77] 6 months; BPI pain-related quality of life – pain severity

Table 27 summarises the set of 8 studies identified for inclusion in a potential NMA. There is no outcome availability for Sirrs 2014 and Hajioff 2003 across all explored endpoints; therefore, these 2 studies were excluded from the evidence base.

Table 27: Summary of studies included in a potential NMA

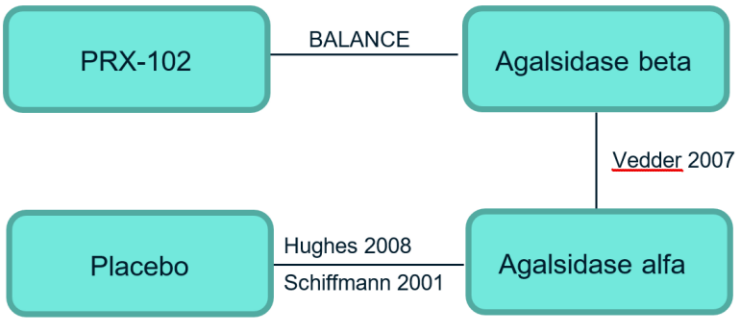
Study name	Intervention	eGFR	LVMI	Plasma Gb3	Urine Gb3	BPI
BALANCE	PRX-102; Agalsidase beta	Y	Y	Y	N	Y
Vedder 2007	Agalsidase alfa; Agalsidase beta	Y	N	Y	Y	Y
Hughes 2008	Agalsidase alfa; Placebo	Y	Y	Y	Y	N
Banikazemi 2007	Agalsidase beta; Placebo	N	N	Y	N	Y
Schiffmann 2001	Agalsidase alfa; Placebo	Y	N	Y	Y	Y
Sirrs 2014	Agalsidase alfa; Agalsidase beta	N	N	N	N	N
Eng 2001	Agalsidase beta; Placebo	N	N	Y	Y	N
Hajioff 2003	Agalsidase alfa; Placebo	N	N	N	N	N

Key: BPI, Brief Pain Inventory; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; GB3, globotriaosylceramide; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; N, no; NMA, network meta-analysis; Y, yes.
Note: Grey shaded rows indicate the studies that had no outcome availability across all explored endpoints, and were therefore excluded from the evidence base.

B.2.9.2. Results of the ITC feasibility assessment

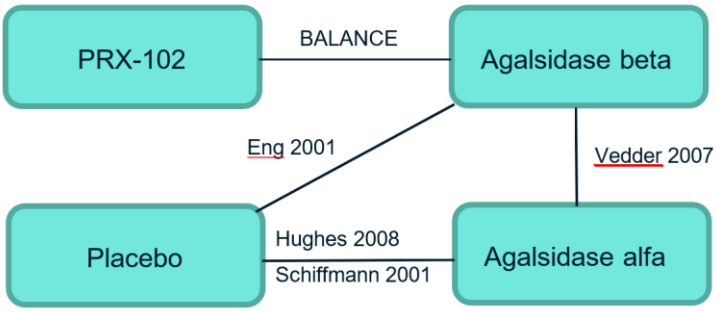
The availability of outcomes across the included studies allows for a connected network to be formed for the following endpoints: eGFR (Figure 20), plasma Gb3 (Figure 21) and pain assessed by the BPI (Figure 22).

Figure 20: Network diagram for analysis of eGFR



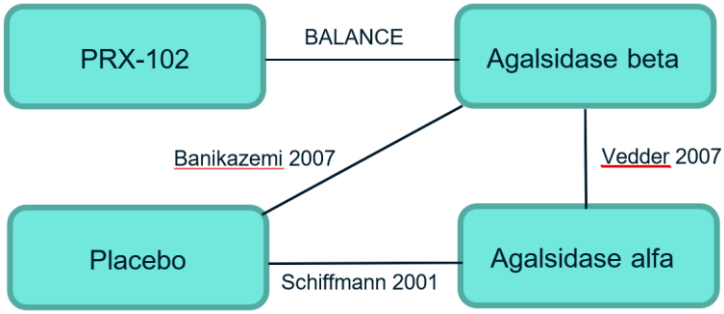
Key: eGFR, estimated glomerular filtration rate.

Figure 21: Network diagram for analysis of plasma Gb3



Key: Gb3, globotriaosylceramide.

Figure 22: Network diagram for analysis of pain assessed by the BPI



Key: BPI, Brief Pain Inventory.

B.2.9.3. Conclusion of the ITC feasibility assessment

Although networks could be formed within the identified evidence base, the overall conclusions from the feasibility assessment are that due to the significant limitations and heterogenous nature of the identified evidence base, any statistical analysis would lead to inconclusive results and is not recommended. It is likely that any estimate of uncertainty will be highly underestimated as such it would be inappropriate to interpret any derived treatment effects. The key limitations identified, are as follows:

- Limited information on baseline characteristics and use of prior treatments were reported, so it is not possible to do a full assessment of heterogeneity
- Age and sex were the only well-reported baseline characteristics; however, the reported baseline age and percentage of sexes between the trials differ substantially. Some studies enrolled only males, which led to different proportions of males being represented across the evidence base. This is important because clinical symptoms and signs of FD manifest earlier and are usually more severe in males.[11, 12, 14] This difference in sex is likely to have a substantial impact on the outcomes
- Studies include patients with both classic and later onset forms of FD highlighting the wide spectrum of disease severity across the studies; this is expected given the wide spectrum of disease severity within FD, so any such attempt to have a similar population across studies based on disease severity would be challenging[11, 12, 14]
- Timepoints vary between studies and endpoints and may not be sufficiently long, which may impact the estimated relative treatment effects
- There are low patient numbers in each of the studies. This means any results from an ITC will be highly uncertain

However, given the availability of the BALANCE data, which provide evidence to support the non-inferiority of PRX-102 E2W compared with agalsidase beta E2W, and the conclusion of clinical equivalence between the ERTs which was accepted

within the NICE submission for migalastat (HST4), we assume that PRX-102 E2W demonstrates equivalent efficacy to both ERTs, as follows:[4, 43]

- BALANCE provides head-to-head data vs. agalsidase beta showing non-inferiority of PRX-102 E2W to agalsidase beta E2W
- BRIDGE and BRIGHT provide supportive switch-over evidence that shows patients treated with PRX-102 E2W and E4W after switching from agalsidase alfa and beta show stable renal function
- The assumption of clinical equivalence between agalsidase beta and agalsidase alfa is further supported by several SLRs and meta-analyses that provide no evidence that one of the existing ERTs is superior to the other[70-72]
- Furthermore, an independent international retrospective cohort study of 387 patients (192 females) found no difference in Fabry clinical events or eGFR slope in patients treated with agalsidase alfa or beta with a median follow-up of 4.9 years (range, 0.8–14.4 years)[73]
- The NICE HST4 appraisal accepted the assumption of clinical equivalence of agalsidase beta and agalsidase alfa
- A naïve comparison between BALANCE, BRIGHT, and BRIDGE suggested there were no significance differences in PRX-102 efficacy for key outcomes of interest between the studies, adding further evidence that the efficacy demonstrated in BALANCE was reflective of the efficacy of PRX-102 in other studies (see Appendix D.1.3.1), although the analyses are very limited due to small patient populations and differing baseline characteristics such as sex and age

In addition, UK clinical experts consulted at an advisory board felt that the non-inferiority conclusion from BALANCE and the precedent in HST4 would be supportive of clinical equivalence of PRX-102 to the existing comparator treatments.[49]

B.2.10. Adverse reactions

B.2.10.1. BALANCE safety data

B.2.10.1.1. Treatment exposure

In BALANCE, both PRX-102 and agalsidase beta were administered as IV infusions E2W at a dosage of 1 mg/kg. Most patients in both arms received at least 24 months of treatment (PRX-102: [redacted]%; agalsidase beta: [redacted]%). Cumulative exposure was [redacted] months for PRX-102 and [redacted] months for agalsidase beta, and median (range) exposure was [redacted] and [redacted] months, respectively.[4]

B.2.10.1.2. Pharmacokinetic data

Based on samples analysed from [redacted] patients who received PRX-102 E2W, a consistent PK profile was reported throughout the study.[4] Results also indicated an important impact of the presence of ADAs. In patients who were negative for ADA at baseline, PRX-102 had a half-life between [redacted] and [redacted] hours over to [redacted] years of treatment, and the area under the curve (AUC) was generally consistent across visits. For the 35% of patients who were ADA-positive at baseline (see Table 8, Section B.2.3) PRX-102 had a shorter half-life of [redacted] hours across visits over [redacted] year of treatment.[4]

B.2.10.1.3. Infusion duration and setting

In the PRX-102 arm, the mean (min; max) infusion duration was reduced from 3.08 (0.6; 4.9) hours at baseline to 1.56 (1.4; 2.1) hours at Week 104. The reduction in infusion duration was less pronounced in the agalsidase beta arm, where mean infusion was 2.96 (2.6; 3.3) hours at baseline and 1.71 (1.4; 3.2) hours at Week 104.

More than 46% of the infusions in the PRX-102 arm and 33% of those in the agalsidase beta arm were administered at home, indicating that the treatment was often considered safe for home infusion especially in the PRX-102 group. [4]

B.2.10.1.4. Summary of adverse events

Table 28 presents an overview of treatment-emergent adverse events (TEAEs) reported in the BALANCE study. Most patients experienced ≥ 1 TEAE: 90.4% with

PRX-102 E2W and 96.0% with agalsidase beta E2W.[4, 5] The rate of treatment-related TEAEs (events per 100 patient-years) was approximately 4-fold higher for agalsidase beta E2W than for PRX-102 (153 vs. 43). However, the proportions of patients experiencing related TEAEs were similar (44% vs. 40%).[5] Event rates were also [redacted] in the PRX-102 E2W arm compared with the agalsidase beta E2W arm for severe TEAEs ([redacted] vs. [redacted] events per 100 patient-years) and for serious TEAEs ([redacted] vs. [redacted] events per 100 patient-years).[4]

[redacted] patients ([redacted]) each had 1 event that led to withdrawal of PRX-102 E2W. One (1.9%) patient withdrew due to a hypersensitivity IRR (serious related TEAE) on the first infusion, and was found to be immunoglobulin E (IgE)-positive at baseline.[4] As expected with biological drugs, this type of reaction may occur early in exposure to a new product. This event was the only serious treatment-related TEAE in the study and the only serious or severe IRR in the study. The [redacted] event leading to withdrawal was not considered treatment-related and occurred in a [redacted] known to have severely deteriorated kidney function before enrolment. During treatment, the [redacted] was diagnosed with end-stage renal disease, and this was defined as an FCE.[4] [redacted] patients treated with agalsidase beta E2W withdrew from the study.

[redacted] adverse events (AEs) led to dose interruptions or adjustments in the BALANCE study, and no deaths were reported in either treatment arm.[4, 5]

Table 28: Summary of treatment-emergent adverse events – Safety population

	PRX-102 E2W (N = 52)		Agalsidase beta E2W (N = 25)	
	Patients with ≥1 event n (%)	Number of events (rate)[a]	Patients with ≥ 1 event n (%)	Number of events (rate)[a]
All TEAEs				
Any TEAE	47 (90.4)	561 (572.36)	24 (96.0)	406 (816.85)
Mild or moderate TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs only				
Any related TEAE	21 (40.4)	42 (42.85)	11 (44.0)	76 (152.91)
Related mild or moderate TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Related severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Related serious TEAE	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to withdrawal	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: [a] per 100 exposure years.
Source: Chiesi, BALANCE CSR.[4]; Wallace et al. 2022.[5]

Given that the patients receiving PRX-102 E2W were starting on a new product while the patients receiving agalsidase beta E2W were continuing on the same treatment, and that AEs are expected to occur more often at the start of a new medication, a higher rate of TEAEs might have been expected for PRX-102 E2W. However, this was not observed.[4]

B.2.10.1.5. Most common adverse events

Table 29 presents individual TEAEs that occurred in ≥ 10% of patients in either treatment group.[4] Among the patients who received PRX-102 E2W, the most common types of events were nasopharyngitis ([redacted]%), headache ([redacted]%), diarrhoea ([redacted]%), nausea ([redacted]%) and fatigue ([redacted]%). Among patients who received agalsidase beta E2W, the most common TEAEs were diarrhoea ([redacted]%), and headache, back pain, cough and bronchitis, all of which were reported in [redacted]%

of patients. In the agalsidase beta E2W arm, bronchitis, abdominal pain upper, blood creatinine increased, paraesthesia, abdominal discomfort, chest pain, influenza-like illness, pharyngitis, fall, rhinorrhoea, pruritus and gastroenteritis were all reported at a rate of over [redacted] higher than in the PRX-102 E2W arm. For PRX-102 E2W, only abdominal pain and proteinuria were reported at a rate of at least [redacted] higher than for agalsidase beta E2W.[4]

Table 29: Adverse events seen in ≥ 10% of patients in either treatment group – Safety set

	PRX-102 E2W (N = 52)		Agalsidase beta E2W (N = 25)	
System organ class	**Number (%) of patients**	**Number of events (rate)[a]**	**Number (%) of patients**	**Number of events (rate)[a]**
At least 1 TEAE	47 (90.4%)	561 (572.4)	24 (96.0%)	406 (816.9)
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]

System organ class	PRX-102 E2W (N = 52)		Agalsidase beta E2W (N = 25)	
	Number (%) of patients	Number of events (rate)[a]	Number (%) of patients	Number of events (rate)[a]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: [a] per 100 exposure-years.
Source: Wallace et al. 2022[5]; Chiesi, BALANCE CSR.[4]

B.2.10.1.6. Immunogenicity and anti-drug antibodies

Table 30 and Figure 23 present the number of patients who tested positive for IgG antibodies and neutralising antibodies to their respective treatment before starting treatment and at the end of the study. For PRX-102 E2W, 18 (35%) patients were ADA-positive at baseline compared with 11 (23%) patients at Month 24 (Figure 23A). For agalsidase beta E2W, 8 (32%) patients were ADA-positive at baseline compared with 6 (26%) patients at Month 24 (Figure 23B). All patients had been receiving agalsidase beta for 1 year or more before study baseline, and there is a high similarity of the protein backbone between the 2 drugs. As such, the presence of antibodies to PRX-102 before exposure is explained by cross-reactivity to the components of PRX-102 that are shared with agalsidase beta.[4] Overall, the treatment-emergent ADA-positive rate at Month 24 was lower for patients who switched to PRX-102 E2W than for patients who remained on agalsidase beta E2W.

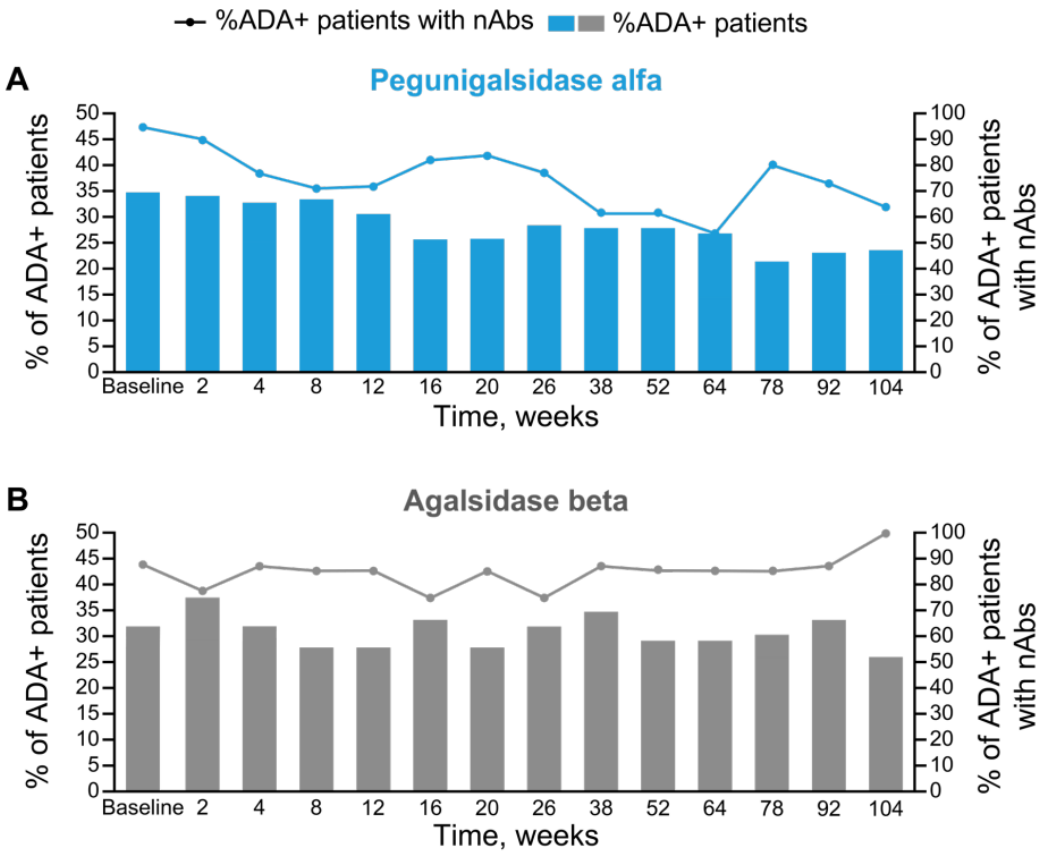
Table 30: Total ADAs and treatment-emergent ADAs

	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)
Baseline n (%)		
ADA-positive	18 (35)	8 (32)
Neutralising antibodies present	17 (94)	7 (88)
ADA-negative	34 (65)	17 (68)
Post-baseline ADAs, n (%)		
Month 24	n = 47	n = 23
ADA-positive	11 (23)	6 (26)
Neutralising antibodies present	7 (64)	6 (100)
ADA-negative	36 (77)	17 (74)

	PRX-102 E2W (n = 52)	Agalsidase beta E2W (n = 25)
Treatment-emergent ADAs, n(%)		
Yes	6 (12)	4 (16)
Titre boosted[a,b]	3 (50)	1 (25)
De novo[a,c]	3 (50)	3 (75)
No	46 (88)	21 (84)

Key: ADA, antidrug antibody.
Notes: [a] % calculated out of patients with treatment-emergent ADAs. [b] Titre at least fourfold baseline values. [c] If the patient was ADA- at baseline and became ADA+ positive at any subsequent time.
Source: Wallace et al. 2022.[5]

Figure 23: Rates of ADA-positive patients and ADA-positive patients with neutralising antibodies over time for (A) PRX-102 E2W and (B) agalsidase beta E2W



Key: ADA, antidrug antibody; nAb+, positive for neutralising antibodies.
Source: Wallace et al. 2022.[5]

The treatment-emergent ADA-positive rate was lower for patients who switched to PRX-102 E2W (6 [11.5%]) than for patients who remained on agalsidase beta E2W (4 [16.0%]).[5] This is despite patients switching to a new product that is expected to induce an immune response. Most patients receiving PRX-102 who were negative at baseline remained negative (91.2%), and most who were positive at baseline did not show a major (≥ fourfold) increase in titre. Although the PRX-102 E2W and agalsidase beta E2W arms were similar at baseline in terms of patients who were positive for IgG ADA (34.6% vs. 32.0%), the rate at any post-baseline visit was lower for PRX-102 ([redacted]% vs. [redacted]%).[4] A higher proportion of patients who were ADA-positive became negative in the PRX-102 arm compared with the agalsidase beta arm ([redacted]% vs. [redacted]% of the ADA-positive patients) at Month 24.

Neutralising antibodies were only assessed in patients who were positive for IgG. In the PRX-102 E2W arm, neutralising antibodies were present in 17/18 (94%) patients at baseline and 7/11 (64%) patients at Month 24.[5] In the agalsidase beta E2W arm, neutralising antibodies were present in 7/8 patients (88%) at baseline and 6/6 (100%) patients at Month 24 (see

Figure 23). The lower proportion of patients with neutralising antibodies in the PRX-102 E2W arm at Month 24 aligns with the greater rate of tolerability to PRX-102, as observed with the overall IgG rate.[4]

B.2.10.1.7. Infusion-related reactions

While similar proportions of patients in both groups experienced IRRs, the number of IRR events and the normalised rate of IRR events were higher for agalsidase beta E2W than PRX-102 E2W by approximately 4-fold and 8-fold, respectively (Table 31).[5] In the PRX-102 E2W arm, within 2 hours of infusion, 11 patients (21.2%) experienced a total of 13 IRRs associated with [redacted] infusions, for an adjusted rate of 0.5 events per 100 infusions.[5] The IRR rate in the agalsidase beta E2W arm was considerably higher, with 6 (24.0%) patients experiencing a total of 51 IRRs associated with [redacted] infusions, for an adjusted rate of 3.9 events per 100 infusions. Only 1 serious IRR was reported.

Table 31: Summary of IRRs occurring within 2 hours of infusion – Safety set

	PRX-102 E2W (n = 52)			Agalsidase beta E2W (n = 25)		
	Number of patients with at least 1 IRR n (%)	Number of infusions with IRR	Number of IRRs (rate)	Number of patients with at least 1 IRR n (%)	Number of infusions with IRR	Number of IRRs (rate)
Any IRR	11 (21.2)	[redacted]	13 (0.50)	6 (24.0)	[redacted]	51 (3.9)
Severe IRR	1 (1.9)	1	1 (0.0)	0	0	0
Serious IRR	1 (1.9)	1	1 (0.0)	0	0	0
IRR leading to withdrawal	1 (1.9)	1	1 (0.0)	0	0	0

Key: CSR, clinical study report; E2W, every 2 weeks; IRR, infusion-related reaction
Source: Wallace et al. 2022[5]; Chiesi, BALANCE CSR[4]

B.2.10.1.8. Use of infusion premedication

The recommendation to use premedication proactively to prevent IRRs to agalsidase beta E2W was challenged during the study, and most patients successfully reduced the use of infusion premedication during the study.[5] At baseline, a higher proportion of patients in the agalsidase beta arm E2W (16 [64%]) received infusion premedication than patients in the PRX-102 E2W arm (21 [40%]). In both groups, there was a notable reduction in patients using premedication by Week 12 (which represented the end of the 3-month tapering-off period) to [redacted] patients ([redacted]%) receiving PRX-102 E2W and [redacted] ([redacted]%) patients receiving agalsidase beta E2W.[4] Over the course of the study, premedication use reduced in both groups but was reduced to a greater extent in the PRX-102 arm, potentially indicating better tolerability. At 24 months, a higher proportion of patients in the agalsidase beta E2W arm (3 [12%]) continued to receive infusion premedication than in the PRX-102 E2W arm (3 [6%]).[5]

Since patients were blinded as to which product they were receiving, the lower rate of premedication in the PRX-102 arm is indicative of a favourable tolerability profile, and this is consistent with the lower rate of IRRs seen in the PRX-102 arm.[4] An analysis correlating IRRs with premedication suggested that, in the agalsidase beta arm, premedication was less successful in preventing IRRs compared with the PRX-102 arm.

B.2.10.1.9. BALANCE safety summary

In BALANCE, PRX-102 E2W showed a favourable safety, tolerability and immunogenicity profile compared to agalsidase beta E2W, especially when assessing exposure-adjusted reporting rates for TEAEs, serious adverse events (SAEs), IRRs and ADA levels. These findings support an acceptable safety profile for PRX-102 E2W, which is important because the rate of AEs usually increases when patients start a new treatment.[5] No major safety concerns were observed, and findings were in line with previous studies. There were no fatalities, and only [redacted] patients in the PRX-102 E2W arm withdrew from the study due to AEs, [redacted] of which was not considered to be treatment-related.[5]

The overall proportion of patients receiving PRX-102 E2W who ≥1 TEAE was slightly lower than for agalsidase beta E2W (90.4% vs. 96.0%, respectively). The rate of events adjusted for exposure was also notably lower (572.4 events for PRX-102 E2W vs. 816.9 events for agalsidase beta E2W per 100 patient years of exposure, PYE).[5] For other important AEs, compared with agalsidase beta E2W, PRX-102 E2W demonstrated a lower rate of SAEs ([redacted]% vs. [redacted]%; exposure-adjusted rates: [redacted] vs. [redacted] events per 100 PYE), and treatment-related TEAEs (40.4% vs. 44.0%; exposure-adjusted rates: 42.9 vs. 152.9 events per 100 PYE). One serious TEAE occurred during the study in a patient receiving PRX-102 E2W.[5] This was a hypersensitivity event that happened on the first day of treatment, and is a reaction that is more likely to occur when first exposed to a new biological drug.[4] While similar proportions of patients in both groups experienced IRRs, the number of IRR events and the normalised rate of IRR events were higher for agalsidase beta E2W than PRX-102 E2W by approximately 4-fold and 8-fold, respectively.

Additionally, the proportion of ADA-positive patients with neutralising antibodies was lower for PRX-102 E2W than for agalsidase beta E2W at 24 months.[5] These observations of low treatment-emergent immunogenicity and increased tolerability are important from a safety and an efficacy perspective, as antibodies developed against an ERT product, especially neutralising antibodies, would be expected to inhibit the treatment's activity and potentially adversely affect the clinical outcome. However, this does not seem to be the case. Clinician experts at an advisory board

highlighted that the reduction in ADAs signals potential improvement in long-term efficacy, which may improve long-term renal and cardiac outcomes.[49]

B.2.10.2. BRIGHT safety data

All 30 patients enrolled in BRIGHT received 1 infusion of PRX-102 dosed E4W (including partial infusions) and were included in the Safety population.[55, 56] Overall cumulative exposure in this population was [redacted] person-months, and the mean exposure per patient was [redacted] patient-months.[51]

Overall, 183 TEAEs were reported in 27/30 (90.0%) patients; 165 events in 22/24 (91.7%) male patients and 18 events in 5 out of 6 (83.3%) female patients.[55, 56] The most frequently reported TEAEs by preferred term (PT) were nasopharyngitis in [redacted] patients, fatigue in [redacted] patients and IRR in [redacted] patients.[51] The TEAEs reported in BRIGHT are summarised in Table 18 in Appendix F.2. All other TEAEs were reported in [redacted] patients. Most TEAEs were mild or moderate in severity (180 TEAEs in 27 [90.0%] patients) and were resolved or resolving at the end of the study.[55, 56] A total of 3 severe TEAEs were reported in 2 (6.7%) male patients. Two of these 3 severe events were also serious TEAEs; all events were considered unrelated to study treatment. Overall, 33 TEAEs reported in 9 (30.0%) patients were considered treatment-related.[55, 56] All treatment-related TEAEs were mild or moderate in severity and most were resolved at the end of the study. Most patients (7 out of 9 [77.8%]) with treatment-related TEAEs were males. Of the treatment-related TEAEs, 27 were IRRs and the remainder included, but were not limited to, single events of diarrhoea, erythema, fatigue, influenza-like illness, UPCR increased, and urine positive for white blood cells. No TEAEs led to death or study withdrawal.[51]

Twenty-seven IRRs were reported in 5 (16.7%) patients, all of which were males. Of these 5 patients, 4 were positive for ADAs against agalsidase beta E2W at baseline and had previously received agalsidase beta. The fifth patient was previously on agalsidase alfa and negative for ADAs at all timepoints.[55, 56] All IRRs occurred during infusion or within 2 hours post-infusion; no events were recorded that occurred between 2 and 24 hours post-infusion. All IRRs were non-serious, mild (17 events in

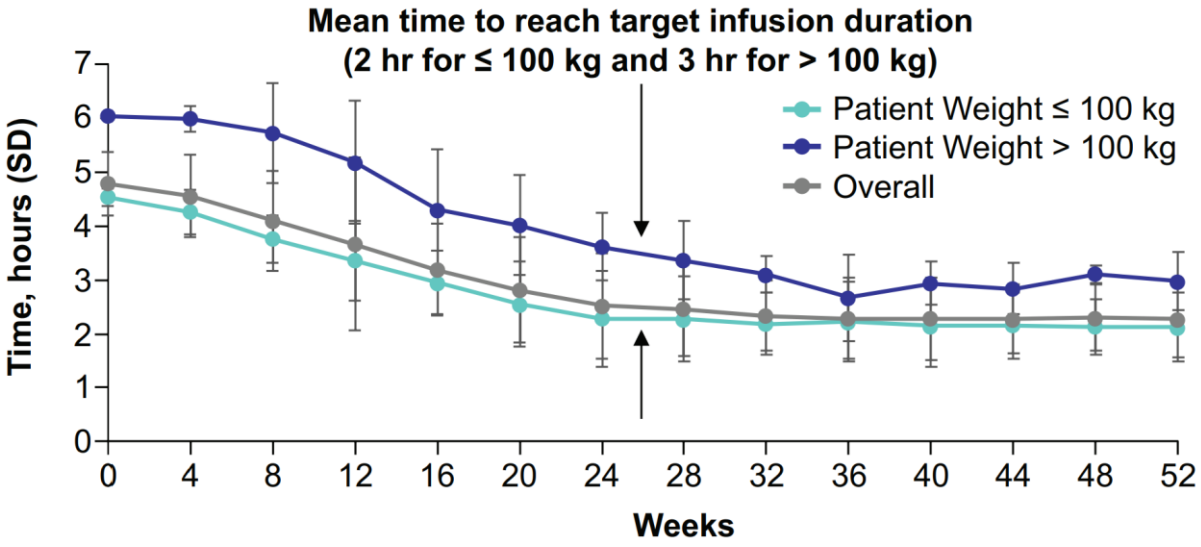
3 [10.0%] patients) or moderate (10 events in 5 [16.7%] patients) in severity, and were all resolved by the end of the study.

Only patients with pre-existing IgG antibodies were positive for ADAs to PRX-102 during the study; no patients developed ADAs de novo following the switch to PRX-102 E4W.

B.2.10.2.1. Infusion duration

Mean (SD) infusion duration of the E4W regimen decreased significantly from 4.8 hours (0.59) at baseline to 2.3 hours (SD 0.7) by Month 12 ($p < 0.001$; Figure 24).[55] [69] Most patients reached the target infusion duration (i.e. 96% reached the target of 2 hours for patients weighing ≤ 100 kg; 100% reached the target of 3 hours for patients weighing > 100 kg) at 52 weeks. Mean (SD) infusion duration times from baseline to Week 52 were 4.54 (0.03) to 2.12 (0.13) hours in patients ≤ 100 kg and 6.05 (0.01) to 2.97 (0.24) hours in patients > 100 kg. The reduction of infusion duration indicated good drug tolerability.

Figure 24: Mean infusion duration of PRX-102 2.0 mg/kg E4W by weight in BRIGHT



Key: E4W, every 4 weeks; SD, standard deviation
Notes: For each timepoint: n=24 for patients weighing ≤ 100 kg; n=5 for patients weighing > 100 kg
Source: Mehta et al, 2022[69]

B.2.10.3. BRIDGE safety data

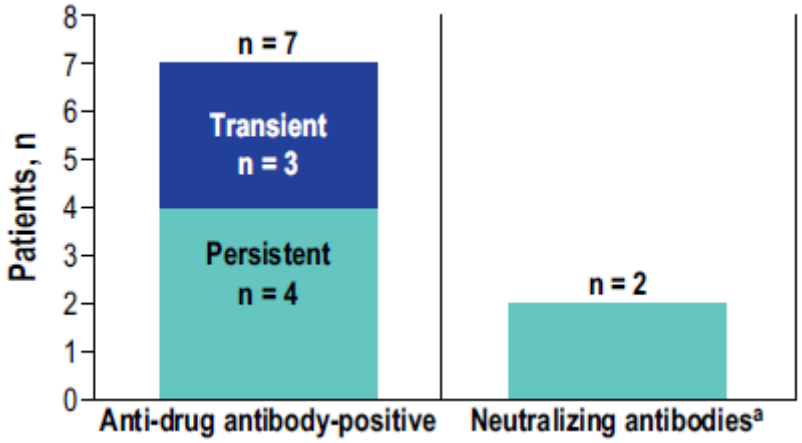
All 22 patients enrolled in the study received ≥1 infusion of PRX-102 E2W (including partial infusions) and were included in the Safety population. The exposure in the Safety population was [redacted] patient-months overall, with [redacted] patient-months in male patients and [redacted] patient-months in female patients.[52]

Overall, 127 TEAEs were reported in 21 patients (95.5%; 14 male patients and 7 female patients).[58] The most frequently reported TEAEs by PT were nasopharyngitis in 7 patients (31.8%), headache in 5 patients (22.7%), and dyspnoea in 3 patients (13.6%). All other TEAEs were reported in ≤ 2 patients. Most TEAEs were mild or moderate in severity (123 TEAEs [96.9%] experienced by 19 patients [86.4%]) and were resolved or resolving. A total of 4 severe TEAEs (3.1%) were experienced by 4 patients (18.2%; 4 [redacted] patients); these events were all SAEs. No other SAEs were reported in the study. Two of the severe TEAEs were considered treatment-related and were Type I hypersensitivity reactions in 2 patients (9.1%; 2 [redacted] patients). The other 2 severe TEAEs (infectious mononucleosis [4.5%; 1 [redacted] patient]), and urinary tract infection [4.5%; 1 [redacted] patient]) were not considered to be treatment-related. All 4 severe AEs were resolved. Additionally, no deaths were reported in the study. A brief summary of TEAEs is presented in Appendix F.3.[52]

Four TEAEs related to IRRs were reported in 3 (13.6%) patients, and 9 TEAEs related to IRRs were reported in 5 (22.7%) patients. All but 2 of these TEAEs (type I hypersensitivity) were considered non-serious and resolved.

Of the 20 patients in the study, 7 (35%) had a positive ADA status at some point during the study (Figure 25).[58] Of the 7 ADA-positive patients, 4 (20%) had a persistent positive status and 3 (15%) had a transient positive status. Of the 4 patients with persistent ADAs, 2 were positive for neutralising antibodies.

Figure 25: Development of anti-drug antibodies over 12 months in BRIGHT

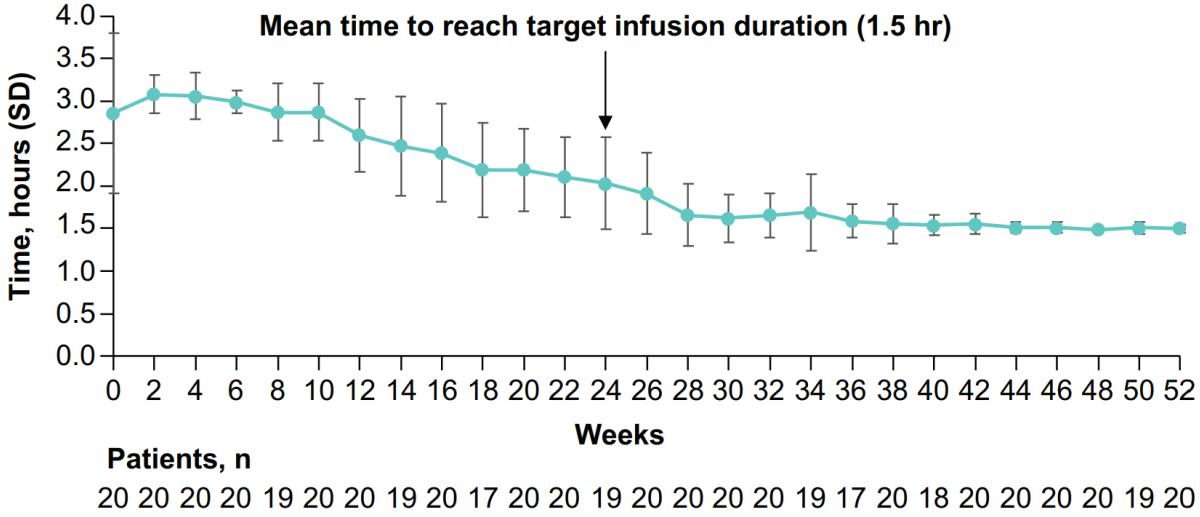


Key: ADA, anti-drug antibody.
Notes: [a], Neutralising ADAs tested only in patients with a positive IgG antibody response. The assays were validated according to the United States' Food and Drug Administration and the European Medicines Agency immunogenicity guidelines and performed centrally, in accordance with the Good Laboratory Practices. Methods were either a solid-phase enzyme-linked immunosorbent assay or an in vitro enzymatic activity procedure.
Source: Jovanovic et al. 2022.[58]

B.2.10.3.1. Infusion duration

In BRIDGE, patients (n = 22) receiving PRX-102 E2W had an initial mean (SD) infusion duration of 2.9 hours (0.9) (Figure 26). Two patients discontinued treatment because of a type 1 IgE-mediated hypersensitivity reaction within 2 hours of the first infusion, and the remaining 20 patients who completed the study reached the minimum protocol-allowed infusion duration of 1.5 hours ± 10 minutes by 12 months, showing a significant reduction from bassline ($p < 0.001$). The reduction of infusion duration indicated good drug tolerability.

Figure 26: Mean infusion duration of PRX-102 1.0 mg/kg E2W in BRIDGE



Key: E2W, every 2 weeks; SD, standard deviation.
Notes: n = 20 at 12 months; p < 0.001 from baseline to 12 months.
Source: Mehta et al. 2022[69]

B.2.10.4. Supportive safety studies

B.2.10.4.1. Phase I/II studies and long-term extension

Supportive safety evidence from the long-term Phase I/II study PB-102-F03 is presented below with further details of this study and the shorter-term Phase I/II studies (PB-102-F01 and PB-102-F02) in Appendix F.4.

PB-102-F03

Long-term safety has been demonstrated for PRX-102 in the PB-102-F03 study. This study enrolled patients who completed Phase I/II studies into an open-label extension in which PRX-102 E2W was received for up to 6 years (n = 15 for > 1 year, n = 10 for ≥ 5 years).[68]

In the overall treatment period of up to 6 years, most (97.5%) TEAEs were mild or moderate in severity.[60, 61, 64] The most common TEAEs were fatigue (8 [53.3%]), back pain (6 [40.0%]), abdominal pain, nausea, upper respiratory tract infection, nasopharyngitis, headache, paraesthesia, vomiting, rash and cough (5 [33.3%] each). In the overall treatment period, TEAEs defined as severe (5 patients [33.3%])

or serious (3 [20.0%]) occurred only in males. No severe or serious TEAEs or deaths were considered related to study treatment.

For IRRs, 2 out of 8 males(25.0%) and 4 out of 7 females (57.1%) experienced ≥ 1 IRR; all were categorised as mild to moderate severity, and only 1 IRR occurred during F03.[60, 61, 64] IRRs noted were dizziness and nausea (both reported by 2 patients), and abdominal pain, chest discomfort, chest pain, dyspnoea, fatigue, hypotension, infusion reaction, maculopapular rash, paranasal sinus hypersecretion, peripheral swelling, pruritus, and sneezing (each reported by 1 patient). No IRRs were serious or severe, or led to withdrawal or death.

Five patients were positive for anti-PRX-102 IgG ADAs: 4 patients were transiently positive for ADAs and 2 of these 4 patients were transiently positive for neutralising antibodies.[55] One patient was positive for non-neutralising antibodies at Visit 1, but remained negative thereafter, and another was positive for ADAs starting at Month 48, and was positive for neutralising antibodies from Month 54 until study completion.

B.2.10.4.2. Pooled safety analysis

A pooled analysis of safety data has been reported, including data from 5 clinical studies (BRIGHT, BRIDGE, the 2 Phase I/II studies [PB-102-F01, PB-102-F02], and their extension study [PB-102-F03]).[69] Data were assessed together although they were not analysed in a formal statistical analysis. The analysis supported the favourable tolerability profile of PRX-102 in patients with FD dosed E2W and E4W, with mean infusion durations being reduced or meeting target rates by the end of the respective studies. The incidence of IRRs ranged from 17% to 28%, which compares favourably to other ERTs administered at the same dose (55%–67%). Most IRRs (57/60) reported during PRX-102 treatment were of mild or moderate severity. The percentage of patients who were IgG ADA-positive was higher in patients with IRRs compared with those without IRRs. Overall, SAEs were reported in 3 of the 60 IRRs, (1 bronchospasm and 2 type 1 hypersensitivity reactions), all of which were IgE-mediated.

B.2.11. Ongoing studies

Table 32: presents 2 ongoing studies investigating PRX-102 in patients with FD that may report data in the next 12 months.

Table 32: Ongoing studies investigating PRX-102 in patients with FD that may report in the next 12 months

Trial no. (name)	Phase	Study design	Population	Intervention	Status	Expected reporting date	Primary reference
NCT03614234 (Bright51-open label extension)	Phase III	Open-label extension study in patients who have completed PB-102-F50	Adult (≥ 18 years) patients with FD (n = 30)	PRX-102 2 mg/kg E4W	Enrolling by invitation	Estimated completion: October 2024	NCT03614234
NCT03566017 (PB-102-F60) BALANCE open-label extension	Phase III	Open-label extension study in patients who have completed studies PB-102-F20, PB-102-F30 or ≥ 36 months in the PB-102-F03 study	Adult (≥ 18 years) patients with FD (n = 110)	PRX-102 1 mg/kg E2W	Enrolling by invitation	Estimated completion: October 2026	NCT03566017
Key: FD, Fabry disease.							

B.2.12. Interpretation of clinical effectiveness and safety evidence

PRX-102 offers an additional treatment option for patients with FD who would usually be treated with an ERT. PRX-102 provides non-inferior efficacy when compared with current ERTs and a well-tolerated safety profile, with potential for a less frequent dosing regimen (E4W). It also shows a reduction in immunogenicity compared with available ERT alternatives, as demonstrated in a comprehensive clinical trial programme.[4, 51, 52]

In BALANCE, PRX-102 E2W demonstrated non-inferiority to agalsidase beta E2W in terms of change in eGFR slope, a key measure of FD progression. PRX-102 also demonstrated similar efficacy to agalsidase beta in other measured outcomes in BALANCE, including proteinuria by UPCR, LVMI, plasma lyso-Gb3 levels, disease severity measured by MSSI, and QoL assessed by EQ-5D. PRX-102 also demonstrated a favourable safety profile when compared to agalsidase beta, including a reduction in ADA production and incidence of IRRs.

Further support for the efficacy and safety of PRX-102 E2W was provided by the Phase III trial, BRIDGE, and long-term Phase I/II trials in adults with FD, including those with stable renal function and in patients who were treatment-naïve.[4, 51, 52] The Phase III BRIGHT trial demonstrated the efficacy and safety of PRX-102 when dosed E4W in patients switching from agalsidase alfa or beta dosed E2W.[51, 55, 56]

Subgroup analyses of BRIDGE, which included patients with and without renal impairment, demonstrated efficacy of PRX-102 in patients with varying eGFR levels at baseline, although these analyses are based on small patient numbers.[51, 52] Furthermore, an integrated analysis has demonstrated that the presence of an amenable mutation [redacted] when treated with PRX-102, from an integrated analysis of [redacted] patients from the PRX-102 studies (see Appendix M5).[81]

B.2.12.1. Principal findings from the clinical evidence base highlighting the clinical benefits and harms of the technology

PRX-102 has demonstrated efficacy and safety in a robust, extensive clinical trial programme

PRX-102 has been studied in a comprehensive clinical trial programme in 142 patients with FD, including patients previously treated with ERTs and those who were treatment-naïve. BALANCE, a pivotal, Phase III double-blind RCT, is the first head-to-head trial comparing ERTs in patients with FD. BALANCE is also the largest Phase III RCT that has been conducted in FD. It provides robust head-to-head data for PRX-102 E2W against an active ERT comparator over 24 months in 78 adult patients with deteriorating renal function. Clinical experts consulted at an advisory board agreed that, of the ERTs, agalsidase beta was the most appropriate comparator, and stated that using agalsidase alfa as a comparator would have led to concerns of over-dosing between the arms.[49]

The Phase III BRIDGE and BRIGHT trials provide supportive efficacy and safety evidence in a broader population (i.e., not only patients with renal impairment) who had previously received ERTs.[51, 52] Long-term efficacy and safety data for treatment-naïve patients is provided by the Phase I/II trials PB-102-F01, PB-102-F02, and PB-102-F03, including data for up to 72 months from the PB-102-F03 study.[4, 23, 51, 52, 68]

The impact of the presence of amenable mutation on the efficacy of PRX-102 was also investigated, through an integrated post-hoc analysis of [redacted] patients from the PRX-102 clinical trial programme (BALANCE, BRIGHT, BRIDGE and Phase I/II studies; Appendix M5).[81] At baseline, mean (SE) eGFR was very similar between the [redacted] patients with an amenable mutation [redacted] mL/min/1.73 m^2) and the [redacted] patients without an amenable mutation [redacted] mL/min/1.73 m^2). The change in eGFR over time (see Appendix M5) also confirms a high degree of overlap between both amenable and non-amenable groups. The mean (standard error) change from baseline in eGFR was also [redacted] between patients with and without amenable mutations [redacted] mL/min/1.73m^2, respectively), demonstrating that the presence of an amenable mutation [redacted] when treated with PRX-102.[81]

PRX-102 has demonstrated non-inferiority to the existing ERT, agalsidase beta, in a head-to-head clinical trial

In the head-to-head BALANCE study, PRX-102 E2W was demonstrated non-inferior efficacy to agalsidase beta E2W with regard to eGFR slope in patients with deteriorating renal function who were previously treated with agalsidase beta. The primary efficacy testing for non-inferiority was based on the measure of difference in median eGFR slopes (see Section B.2.6.1.2). There was a good overlap of the CIs for the eGFR values over time and the eGFR slopes of the 2 arms, with the lower bound of the CI being well above the non-inferiority margin. Other efficacy outcomes were similar between treatment arms.[4]

PRX-102 has a favourable tolerability profile

PRX-102 E2W was well-tolerated in BALANCE, with no new safety concerns observed. Compared with agalsidase beta, the overall proportion of patients with TEAEs was slightly lower, and the rate of events adjusted for exposure was notably lower (PRX-102, 42.85 per 100 exposure years; agalsidase beta, 152.91 per 100 exposure years). In particular, injection site reactions occurred at a lower rate with PRX-102 compared with agalsidase beta, and all were resolved without sequalae. PRX-102 also led to a lower rate of IRRs vs. agalsidase beta (21.2% [0.5 per 100 infusions] vs. 24.0% [3.9 per 100 infusions]) within 2 hours of completing the infusion. The lower rate of IRRs with PRX-102 is particularly encouraging as patients had previously received agalsidase beta for ≥ 1 year, and such reactions are a concern with ERTs because they usually occur at a higher frequency when starting treatment with a new biologic. Further support was provided by the Phase III trials BRIDGE and BRIGHT in patients with stable renal function and the Phase I/II trials in the treatment-naïve population, all of which reported a safety profile consistent with that seen in BALANCE.[4, 51, 52]

PRX-102 has a favourable immunogenicity profile

Current ERTs are associated with the production of ADAs, which are not only detrimental from a safety perspective but may also reduce efficacy in the long term. This is because ADAs, especially neutralising antibodies, can inhibit the product's

activity and potentially adversely affect the clinical outcome.[46, 47] At an advisory board, clinicians agreed that the reduction in ADAs may limit the reduction in long-term efficacy and potentially improve long-term renal and cardiac outcomes.[4, 49]

In BALANCE, the rate of treatment-emergent IgG ADAs was lower for PRX-102 E2W compared with agalsidase beta ([redacted]), and most patients ([redacted]) receiving PRX-102 who were negative at baseline remained negative (see section B.2.10.1).[4] However, of the patients who were ADA-positive at baseline, a greater proportion in the PRX-102 arm became ADA-negative compared with the agalsidase beta arm ([redacted]) at Week 104. Of the patients who were IgG ADA-positive at Week 104, patients receiving PRX-102 arm had a lower rate of neutralising antibodies compared with agalsidase beta ([redacted]). The low immunogenicity status was consistently reported in BRIGHT and BRIDGE, as well as in treatment-naïve patients in the Phase I/II trials.[4] This is further supported by an in vitro study demonstrating that the affinity of ADAs against agalsidase alfa or beta from pooled patient sera was significantly lower for PRX-102 compared to agalsidase alfa and agalsidase beta by an average of 1.8-fold lower (both $p < 0.05$).[82]

PRX-102 can be administered at a lower frequency than existing treatments

Existing ERTs are administered by IV infusion E2W, often requiring the use of pre-medication and prolonged infusion times (for agalsidase beta) to prevent the occurrence of IRRs, which may cause the patient to stop treatment. In the BRIGHT study, PRX-102 has been investigated with E4W dosing at 2 mg/kg.[4, 51] Despite the lower administration frequency, results showed that PRX-102 was as effective and well-tolerated in adult patients with FD who had previously received ERT. The switch from agalsidase alfa or agalsidase beta to PRX-102 at this less frequent dosing regimen was well-tolerated with no safety issues. The switch also led to stability in renal function and plasma lyso-Gb3 levels, and improved or stable cardiac function.[51] This less frequent dosing would provide a key benefit to patients in terms of improved QoL, with the potential to provide patients with an additional 13 infusion-free days per year. The less frequent administration resulting from the E4W dosing

regimen may also have sustainability benefits to the healthcare system, including potential reductions in the need for travel of homecare nurses, and in plastic waste.

The lower administration frequency is supported by PK data provided by the Phase I/II studies (see Section B.2.2 and Appendix M.4 for more details).[62-64] These data demonstrate the longer half-life of PRX-102 (mean ~80 hours), compared with agalsidase alfa (108 minutes in males; 89 minutes in females) and agalsidase beta (80–120 minutes).[1, 44, 45] The extended half-life of PRX-102 provides biological rationale for the stable efficacy of PRX-102 when administered at E4W.

PRX-102 demonstrates non-inferior efficacy to the other ERTs

BALANCE provides head-to-head data vs. agalsidase beta demonstrating that PRX-102 E2W is non-inferior to agalsidase beta in patients with declining renal function. BRIDGE and BRIGHT provide supportive efficacy data for PRX-102 E2W and E4W from 2 switchover studies in patients with stable renal function who were previously treated with agalsidase alfa and agalsidase beta. Additionally, the NICE HST4 submission provides support for assuming equivalence between agalsidase beta and agalsidase alfa, and this is further supported by several literature reviews and meta-analyses that provide no evidence that one of the existing ERTs is superior to the other.[70-72] The assumed equivalence between agalsidase beta and agalsidase alfa is also supported by an independent international retrospective cohort study, which found no difference in Fabry clinical events or eGFR slope between the 2 treatments after a median follow-up of 4.9 years.[73] Based on discussions at an advisory board, clinical experts felt that an approach of using BALANCE and the precedent in HST4 would support clinical equivalence of PRX-102 to ERTs.[49]

B.2.12.2. Strengths and limitations

B.2.12.2.1. Internal validity of the clinical evidence base

BALANCE, BRIGHT and BRIDGE were all multicentre, Phase III trials designed to investigate the efficacy and safety of PRX-102 for the treatment of adults with FD.[4, 51, 52] For these trials, an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) reviewed and approved the study protocols and any amendments prior to implementation. The IRB/IEC also reviewed the informed consent forms

(ICFs) and any written materials given to patients. BALANCE, BRIGHT and BRIDGE were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and in compliance with the approved protocol, good clinical practice (GCP) guidelines, and applicable regulatory requirements, which provides confidence in their internal validity.[4, 51, 52] A quality assessment (see Section B.2.5 and Appendix D) determined the trials to be at a low risk of bias, with a robust overall design and execution, according to the NICE criteria for assessment and risk of bias for RCTs and the Critical Appraisal Skills Programme (CASP) tool.

B.2.12.2.2. External validity of the clinical evidence base

The baseline characteristics in BALANCE were similar to those in a UK real-world CPRD study that was conducted between 2000 and 2019.[8] Patients in BALANCE were slightly older than those in the UK real-world study (mean [SE] of 44.3 [1.1] vs. mean [SD] of 37 [20] years) and body weight was similar between the 2 studies (mean [SD]: 78.9 [17.5] kg vs. 72.2 [20.4] kg).[4, 8] At an advisory board, clinical experts were questioned on the generalisability of the patients in BALANCE to UK clinical practice, and noted a few variations.[49] Conversely to the comparison with the UK CPRD study, the experts commented that patients were slightly younger than seen in UK clinical practice. This was interesting because younger patients, especially younger female patients, tend to have better renal function. BALANCE also included a slightly higher proportion of patients with classic FD compared with UK clinical practice, although this was not considered to be highly relevant.[49] Although there was no concern that this would impact the conclusion of equivalence, treatment effect against PRX-102 may be underestimated, which should be acknowledged.

BALANCE included 5 patients at 4 sites in the UK where PRX-102 was used in a research setting in UK NHS hospitals. Results should therefore be generalisable to UK clinical practice.[4] Of the 12 countries included in the study, 11 were in Europe, enrolling 27 patients in total into the BALANCE study at 14 of the 19 sites. As PRX-102 is administered by IV infusion with a dosing regimen of either E2W or E4W and requires no additional equipment compared with existing ERTs, it should be easily integrated into routine UK clinical practice and homecare settings.

In a targeted literature review conducted to establish the relationship between PRX-102 trial endpoints and long-term clinical events in FD,[83] multiple studies were identified suggesting that endpoints collected in the PRX-102 trials are relevant surrogate outcomes in FD for predicting long-term events.[84-91] Specifically, eGFR, which was the primary endpoint of BALANCE, was found to be a significant predictor of outcomes (renal, cardiac and cerebral events) in both mixed-effects and multivariate analyses in the study by Arends et al. (2017). This further supports eGFR being a valid measure of disease progression in patients with FD.[92] Other outcomes measured in the clinical trials are relevant to clinical practice, including: cardiac outcomes such as LVMI, which has also been shown to be a significant predictor of long-term clinical outcomes[92]; symptoms of FD such as pain severity, and occurrence of FCEs; safety; and measurement of ADAs.

B.2.12.2.3. Limitations of the clinical evidence base

Limitations of the clinical evidence base for PRX-102 include the lack of a direct head-to-head comparison with the other ERT used in UK clinical practice, agalsidase alfa, and in patients who were switched from the oral therapy, migalastat. However, the evidence base supports PRX-102 being equivalent to agalsidase alfa. Data supporting this include: robust head-to-head data vs. agalsidase beta in BALANCE; supporting switchover evidence from BRIDGE and BRIGHT; the conclusions in HST4 assuming equivalent efficacy of agalsidase alfa and agalsidase beta; published evidence from literature reviews;[70-72] long-term real-world cohort studies showing equivalent efficacy of agalsidase alfa and beta[73], and a meta-analysis showing no superiority of one of the existing ERTs over the other. In addition, a panel of UK clinical experts strongly supported the assumption of equivalent efficacy of current ERTs at an advisory board.[49] In an integrated analysis of [redacted] patients from the PRX-102 studies (BALANCE, BRIGHT, BRIDGE, and the phase I/II trials), including [redacted] patients with amenable mutations and 64 without, results confirmed very little difference between the groups in change from baseline eGFR (Appendix M5).[81] The results suggest that the presence of an amenable mutation has [redacted].

An additional limitation is that BALANCE was conducted in a renally impaired population only. The rationale for this was present in the original superiority design,

as BALANCE was designed to detect statistically significant differences in renal outcomes over 24 months in patients with FD, which is a slowly progressing LSD. In addition to the evidence from BALANCE, data from BRIDGE and BRIGHT were in patients without renal impairment and provided consistent results.[51, 52] Furthermore, a naïve comparison between the Phase III PRX-102 trials (BALANCE, BRIGHT, and BRIDGE) was also attempted (see Appendix D.1.3.1). Although the analyses are very limited due to small patient populations and differing baseline characteristics between the patients in the trials such as sex and age, the results suggested that there are [redacted] between the efficacy of PRX-102 in key outcomes of interest between BALANCE (PRX-102 E2W in renally impaired population and BRIDGE (PRX-102 E2W in non-renally impaired). The Phase III trials were conducted in patients who had been previously treated with ERTs. However, the Phase I/II studies were conducted in a treatment-naive population and included data for up to 72 months and provided efficacy consistent with the results of the Phase III trials.[62-64]

BALANCE was originally designed to demonstrate superiority of PRX-102 to agalsidase beta. However, given the changed regulatory landscape in the US with the full approval of agalsidase beta in March 2021, it was agreed with the Food and Drug Administration (FDA) that demonstrating superiority was unnecessary, as this was no longer required under FDA guidelines.[93] The primary analysis of the BALANCE study was therefore changed from demonstrating superiority to demonstrating non-inferiority to agalsidase beta, as the FDA agreed that this analysis has the potential to support the approval of PRX-102 for the treatment of FD. Clinical experts consulted at an advisory board acknowledged this change in objectives, but had no concerns about the impact of this change on the conclusion of non-inferiority.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

A systematic review of the published literature was conducted to identify all relevant economic evaluations and modelling studies for the treatment of patients with FD, irrespective of their previous treatment status and age group. Full details of the economic SLR are presented in Appendix G.

Five studies were identified as relevant in the economic modelling review. All 5 studies were economic evaluations or publications supporting economic evaluations conducted across the UK and Canada. A comparison of migalastat vs. ERT was assessed in 3 studies, while the other 2 studies assessed ERT (agalsidase beta) vs. no treatment and agalsidase alfa vs. usual care.[17, 32, 94-96].

A summary of the identified studies and implications for the economic modelling of PRX-102 is discussed in Table 33.

Table 33: Summary of published cost-effectiveness studies

Study	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
CADTH [Migalastat], 2018[95]	• Markov model • 10 health states • 50 year time horizon	• Migalastat: 18.26 • ERT (blended): 17.25 • Incremental: 1.01	• Migalastat: $6,168,792 • ERT (blended): $6,519,745 • Incremental cost: -$350,953	Migalastat is dominant compared with the blended ERT comparator
NICE [Migalastat], 2017[17]	• Cost consequence model (based on Markov model) • 10 mutually exclusive health states • 48 year time horizon	Company base case • Migalastat: 14.33 • ERT (blended): 13.36 • Incremental QALYs: 0.98 ERG preferred analysis • Incremental QALYs: 0.34	• Migalastat: £3,086,992 • ERT (blended): £2,196,454 • Agalsidase beta: £2,047,431 • Agalsidase alfa: £2,260,321 • Incremental costs (vs migalastat): • ERT (blended): £890,539 • Agalsidase beta: £1,039,561 • Agalsidase alfa: £826,672 Results are reported for drug list prices. Results with PAS discounts were commercial in confidence and redacted in the report.	NR - The committee noted that the company presented a cost–consequence analysis based on a Markov model. The committee considered that the company's approach and the structure of the model were generally reasonable, after discussion with the clinical and patient experts. The committee concluded that the overall results were highly uncertain but consistent with migalastat providing additional health benefits at a lower cost compared with ERT, but the size of any additional benefits was highly uncertain.
SMC [Migalastat], 2016[96]	• Cost minimisation model comparing migalastat with ERTs • Drug acquisition and administration costs included	N/A – cost minimisation approach	Incremental cost of migalastat (without PAS): £1,157,518	With the PAS, migalastat became a cost-effective treatment option, providing health benefits at a lower overall cost than ERT.

Study	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
AWMSG [Agalsidase alfa], 2007[94]	Connock model and the agalsidase alfa model	• Agalsidase alfa: 3.51 (Agalsidase alfa model) • Agalsidase beta: 10.07 (Connock model)	• Agalsidase alfa: £887,858 • Agalsidase beta: £2,537,792	• Agalsidase alfa vs. usual care: £252,951 • Agalsidase beta vs. usual care: £252,112
Connock, 2006[32]	• Decision model • Lifetime horizon	• Untreated cohort: 14.6 • Agalsidase beta: 24.76 • Incremental: 10.07	• Untreated: £34,329.88 • Agalsidase beta: £2,572,122 • Incremental: £2,537,792	• ERT (agalsidase beta) vs. Untreated: • Cost/QALY: £252,112
Key: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CDR, Common Drug Review; ERT, Enzyme Replacement Therapy; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life-year gained; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; NR, not reported; PAS, patient access scheme; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium.				

B.3.2. Economic analysis

No relevant studies comparing PRX-102 with relevant comparators were identified in the economic SLR. However, a number of references for health technology assessments (HTAs) of ERTs and/or migalastat across multiple countries were identified, including:

- NICE HST4, which assessed the cost-effectiveness of migalastat in the UK
- Scottish Medicines Consortium (SMC) ID1196/16, which assessed the cost-effectiveness of migalastat in Scotland
- A Canadian Agency for Drugs and Technologies in Health (CADTH) appraisal, which assessed the cost-effectiveness of migalastat in Canada
- All Wales Medicines Strategy Group (AWMSG) Advice Number 1107, which assessed the cost-effectiveness of agalsidase alfa in Wales

The submissions to NICE, the AWMSG and the CADTH adopted a Markov approach with 10 mutually exclusive health states that covered key clinical manifestations in FD. All of these models developed for HTA submissions compared migalastat with ERT. For the SMC and NICE submissions, a cost-minimisation analysis was submitted as the base case, with a cost–utility model included as a secondary analysis.

In the NICE and CADTH submissions, migalastat and ERTs were assumed to have equal efficacy. Agalsidase alfa and agalsidase beta were considered as a blended comparator, as there was no head-to-head evidence to support independent modelling of efficacy for these 2 treatments. The equal efficacy assumption for migalastat was justified given results from the ATTRACT trial, which was powered to demonstrate non-inferiority of migalastat.[36]

The Markov approach used in NICE HST4 was based on a cost-effectiveness study by Rombach et al.[28] This study used data from a registry of Dutch patients with FD to inform transition probabilities and other key assumptions. The assumptions of equal efficacy allowed the Rombach transition probabilities that were calculated for ERT to be applied to all treatments. Patients who discontinued treatment were assumed to follow the state transition probabilities estimated from untreated patients. This

approach to modelling FD was considered to be reasonable by the Evidence Review Group (ERG) in HST4.

The analysis presented in this submission is therefore adapted from the HST4 model, accounting for feedback from the ERG and NICE at the time. The ERG had several concerns about certain assumptions made in the model. A description of this feedback, and its consideration in the PRX-102 analysis, is presented in Table 34.

Given that BALANCE demonstrated the non-inferiority of PRX-102 E2W compared to agalsidase beta (Section B.2.6.1), equal efficacy is assumed between the PRX-102 E2W and ERT arms in the model. The same set of transition probabilities that were estimated from patients receiving ERT in Rombach is applied to both treatment arms. This is consistent with the approach adopted in HST4. This approach was supported by clinical experts consulted in the advisory board, who stated that there is no reason to suggest a difference in efficacy between each treatment, and that demonstrating non-inferiority vs. agalsidase beta was sufficient to also assume equal efficacy with agalsidase alfa. Consistent with HST4, it is assumed that patients can discontinue treatment with PRX-102 and ERT, with those patients assumed to experience the same efficacy outcomes as patients receiving best supportive care in Rombach.[28]

As a result, the base case analysis adopts a cost-comparison approach for the PRX-102 E2W regimen only, with only differences in costs between the treatment arms are considered. Additional analyses are presented that investigating an alternative cost–utility approach to capture the potential health benefits that PRX-102 offers over comparator ERTs. Scenarios are included for both approaches to understand the additional benefits associated with the PRX-102 E4W regimen.

Table 34: Feedback from HST4 and updates made for PRX-102 analysis

Issue	Critique	How this is addressed in the PRX-102 analysis
Baseline health state distribution	The medical history data from the ATTRACT trial used to allocate patients to starting health states showed that the patients had lower rates of events than would be expected according to data on patients registered in the global Fabry registry, and therefore, the ERG preferred use of the data from the registry study to inform the baseline health state distribution	Baseline health state distributions were taken from the Fabry registry study which was validated by UK clinical experts.
Modelled life expectancy	Mortality estimates used in the HST4 submission were taken from UK life tables and Fabry specific mortality rates from the Dutch Fabry cohort, with the highest value applied. However, the ERG noted that background mortality rates did not match data reported by the ONS. For disease specific mortality rates, mortality did not differ with age. Both these issues lead to an underestimation of mortality in the model and unrealistic life expectancy.	Transition probabilities into the death health state have been adjusted so that average life expectancy equals 58.2 for males and 74.7 for females. These clinically validated values were sourced from the literature[21] and were consistent with the preferred analysis by the ERG in HST4.
Patient characteristics	Patient characteristics were taken from the ATTRACT trial however the ERG did not consider patient characteristics from this trial to be reflective of the UK population. The ERG instead preferred the use of patient characteristic data from the Fabry registry.	Patient characteristics used in this model follow the ERGs preferred approach of using real-world evidence, utilising data from the Fabry registry and a UK cohort study newly published since HST4.[8]
Health state utilities	Health state utility values for ESRD, cardiac complications and stroke were all considered equal. The ERG considered this to be unrealistic given large differences between quality of life in these health states.	The economic model used health state utility values from Arends[24], which provided more granularity in health state utility values between health states.
Key: CEFD; clinically evident Fabry disease, ERG, evidence review group; ESRD, end-stage renal disease; HST; highly specialised technology; ONS, Office for National Statistics.		

B.3.2.1. Patient population

As noted in Section B.1.1, PRX-102 is positioned as an additional treatment option for adults with FD who would be treated with an ERT. This would include treatment-naïve patients who would usually be treated with agalsidase alfa or agalsidase beta, and those previously treated with currently available therapies, such as agalsidase alfa, agalsidase beta or migalastat. The eligible patient population would also include patients with an amenable mutation, but only those who are unsuitable for treatment with migalastat, as these patients would usually be treated with migalastat in UK clinical practice.

This patient population is broadly aligned with BALANCE, which is the pivotal RCT for PRX-102. It has been used to inform the economic modelling and is the largest study that has been conducted in FD, providing robust head-to-head comparison data against an active treatment. BALANCE includes adult patients with FD with deteriorating renal function who have been treated with agalsidase beta for at least 1 year. Although the population in BALANCE only included patients with renal impairment, the subgroup analysis presented in BALANCE demonstrates that no statistically significant differences were identified for the primary outcome measure across all pre-specified subgroups (Section B.2.7). UK clinicians consulted at an advisory board believed the BALANCE trial population to be broadly generalisable to the wider FD population, including those with stable renal function. In addition, as shown in Section B.2.7, results from BRIDGE and BRIGHT demonstrated that PRX-102 is efficacious when assessed in a broader group of patients who were pre-treated but did not necessarily have declining renal function. Clinicians consulted at an advisory board also confirmed that, based on all of the trial evidence, they considered PRX-102 to be at least as efficacious as existing ERTs in the relevant population of interest for this appraisal.

B.3.2.2. Model structure

As discussed in Section B.3.1, previous modelling of FD in HST4 adopted a state-transition model based on the study by Rombach[28], with health states based around key clinical manifestations in FD. This model was designed to capture long-term outcomes in patients with FD over a lifetime horizon while receiving migalastat or

ERTs. Key differences between the model structure used in HST4 compared with the Rombach[97] model are described in Table 35.

Table 35: Differences between Rombach[28] and HST4[43]

Issue	Difference between HST4 and Rombach	Rationale
Re-labelling of health states	HST4 renamed the acroparaesthesia health state to pain and the symptoms state to CEFD	These states were renamed for simplicity and but do not change the model structure
No asymptomatic health state	In Rombach, patients could enter the model in an asymptomatic health state and therefore experience diagnostic and treatment initiation costs	The evidence base used to support the submission contained data on patients who already displayed clinical manifestations of FD, therefore it was not appropriate to model patients starting in an asymptomatic health state using key migalastat trials.
No disease regression	Rombach allowed patients to have disease regression from ESRD if they were to have a renal transplant, whilst the HST4 submission model did not allow any health state improvement.	This was a simplification of the disease pathway which is not expected to have a meaningful impact on the results
Transition probabilities calculated from birth	Rombach publication has patients starting from birth and in the HST4 model patients start at age 48	This was to align with the population who were expected to receive migalastat in the UK clinical practice
Key: CEFD; clinically evident Fabry disease; ESRD, end-stage renal disease; FD, Fabry disease; HST; highly specialised technology.		

NICE considered the Markov model used in HST4 to be appropriate for decision-making. After discussion with the clinical and patient experts, the Committee considered that the company's approach and the structure of the model were generally reasonable. Expert feedback from an advisory board (see Appendix P) confirmed that the proposed model structure for this submission (based on HST4) was an appropriate representation of FD, and that the health states were appropriate to model progression of the disease to capture differences in QoL, mortality and costs. The Markov modelling approach is therefore considered to be appropriate to capture patient costs and outcomes for PRX-102 compared with ERTs.

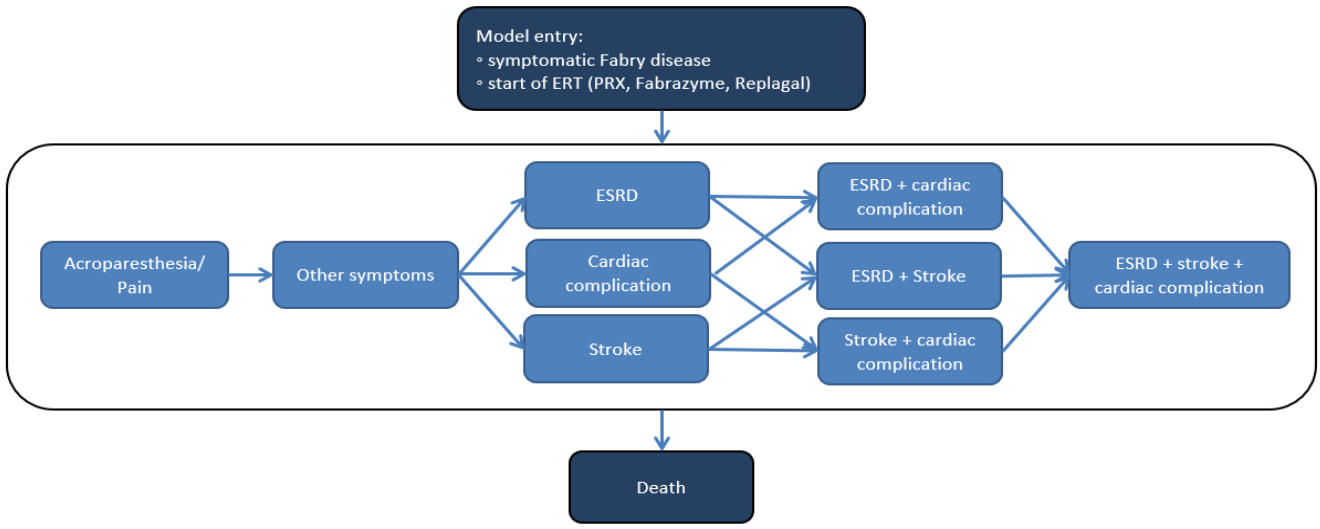
The health states applied in the model are considered to reflect the natural course of FD. As highlighted in Section B.1.3.3.2, a UK cohort study from 2000-2019 conducted by Malottki et al. that assessed the clinical characteristics of patients with FD in England showed that 9.2% of patients experience renal symptoms, 16.3%

experience CV symptoms and 14.6% experience neurological symptoms. A multinational retrospective cohort study conducted by Arends et al. in 293 patients treated with ERT in the UK, the Netherland and Germany highlighted the significant prevalence of cardiac, renal and cerebral events.[73] Findings from the Fabry Outcome Survey further support the multisystemic and progressive nature of the disease and the significant risk of organ involvement.[26, 92]

However, as the ERG and the NICE committee challenged some of the assumptions adopted by the company in HST4, we have attempted to address these where possible. Further detail is outlined in the subsequent relevant sections.

The model contains 10 health states rather than the 11 included in the Rombach model. This because the 'no symptoms' health state has been excluded from the model, as data informing the model is taken from trials with symptomatic patients with FD and is not aligned to the patient population for PRX-102, who would be patients who were eligible for an ERT in line with clinical guidelines. The model structure is presented in Figure 27.

Figure 27: Model schematic



Key: ERT, enzyme replacement therapy; ESRD, end-stage renal disease.

The 10 included health states are as follows:

- Pain: neuropathic pain in the extremities
- Other symptoms: clinical signs and/or symptoms of left ventricular hypertrophy, CKD Stages 1–4 or white matter lesions
- End-stage renal disease (ESRD): chronic kidney disease (CKD) Stage 5 or kidney transplant
- Cardiac complications: atrial fibrillation, any other rhythm disturbance needing hospitalisation, a pacemaker or an implantable cardiac defibrillator (ICD) implantation, cardiac congestion for which hospital admittance was needed, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft
- Stroke: as diagnosed by a neurologist
- ESRD and cardiac complications
- Cardiac complications and stroke
- ESRD and stroke
- ESRD, cardiac complications and stroke
- Death

As patients can initiate treatment at any point in the disease pathway, they can enter the model in any of these health states, with an assumed initial health state distribution applied in the model (further details outlined in Section B.3.3.1). Given the progressive nature of FD, patients can only remain in their current state or progress to more severe health states with no backwards transition. Most patients enter the model either in the ‘pain’ or ‘other symptoms’ health states, and as they progress through the model, they develop a more severe form of disease, experiencing a range of comorbid conditions. The model also accounts for the fact that patients can develop multiple complications and reflects the resulting decline in health-related quality of life (HRQL) and increase in required healthcare resource use. Patients can transition to death from any health state, but the mortality risk varies by health state, increasing as patients enter more progressive disease states.

Consistent with HST4, transition probabilities used in the model are taken from Rombach.[28] This study used Dutch Fabry cohort data to undertake a Kaplan–Meier

analysis, which was then used to estimate transition probabilities. Further details on the calculation of the transition probabilities are provided in Section B.3.3.2.

As noted in Section B.3.2, given that BALANCE demonstrated the non-inferiority of PRX-102 compared with agalsidase beta, equal efficacy is assumed between PRX-102 and both ERT treatments in the model, with the same set of transition probabilities estimated from patients receiving ERT in Rombach applied on both treatment arms.

B.3.2.2.1. Features of the de novo analysis

The model time horizon is set to 60 years based on a mean age of 40, consistent with the age applied by the ERG in HST4. This is also consistent with the PRX-102 trials, with average ages ranging from 40.5–44.3 years across BALANCE, BRIDGE and BRIGHT. This is further supported by a recent UK cohort study by Malottki et al., a cohort study that linked patient characteristics to hospital episode statistics and found that the mean age of diagnosis was 37 years.[8] This allows the model to capture all relevant costs and benefits given the chronic nature of the disease and the prophylactic nature of the treatment.

As per the NICE reference case, both costs and effects were discounted at a rate of 3.5% per year. A cycle length of 1 year is used in the model to remain consistent with Rombach[28], with a half-cycle correction applied to adjust for events happening at any point within a cycle. The economic analysis is summarised in Table 36 below.

Table 36: Features of the economic analysis

Factor	Previous evaluations	Current evaluation	
	HST4[98]	Chosen values	Justification
Baseline health state distribution source	ATTRACT[36]	Fabry Registry data	ERG preference based on HST4 submission and validated by UK clinical experts
Health states	• Pain • CEFD • Cardiac complications • Stroke • ESRD • ESRD and cardiac complications • ESRD and stroke • Cardiac complications and stroke • ESRD, cardiac complications and stroke • Death	As HST4	Based on the structure of a cost-effectiveness model for ERT by Rombach et al. (2013) that allows differentiation of the consecutive phases of FD with some re-labelling of states to better reflect the stages of the disease
Source of efficacy data	Transition probabilities taken from Rombach et al (2013), based on Dutch Fabry cohort[28]	As HST4	Key trials for PRX-102 were not sufficiently powered to demonstrate clinical outcomes of relevance, and the follow-up of the trials did not allow for a robust set of probabilities between all health states to be calculated
Time horizon	Lifetime	Lifetime (60 years)	To capture all relevant costs and benefits given the chronic nature of the disease and the prophylactic nature of the treatment.
Cycle length	1 year	As HST4	Consistent with Rombach et al (2013)
Source of utilities	Values reported in Rombach et al (2013)[28]	BALANCE & Arends et al. [5,24]	Trial data alone did not have enough events to calculate robust estimates of health state utilities. Baseline HRQL is therefore calculated from BALANCE and certain health states are supplemented from the literature
Source of costs	NHS reference costs and PSSRU	NHS reference costs and PSSRU updated to 2022	To reflect a UK payer perspective

Key: CEFD, clinically evident Fabry disease; FD, Fabry disease; HST, highly specialised technology; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.2.3. Intervention technology and comparators

The recommended dose of PRX-102 is 1 mg/kg of body weight administered once E2W, or 2 mg/kg of body weight administered once E4W by IV infusion. The choice between the 2 posology options is based on the clinician's judgement, patients' compliance and response to treatment.[1, 7]

Clinical experts consulted at an advisory board noted that the E4W regimen could potentially result in significant improvements in patients' QoL and well as productivity benefits, as it could allow up to 13 additional days per year where a patient did not have to receive an IV infusion. However, the clinicians noted that there was uncertainty regarding the proportion of patients who would receive this regimen in UK clinical practice. The base case analysis therefore conservatively assumes that all patients will receive the E2W regimen, and scenario analysis are presented to demonstrate the benefits of a greater proportion of patients transitioning to the E4W regimen, including productivity gains.

The PRX-102 and comparator dosing schedules in the model are based on their licensed regimens and are summarised in Table 37. For PRX-102, depending on the regimen (E4W or E2W) and a patient's body weight, patients are given a longer initial infusion of not less than 3 hours (E2W) or 4.5 hours (E4W) to minimise the occurrence of IRRs, which is reduced to not less than 1.5 hours (E2W) or 2–3 hours depending on body weight (E4W) and tolerability.[7, 69] This is consistent with the BRIDGE and BRIGHT trials, which investigated the E4W and E2W dosing regimens, respectively. They found that 100% and 97% of patients who completed each study, respectively, achieved the target maintenance infusion duration.[4,51,52.]

This is similar for agalsidase beta, which is dosed at 1 mg/kg over 3 hours for the first infusion and 2 hours subsequently. The slightly longer relative infusion duration for those receiving agalsidase beta was confirmed in BALANCE, with a mean infusion duration at Week 104 of 1.56 hours on the PRX-102 arm and 1.71 hours on the agalsidase beta arm.[4] For agalsidase alfa, a dose of 0.2 mg/kg is given over 0.7 hours for the entire time on treatment. The infusion durations for agalsidase alfa and beta are consistent with those assumed in NICE HST4.[43]

All ERTs in the model are given via IV infusion. When a patient is starting a new ERT regimen it is common practice for the first few infusions to be administered in hospital as a precautionary measure. After this any of the treatments can be administered in the homecare setting. Patients will require a homecare nurse visit for the first 4 homecare infusions after which, 50% of patients will continue to have a nurse visit for each infusion and 50% will self-administer. Self-administering patients will have 1 nurse homecare visit per year.

Table 37: Treatment dosing schedules

Treatment	Dose per administration	Dosing schedule	Source
PRX-102	1 mg/kg	E2W	PRX-102 draft SmPC[7]
	2 mg/kg	E4W	PRX-102 draft SmPC[7]
Agalsidase alfa (Replagal)	0.2 mg/kg	E2W	Replagal SmPC[99]
Agalsidase beta (Fabrazyme)	1 mg/kg	E2W	Fabrazyme SmPC[100]
Key: E2W, every 2 weeks; E4W, every 4 weeks.			

B.3.2.4. Comparator

The comparators considered in the model are the ERTs agalsidase alfa and agalsidase beta. Although no head-to-head trial has been conducted comparing agalsidase alfa and agalsidase beta, the available clinical trial evidence that assesses the efficacy of both treatments separately, real-world data comparing ERTs,[73] and clinical feedback elicited for both HST4[98] and this appraisal,[49] demonstrate that it is reasonable to assume that both treatments are equally efficacious. The model therefore considers agalsidase alfa and agalsidase beta as separate treatment regimens and also as a blended comparator, consistent with the approach that was adopted and accepted by the Committee in HST4. In HST4, the ERG noted some concerns in deviating from the NICE reference case, but did state that the differences between the costs of individual ERTs using a blended analysis are unlikely to be significant, and therefore accepted the approach.

For the blended ERT comparator, costs for treatment and administration are based on the estimated market share of the 2 therapies (70% and 30% for agalsidase alfa and agalsidase beta, respectively). These estimates are taken from HST4, and

although the clinicians who were consulted as part of a healthcare resource use survey noted that there is variation across centres, most clinicians cited estimates that were close to these values.[101]

Although migalastat is listed in the final scope, as highlighted in Section B.1.1, it is not considered a relevant comparator for this appraisal. Migalastat is indicated for patients ≥12 years with a confirmed diagnosis of FD and who have an amenable mutation, a subset of the PRX-102-eligible population. Treatment choice in FD is individualised, but it is anticipated that migalastat would continue to be used in patients with an amenable mutation because of its targeted nature and established use in UK clinical practice. PRX-102 would only be considered in patients with an amenable mutation if they were unsuitable for treatment with migalastat for any reason, which would mean that ERT was being considered as a treatment option. This positioning means that migalastat is not considered a relevant comparator for PRX-102 and results including migalastat are not presented in this submission.

B.3.3. Clinical parameters and variables

Table 38 contains a summary of the key clinical parameters used in the base case analysis. Transition probabilities used in each health state (on and off treatment) for males and females are presented in Table 40–Table 43.

Table 38: Summary of key clinical parameters used in the base case analysis

Parameter		Value	Source
Baseline characteristics	Weight	72.2kg	Malottki et al 2022[8]
	Age	40 years	NICE HST4 (ERG preferred assumption)[43]
	Proportion male	50%	Fabry registry[102]
Baseline health state distribution	Pain	15.3%	Fabry registry[102]
	CEFD	60.0%	
	Cardiac complications	18.1%	
	ESRD	0.0%	
	Stroke	6.7%	

Parameter		Value	Source
Efficacy	PRX-102 Q2W dosing distribution	100%	Clinical opinion[49]
	PRX-102 Q4W dosing distribution	0%	Clinical opinion[49]
	Life expectancy (males)	58.2	Waldek et al 2009[102]
	Life expectancy (females)	74.7	
	Treatment discontinuation	0.05% (per year)	HST4[98], clinical opinion[49]
Administration	% of patients assumed to self-administer ERTs	50%	Clinical opinion[49]
	Number of initial infusions given in hospital	2	Clinical opinion[49]
Key: CEFD, clinically evident Fabry disease; ERG, evidence review group; ESRD, end stage renal disease; HST, highly specialised technology; Q2W, every 2 weeks; Q4W, every 4 weeks.			

FD is characterised by a lifetime of progression into different symptomatic health states and clinical complications. Given the rarity of FD, clinical studies in FD often have low patient numbers and limited length of follow-up, and trials considering treatments for FD are often not powered to capture the long-term patient outcomes of interest. These challenges make it difficult to estimate long-term treatment efficacy directly from the PRX-102 clinical trials and to use the data robustly in the cost-effectiveness model, which aims to capture lifetime outcomes and costs.

A targeted literature review was conducted to establish the relationship between PRX-102 trial endpoints and long-term clinical events in FD.[83] Multiple studies were identified that suggested that the trial endpoints collected in key PRX-102 trials are relevant surrogate outcomes in FD for predicting long-term events.[84-91] The study reported by Arends et al. was considered to be the best source of evidence for a surrogacy relationship as eGFR was found to be a significant predictor of outcomes (renal, cardiac and cerebral events) in both mixed-effects and multivariate analyses. LVMI was also found to be a significant predictor of Fabry clinical events in most scenarios.[92]

Taken together, the evidence base supports that the improvements in eGFR and LVMI observed in the PRX-102 clinical trials will translate to significant reductions in the rate at which patients experience long-term clinical events. The evidence also indicates that equivalence between PRX-102 and ERTs in eGFR and LVMI outcomes is also likely to translate to equivalence in the rate of experiencing clinical

events. It was therefore considered appropriate to apply the same set of transition probabilities employed in Rombach[28] to both treatment arms in the model. This is because:

- There are limited long-term data from trials investigating PRX-102
- Evidence from BALANCE highlighting that there are no meaningful differences in efficacy between PRX-102 and agalsidase beta
- Evidence suggests that a surrogacy relationship exists between PRX-102 trial outcomes and key Fabry clinical events
- This approach is consistent with the modelling methods adopted in HST4 and was deemed appropriate by UK clinical experts.[43, 49]

B.3.3.1. Baseline patient characteristics

In HST4, patient characteristics, including mean starting age, the distribution of male and female patients and the baseline distribution between health states were initially taken from the pivotal migalastat trial ATTRACT.[36] However, the ERG preferred the use of data from the Fabry Registry as it was deemed more reflective of patients in a UK setting. The Fabry Registry is an international and ongoing observational programme that tracks clinical outcomes of people with FD annually, regardless of treatment status. UK clinicians consulted at an advisory board also confirmed that, although the baseline characteristics from the Fabry Registry may not necessarily precisely reflect those observed in the UK, they are a reasonable reflection of the population of interest. Additionally, after the HST4 appraisal was completed, Malottki et al. conducted a study in 2022 that used data from the CPRD between January 2000 and December 2019 (n = 535) and reported key characteristics of patients with FD in England.[8] The model for this appraisal therefore adopts the ERG's preferred approach of using real-world evidence to inform baseline characteristics, using both the Fabry registry data and the results reported in Malottki et al. 2022.[8]

Consistent with HST4, the starting distributions from the ERG's preferred analysis were taken from the Fabry Registry, but were reweighted in order to exclude patients with ESRD as these patients were not considered appropriate to start a new therapy. Although Malottki et al. 2022[8] reported the proportion of patients experiencing each clinical event in England, the study does not distinguish between patients who

experience a single event and patients who experience multiple events. It also does not allow patients to be allocated between mutually exclusive health states in the model, so the Fabry registry data was preferred.

Fabry Registry data suggested that CV events are experienced at a mean age of 39 years for males and 47.6 years for females, while stroke events occur at a median age of 38.6 years and 43.2 years for males and females, respectively. To capture these events in the model cycles, a model starting age of 40 years was therefore deemed appropriate by the ERG, compared with 48 years used in the HST4 company submission. As patients are diagnosed between a median age of 23 years in males and a median age of 32 years in females, according to the Fabry Registry, an additional 8 years added to the model time horizon more accurately reflects Fabry patient outcomes.[102] This is further supported by a Malottki et al. 2022[8] UK cohort study, which estimated a mean diagnosis age of 37 years.

Patient weight data was taken from Malottki et al. 2022[8]. This approach is broadly consistent with the ERG's preferred approach in HST4, where it was noted that the weight of patients with FD appeared to be lower than the general population. Owing to this, the ERG preferred to use data from Fabry patients exclusively. As the Malottki et al. 2022 study reports data on all patients with FD diagnosed in England over the last 20 years, this was considered the most appropriate source of weight data for patients in UK clinical practice. The baseline characteristics are summarised in Table 38.

B.3.3.2. Treatment efficacy

As mentioned in Section B.3.2.2, transition probabilities are taken from Rombach[28]. The same set of probabilities are applied across both treatment arms because of the assumption of equal efficacy between PRX-102, agalsidase alfa and agalsidase beta.

In the cost-effectiveness study by Rombach[28], data were gathered retrospectively and prospectively from the Dutch Fabry cohort to calculate transition probabilities. Details of patient characteristics and patient numbers from the Dutch cohort can be found in Table 39 and Figure 28. In an advisory board, clinicians noted that, as this

study is focused on a single centre and included all patients (i.e. it is a 100% case series that incorporated all data), it is the most robust data available to inform the transition probabilities between health states. Although newer registry studies are available, these can be prone to selection bias in terms of patient inclusion in the registry. This is not seen with Rombach because of the study design.[49]

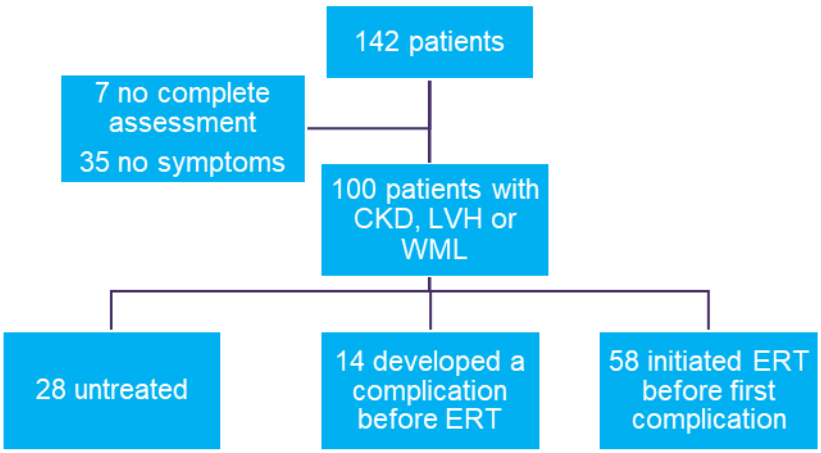
In Rombach, Kaplan–Meier survival analysis was used to calculate the yearly transition probabilities for untreated patients in the cohort.[28] Median Kaplan–Meier values for untreated patients were used to calculate constant transition probabilities. For the ERT cohort, odds ratios (ORs) for treatment durations were applied to calculate the relative risk reduction during that median period (compared with untreated patients). This is because ERT duration in years was found to have a greater effect on the odds of developing a major complication compared to just being on treatment with ERT (from symptoms to a first complication: OR 0.82 [95% CI: 0.68, 0.96; p = 0.015]; from one complication to the second complication: OR 0.52 [95% CI: 0.31, 0.88; p = 0.014]).

The relative risk of reduction for disease states in a single model cycle was calculated next. Transition probabilities for those receiving ERTs in each state could then be calculated as the yearly transitions for untreated patients multiplied by 1 minus the relative risk reduction of being on ERT. These calculated transition probabilities were validated against literature sources by clinical experts. If patients discontinue treatment, they then experience the untreated transition probabilities per cycle until death. Table 40–Table 43 show the transition probabilities for males and females who are untreated or treated with ERTs used in the model.

Table 39: Baseline characteristics of the Dutch cohort (1999–2010): Rombach[28]

	Untreated cohort	ERT cohort	P value
N	42	58	
Male (%)	21 (50)	27 (46.6)	0.74
Atypical (%)	13 (30.9)	3 (5.2)	0.001
Mean (± SD) and median (range) age at first presentation	45.0 ± 14.7	36.8 ± 14.1	0.009*
Plasma Lyso-Gb3 (nM)	44.5 (10.8–72.2)	40.3 (13.6–71.2)	< 0.001
Proteinuria (%)	5 (0–137)	11 (4–124)	0.03
Other comorbidity	8/36 (22.2)	25/57 (43.9)	0.2
1 symptom only at presentation (%)	5	3 (5.2)	0.58
≥ 1 symptom or presenting with a first complication (%)	16 (38.1)	30 (51.7)	0.58
Key: ERT, enzyme replacement therapy; SD; standard deviation			

Figure 28: Patient numbers from the Dutch cohort (1999–2010): Rombach



Key: CKD, chronic kidney disease; ERT, enzyme replacement therapy; LVMI, left ventricular mass index; WML, white matter lesions.

Table 40: Transition probabilities for PRX-102 and ERTs (male patients)[28]

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.9289	0.0711	0	0	0	0	0	0	0	0
Other symptoms		0.9869	0.0017	0.0085	0.0029	0	0	0	0	0.0006
ESRD			0.9851	0	0	0.0086	0	0.0063	0	0.0109
Cardiac complications				0.9873	0	0.005	0.0077	0	0	0.0134
Stroke					0.9861	0	0.0094	0.0045	0	0.012
ESRD and cardiac						0.8621	0	0	0.1379	0.4068
Cardiac and stroke							0.8621	0	0.1379	0.4068
ESRD and stroke								0.8621	0.1379	0.4068
ESRD, cardiac and stroke									1	0.4068

Table 41: Transition probabilities for patients who discontinue treatment (male patients)[28]

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.9289	0.0711	0	0	0	0	0	0	0	0
Other symptoms		0.9849	0.002	0.0097	0.0034	0	0	0	0	0.006
ESRD			0.9769	0	0	0.0133	0	0.0098	0	0.0169
Cardiac complications				0.9805	0	0.0077	0.0118	0	0	0.0206
Stroke					0.9784	0	0.0146	0.007	0	0.0186
ESRD and cardiac						0.8621	0	0	0.1379	0.4068
Cardiac and stroke							0.8621	0	0.1379	0.4068
ESRD and stroke								0.8621	0.1379	0.4068
ESRD, cardiac and stroke									1	0.4068

Table 42: Transition probabilities for PRX-102 and ERTs (female patients)[28]

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.898	0.102	0	0	0	0	0	0	0	0
Other symptoms		0.9898	0.0016	0.0062	0.0024	0	0	0	0	0
ESRD			0.9851	0	0	0.0086	0	0.0063	0	0.011
Cardiac complications				0.9873	0	0.005	0.0077	0	0	0.0134
Stroke					0.9861	0	0.0094	0.0045	0	0.012
ESRD and cardiac						0.8621	0	0	0.1379	0.4068
Cardiac and stroke							0.8621	0	0.1379	0.4068
ESRD and stroke								0.8621	0.1379	0.4068
ESRD, cardiac and stroke									1	0.4068

Table 43: Transition probabilities for patients who discontinue treatment (female patients)[28]

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.898	0.102	0	0	0	0	0	0	0	0
Other symptoms		0.988	0.0018	0.0071	0.0027	0	0	0	0	0
ESRD			0.977	0	0	0.0133	0	0.0098	0	0.0169
Cardiac complications				0.981	0	0.0077	0.0118	0	0	0.0206
Stroke					0.978	0	0.0146	0.007	0	0.0186
ESRD and cardiac						0.862	0	0	0.1379	0.4068
Cardiac and stroke							0.862	0	0.1379	0.4068
ESRD and stroke								0.862	0.1379	0.4068
ESRD, cardiac and stroke									1	0.4068

Key: ERT, enzyme replacement therapy; ESRD, end-stage renal disease.

B.3.3.3. Mortality risk

Transition probabilities for death are estimated from Rombach for each health state.[28] In HST4, background mortality was age- and sex-dependent based on UK life tables. In states where patients can die from Fabry-specific complications or background mortality, the maximum of the 2 mortality rates is applied. However, the ERG noted that in HST4, background mortality applied in the model was too low and did not match values reported by ONS life tables. This resulted in patients having an unrealistically high life expectancy of 83.4 years, which is not reflective of the UK population. To address this concern in this submission, transition probabilities to death have been adjusted so that the average life expectancy in the model matches that expected in the Fabry population (58.2 years for males and 74.7 years for females). These ages are taken from Waldek 2009[21] and are consistent with the preferred analysis conducted by the ERG in HST4. The values reported in Waldek 2009 were validated by UK clinical experts in an advisory board. These values are also consistent with survival data from Malottki[8], published after HST4. One clinician noted that these values aligned closely with their recent review of patient records that showed median survival estimates of 61.5 and 72 years for males and females, respectively.

B.3.3.4. Treatment discontinuation

Current ERTs are considered long-term treatment options because of the chronic nature of FD, so most patients will not discontinue treatment. However, some patients may discontinue due to infusion reactions, lack of efficacy or a deterioration in health.

In the ATTRACT trial, around 1% of patients discontinued from ERTs.[36] However, the clinicians consulted in HST4 stated that most discontinuations came from IRRs and that, in clinical practice, these could be managed with additional medication. The model submitted in HST4 therefore assumed a lower annual probability of discontinuation of 0.05% per annum on ERT.

In the PRX-102 trials, BRIDGE, BRIGHT and BALANCE, a small number of patients discontinued treatment on both PRX-102 and ERTs, as summarised in Table 44. During the advisory board, clinicians indicated that IRRs would be manageable in

clinical practice, and that the data did not highlight any reason to suggest differences between treatments. A discontinuation rate of 0.05% per annum was therefore applied to both the PRX-102 and ERT arms in the model. In the long-term extension of the Phase I/II trials, 10 patients were treated with PRX-102 E2W for 6 years. In this overall treatment period, no IRRs were serious, severe or led to withdrawal or death.[68]

Table 44: Discontinuation rates from PRX-102 trials

Trial	Discontinuation rate			Reason
	PRX-102	Agalsidase alfa	Agalsidase beta	
BALANCE[4]	[redacted]	N/A	[redacted]	[redacted]
BRIGHT[51]	[redacted]	N/A	N/A	[redacted]
BRIDGE[52]	[redacted]	N/A	N/A	[redacted]

B.3.3.5. Adverse events

Table 26 in Section B.2.9 shows the rate of reported AEs for treatments included in BALANCE. The results suggest that PRX-102 has a favourable tolerability and immunogenicity profile compared to agalsidase beta. Clinicians noted in an advisory board that they would expect the safety profiles of the 2 treatments, and by extension agalsidase alfa, to be similar in clinical practice.[49]

As a simplifying assumption, the base case does not formally consider the impact of treatment-related AEs given the expected similarities in toxicity profiles. A scenario considering the costs associated with managing AEs is included in the analyses.

B.3.4. Measurement and valuation of health effects

As discussed in Section B.1.3.3.2, patients with FD experience a broad range of symptoms because glycolipids accumulate in a variety of cells throughout the body. The most common symptoms experienced by patients are neuropathic pain, GI symptoms, fatigue, chest pains and angiokeratoma[15, 24], which lead to more severe CV, renal and cerebrovascular complications. As a result of the symptomatic burden,

patients with FD experience a poorer QoL compared with the general population, particularly in terms of physical functioning.[24]

As discussed in Section B.3.2, the primary analysis assumes equivalent efficacy between PRX-102 and both ERTs, so it does not consider quality-adjusted life year (QALY) differences between treatment arms. In the scenario analysis that considers differential outcomes, health states are measured in QALYs. Further details of the utilities used to measure the health states are described in Appendix H. The sections below present the HRQL data considered and used in the economic model.

B.3.4.1. Health-related quality-of-life data from clinical trials

EQ-5D-5L data were collected in the key PRX-102 trials: BRIDGE, BRIGHT and BALANCE. EQ-5D-5L data was collected every 6 months across all trials. Responses to the EQ-5D-5L collected in clinical studies were scored using a visual analogue scale (EQ-VAS).

Table 45 shows that the mean EQ-5D utility values were broadly similar across each of the 3 key PRX-102 trials for the timepoints at which comparable data are available. However, most of the Fabry clinical events (FCE) that occurred over the follow-up period were attributed to BALANCE due to its length of follow-up and larger sample size (Table 46). Only 1 FCE occurred in BRIDGE, and no FCEs occurred in BRIGHT.

Table 45: Mean EQ-5D-5L values over 2 years for PRX-102 trials for all patients

	BALANCE[4]		BRIDGE[52]		BRIGHT[51]	
	Utility	**n**	**Utility**	**n**	**Utility**	**n**
Mean EQ-5D at baseline (SD)	0.762 (0.236)	75	0.826 (0.185)	20	0.786 (0.243)	29
Mean EQ-5D at Week 26 (SD)	0.799 (0.205)	71	0.823 (0.189)	20	0.821 (0.202)	29
Mean EQ-5D at Week 52 (SD)	0.781 (0.221)	68	0.805 (0.225)	20	0.809 (0.208)	28
Mean EQ-5D at Week 78 (SD)	0.780 (0.232)	65	-	-	-	-
Mean EQ-5D at Week 104 (SD)	0.742 (0.261)	68	-	-	-	-
Key: SD, standard deviation.						

Table 46: Comparison of Fabry events for PRX-102 trials

		BALANCE[4] n(%)	BRIDGE[52] n(%)	BRIGHT[51] n(%)
Had ≥1 FCE	No	64 (85.3%)	19 (95.0%)	29 (100.0%)
	Yes	11 (14.7%)	1 (5.0%)	-
Had ≥1 FCE, by type	No	64 (85.3%)	19 (95.0%)	29 (100.0%)
	Cardiac	7 (9.3%)	-	-
	Cerebrovascular	2 (2.7%)	-	-
	Cardiac + cerebrovascular	1 (1.3%)	1 (5.0%)	-
	Renal	1 (1.3%)	-	-
Key: FCE; Fabry clinical event.				

Given the similarity in observed EQ-5D-5L values between the trials, and comparably low numbers of events in BRIDGE and BRIGHT (as shown in Table 46), a regression analysis using only BALANCE data was undertaken to establish health state utility values. BALANCE is the pivotal Phase III trial for PRX-102 and collected the most EQ-5D-5L data for use in statistical analyses. The majority of the FCEs also occurred in this trial. BALANCE is the only head-to-head trial for PRX-102, so a utility analysis from this trial enables treatment-related drivers of HRQL to be explored.

For the BALANCE regression analysis, stepwise variable selection was used to determine which patient demographic, disease characteristics and AEs should be included in a final regression model. Stepwise variable selection was chosen to

avoid unnecessary complexity in the models. The stepwise variable selection process tests the statistical fit of the model after adding/removing each potential variable considered for analysis in turn, and the variable that least improves the statistical fit of the regression model is removed. Statistical fit is based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). This process continues until the addition/removal of further variables no longer reduces the AIC or BIC value. This indicates the point where the additional benefit of further variables does not compensate for the additional model complexity.

However, as there were limited numbers of FCEs in BALANCE, there are challenges informing all of the health state utility values. To overcome this, the model uses a combination of trial data and data from the published literature to inform utility values (further detail is included in Section B.3.4.4).

B.3.4.2. Mapping

As per the NICE methods guide, the EQ-5D-5L data were mapped to the EQ-5D-3L tool using the crosswalk method as described by Hernández Alava et al. 2017 for use in economic analysis.[103]

B.3.4.3. Health-related quality-of-life studies

A systematic review of the published literature was conducted to identify all relevant studies reporting utility data and disutilities associated with treatments and treatment-related AEs for patients with FD. An outline of the databases searched is provided in Section B.3.1. Further details on search strategy, identification of studies and quality assessment of the identified studies can be found in Appendix H.

Database searches were performed on 18 May 2021 and identified a total of 331 records, with 7 records excluded at the de-duplication stage. Following screening, 14 relevant unique studies were identified from 22 publications.

Most of the identified utility evidence included HTAs (n = 4)[94, 95, 98, 104] and retrospective observational studies (n = 4)[73, 105-107], followed by economic modelling studies (n = 3)[32, 108, 109], 1 cross-sectional study[110], 1 population-based survey[111] and 1 non-RCT.[112] Most of the included studies reported that the EQ-5D was used to elicit utility values from patients, although valuation methods were not reported in 6

studies.[32, 73, 98, 104, 107, 109] A vignette study by Hughes et al. 2022 was identified separately after the SLR was completed, which used elicitation techniques to value 6 health states.[113]

The most relevant studies identified for inclusion in PRX-102 modelling were considered to be the Rombach 2013[28], Arends 2018[73] and Hughes 2022[113] studies. In Rombach, these values were collected using the EQ-5D questionnaire with the UK tariff, and were completed by 57 patients treated with ERT. Values from this study were used in HST4 and were accepted for decision-making. The Arends study considers a relevant population in 439 patients pooled from the AMC (Academic Medical centre, Netherlands) and the RFH (Royal Free London NHS Foundation Trust, United Kingdom). It collected a range of data on patient and disease characteristics, performed statistical analyses to establish the impact of different parameters on utility values, and calculated a set of health state utility values. A strength of the Arends paper is that it captures more granularity between health states, allowing utility values to vary for different complications. This was an issue raised by the ERG in HST4, as it assumed the same utility for ESRD, cardiac complications and stroke despite large differences in QoL for these complications.[114] The Hughes paper developed health states to be valued by a UK general population using the time trade-off (TTO) method. Six health states were valued: pain; clinically evident Fabry disease (CEFD); severe CEFD; ESRD; stroke; and CV disease. Combinations of some of these health states were also valued. However, this study was not considered to be as relevant for inclusion in the model as the Rombach et al. and Arends et al. studies, as it did not elicit utility values from patients, and it resulted in utility values that were substantially lower than the existing literature and with the BALANCE trial. A summary of the key characteristics and calculated health state utility values from these studies is presented in Table 47 and Table 48.

Table 47: Key HRQL studies identified in the SLR

Study	Year	Elicitation methods	Number of patients
Rombach et al./HST4[28, 43]	2013 2017	EQ-5D, TTO	57
Arends et al.[73]	2018	EQ-5D, TTO	286
Key: HST; highly specialised technology.			

Table 48: Rombach (2013) and Arends (2017) health state utility values

	Rombach/HST4 (2013)[28]		Arends (2018)[73]	
Symptoms/event	**Health state**	**Value (95% CI)**	**Health state**	**Value (95% CI)**
No symptoms	Asymptomatic	0.874 (0.804, 0.934)	No organ involvement	0.851 (0.77, 0.93)
Acroparaesthesia	Acroparaesthesia/ symptomatic	0.762 (0.699, 0.822)	Neuropathic pain	0.725 (0.63, 0.82)
Clinical signs and/or symptoms of left ventricular hypertrophy, chronic kidney disease Stages 1–4, or white matter lesions			Organ involvement	0.783 (0.75, 0.81)
ESRD	Single complication	0.744 (0.658, 0.821)	ESRD	0.828 (0.67, 0.99)
Cardiac complications			Cardiac complication	0.705 (0.60, 0.81)
Cerebrovascular accident			Cerebrovascular accident	0.732 (0.67, 0.80)
ESRD + cardiac complications	Multiple complications	0.584 (0.378, 0.790)	Multiple complications	0.53 (0.42, 0.64)
ESRD + cerebrovascular accident				
Cardiac complication + cerebrovascular accident				
ESRD + cardiac complication + cerebrovascular accident				
Key: CI, confidence interval; ESRD, end-stage renal disease.				

B.3.4.4. Health-related quality-of-life data used in the cost-effectiveness analysis

As discussed in Section B.3.4.1, there are some challenges associated with calculating utility values for all health states in the model from PRX-102 trials alone. The base case utility values are therefore based on a combination of BALANCE regression output and literature values.

Due to low event numbers in BALANCE, robust coefficients for FCE health states could not be estimated, so base case regression did not include clinical event covariates. The regression output from BALANCE therefore provided values to inform baseline utility in health states before experiencing a complication.

To inform health state utilities for the remaining health states, BALANCE regression output was combined with literature values. For the reasons outlined in Section B.3.4.3, Arends et al. 2018[73] was considered the most appropriate data source to inform the utility values for the clinical complications health states, so it was used in the base case analysis.

As 2 different sources of utility values were used, these were combined using the multiplier approach outlined in NICE technical support document (TSD) 12[115], which assumes a constant proportional decrement relative to baseline values. The formula used to adjust the Arends utility values is presented in Equation 1.

Equation 1: Utility adjustment formulae

$$Arends\ clinical\ event\ utility\ \times \frac{BALANCE\ baseline\ utility}{Arends\ baseline\ utility}$$

Using the BALANCE mean baseline utility value of [redacted] results in a multiplier of [redacted], which is then applied to each health state utility value from Arends[73]. The resulting utility values are reported in Table 49.

The same approach was applied to the utility values reported in Rombach et al. 2013 and the results are reported in the scenario analysis. Scenarios using the utility values reported in Arends et al. 2018 or Rombach et al. 2013 without adjusting for the BALANCE baseline utility were also explored.

Additionally, utility values were adjusted over time to account for the natural decline in QoL associated with age. The utility values are capped in the model using the algorithm for general population utility developed by Ara and Brazier (2010)[116].

Table 49: Summary of health state utility values for cost-effectiveness analysis base case

Baseline utility values (Arends)[73]				
State	**Utility value: mean (standard error)**	**95% confidence interval**	**Value after adjustment to BALANCE baseline**	**Justification**
Pain	0.73	0.63, 0.82	[redacted]	Provides most granularity in health state utility values and is comparable to other sources
Other symptoms	0.78	0.75, 0.81	[redacted]	
ESRD	0.83	0.67, 0.99	[redacted]	
Cardiac complications	0.71	0.60, 0.81	[redacted]	
Stroke	0.73	0.67, 0.8	[redacted]	
ESRD & cardiac	0.53	0.42, 0.64	[redacted]	
Cardiac & stroke	0.53	0.42, 0.64	[redacted]	
ESRD & stroke	0.53	0.42, 0.64	[redacted]	
ESRD, cardiac & stroke	0.53	0.42, 0.64	[redacted]	
Key: ESRD, end-stage renal disease.				

B.3.4.5. Adverse reactions

As discussed in Section B.3.3.5, no meaningful differences in treatment-related AEs associated with PRX-102, agalsidase beta and agalsidase alfa have been observed in BALANCE or anticipated by clinicians. As a result, no disutilities associated with AEs have been included in the economic model.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Costs included in the model reflect the UK NHS and Personal Social Services (PSS) perspective in line with the NICE reference case. As such, only direct medical costs were considered in the base case. NHS Reference Costs, the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care and the Monthly Index of Medical Specialities (MIMS) were used to inform unit costs in the model.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Drug acquisition costs

This section details drug acquisition costs for the treatments used in the model. A description of the cost per pack, source and the proposed patient access scheme (PAS) is presented in Table 50.

Table 50: Drug acquisition costs

Treatment	Pack size x formulation	Unit cost per pack (£)	Cost per mg (£)	Cost per dose 2 weeks at 72.2 kg (£)	Source
PRX-102	1 vial x 20 mg	£1,255.19 [redacted] with PAS)	£62.76 ([redacted] with PAS)	£4,531.13 ([redacted] with PAS)	List price with [redacted] PAS applied
Agalsidase alfa (Replagal)	1 vial x 3.5 mg	£1,049.94	£299.98	£4,330.32	BNF 2022
Agalsidase beta (Fabrazyme)	1 vial x 5 mg	£315.08	£63.02	£4,533.61	BNF 2022
	1 vial x 35 mg	£2,196.59	£62.76		
Key: BNF, British National Formulary; PAS, patient access scheme.					

The dosing schedules by treatment considered in the model are presented in Section B.3.2.3 and Table 37. To account for the variation in patient weights, the per-cycle treatment cost for PRX-102 and ERTs is calculated using the Method of Moments approach. The mean weight of patients and its SD is taken from Malottki et al. 2022[8], which is a retrospective study of patients with FD in England from 2000-2019, to calculate the average cost per cycle. The model then includes 3 options related to drug wastage: no wastage, full wastage or pragmatic dosing.

The pragmatic dosing approach was developed as clinicians indicated that, in UK practice, dosage is rounded up or down to the nearest vial in order to minimise wastage, rather than dosing patients strictly to the dose specified for their weight. This is also aligned with the clinical advice received during TA821 from the 8 LSD centres in the UK, which concluded there is little to no vial wastage during administration of ERTs in real-world NHS practice. After technical engagement, the ERG for TA821 accepted the model that did not consider vial wastage.[117]

Therefore, in the model base case the Method of Moments approach is used to distribute patients across doses that increase in whole vial (20mg) increments, to reflect the pragmatic dosing approach. Scenarios with no wastage and full wastage are also explored.

B.3.5.1.2. Treatment administration costs

Drug administration costs include the cost of infusion required for ERT administration. Costs are sourced from NHS Reference Costs 2020–2021 and PSSRU 2021.[118, 119]

As noted in Section B.3.2.3, all treatments are associated with E2W administration costs in the base case, with E4W administration of PRX-102 considered in scenario analysis. Reflecting the administration process for the infusions following the initiation of a new treatment, the first 2 administrations are assumed to be in a hospital setting with all subsequent infusions delivered at home. Any remaining infusions at the 'initial' infusion duration are conducted with a nurse home visit. After this a proportion of patients will self-administer. HST4 precedent and advice from a clinical advisory board indicated that 50% of patients require a nurse to deliver infusions, while the remaining 50% of patients self-administer or have infusions administered by an informal caregiver and only receive 1 visit per year. Table 52 presents the costs associated with drug administration. The homecare infusion cost includes home delivery of the medication, the cost of pre-infusion medications and disposing of waste. The nurse hourly rate is then included for any homecare infusions that require a nurse visit, including initial infusions and for patients who have a nurse supported infusion long-term.

For PRX-102 and agalsidase beta, initial infusions are of a longer duration compared with subsequent treatments to control against any IRRs when starting treatment.[69] These differences in initial infusion duration is captured in the model and it is assumed that patients will receive the shorter maintenance dose after the initial 6 infusions, in line with the SmPC.[7]

Table 51: Initial and reduced infusion times for treatments in the model

Treatment	Dosing per admin	Duration of infusion (hours)		No. infusions at initial duration	Dosing frequency/month	
		Initial	Reduced			
PRX-102[7]	1 mg/kg	3	1.5	6	E2W	2
	2 mg/kg	4.5	2	3	E4W	1
Agalsidase alfa[99]	0.2 mg/kg	0.67	0.67	6	E2W	2
Agalsidase beta[100]	1 mg/kg	3	2	6	E2W	2
Key: E4W; every 4 weeks.						

Table 52: Drug administration costs

Item	Cost (£)	Reference
Cost of homecare for ERT infusion (includes home delivery, cost of preinfusion medication and disposal of waste)	£232.55	HST4[98]. £200 inflated to the 2022 price level
Cost of ERT infusion in hospital	£393	NHS national tariff payment system 20/21, Outpatient procedure tariff 56
Cost of nurse visit (per hour)	£57	PSSRU (2021, Cost of 60 minutes of Band 6 nurse)
Key: ERT, enzyme replacement therapy.		

Table 53: Annual drug and administration costs per year

Treatment	Cost per admin (£)		Admin cost/year (£)		Drug cost* (No PAS discount)	Drug cost* (With PAS discount)
	Initial	Maintenance	Initial	Maintenance		
PRX-102 E2W	£474	£299	£9,197	£7,745	£118,214	[redacted]
PRX-102 E4W	£524	£316	£5,198	£4,065	£118,190	[redacted]
Agalsidase alfa	£405	£274	£8,061	£7,143	£112,975	N/A
Agalsidase beta	£474	£313	£9,482	£8,129	£118,279	N/A
Blended ERT (70% Fabrazyme/ 30% Replagal)	£453	£302	£9,056	£7,833	£116,688	N/A
Key: E2W, every 2 weeks; ERT, enzyme replacement therapy; PAS, patient access scheme. *With the base case pragmatic dosing approach.						

B.3.5.2. Health-state unit costs and resource use

An SLR was conducted to identify the cost and resource use evidence in FD. Details of databases searched is discussed in Section B.3.1 and further details on search strategy, identification of studies and quality assessment of the identified studies can be found in Appendix I.

Database searches were performed on 18 May 2021 and identified a total of 720 records, with 7 records excluded at the de-duplication stage. Following the preliminary screening of abstracts, 681 records were excluded, and 32 records were included for secondary screening. A total of 22 studies from 24 publications were included in the cost and resource review. Most of the studies (n = 13) were conducted in Europe, followed by the United States (n = 3) and Columbia (n = 2), while the remaining 4 studies were conducted in other countries.

From the SLR, HST4 was considered the most relevant source of data as it provided a full set of cost and resource use parameters that had previously been validated by UK clinicians and accepted by NICE in 2017. These values were therefore used as the primary source for cost and resource use estimates in the model. These values were re-validated by clinicians via a resource use questionnaire as part of an advisory board, which ensured that these values were reflective of current clinical practice.

To apply these costs appropriately in the model, patient traces are split to calculate the proportion of new incidence patients entering each health state, in addition to the proportion of patients in that health state in each cycle. The transitions to state traces can then be used to calculate first year health costs of a newly developed complication. For patients who then remain in a complication health state, complication management costs are applied per cycle until progression or death.

Table 54: Costs for health state events

Resource	Unit cost	Weighting	Ref
Acroparaesthesia/Pain	£0.00		
Other symptoms			
White matter lesions	£2,554.00	51%	NHS reference costs 20/21 - AA25C-G (average)

Resource	Unit cost	Weighting	Ref
Left ventricular hypertrophy	£2,368	49%	NHS reference costs 20/21 - : AA25C-G (average)
Chronic kidney disease (Stage 1–4)	£2,301.04	0%	NHS reference costs 20/21 - : LA08N, LA08P elective patients (average)
Total annual cost of 'Other symptoms'	**£1,793**		
ESRD			
Chronic kidney disease (Stage 5)	£3,615.35	100%	NHS reference costs 20/21 -: LA08K - LA08M elective patients (average)
Renal transplant	£21,610.32	27%	NHS reference costs 20/21 -: LA01A, LA02A,LA03A elective inpatients (average)
Total annual costs of 'ESRD'	**£9,450**		
Cardiac complications			
Atrial fibrillation/ Rhythm disturbance requiring hospitalisation	£2,529.23	23%	NHS reference costs 20/21 -: EB07A-E elective inpatients (average)
Pacemaker	£5,473.78	1%	NHS reference costs 20/21 -: EY08A-E elective inpatients (average)
Cardiac congestion requiring hospitalisation	£3,591.77	39%	NHS reference costs 20/21 -: EB03A-E non-elective inpatients (average)
Myocardial infarction	£3,362.92	34%	NHS reference costs 20/21 -: EB05A-C non-elective inpatients (average)
Percutaneous coronary intervention	£7,452.59	0%	NHS reference costs 20/21 -: EY23A-C non-elective inpatients (average)
Implantable cardiac defibrillator	£10,004.79	1%	NHS reference costs 20/21 -: EY02A-B non-elective inpatients (average)
Coronary artery bypass graft	£16,548.50	2%	NHS reference costs 20/21 -: ED28A-C non-elective inpatients (average)
Total annual cost of 'Cardiac complications'	**£3,612**		
Stroke			
Stroke	£8,909.83	100%	NHS reference costs 20/21 -: AA35A-F non elective inpatients (average)

Key: ESRD, end-stage renal disease; NHS, National Health Service.
Source: HST4[120] (inflated to 2021 costs)

Follow-up costs for FD management include: ambulatory care; diagnostics; imaging; and laboratory testing. Ambulatory care comprises annual visits to health care workers at a frequency that varies by health state. The frequency of visits was taken from Rombach et al., but were then subsequently modified and validated by UK clinical experts to ensure that they aligned with current UK clinical practice.[28, 49, 101] This also aligns with recent evidence from Malottki 2022[8] which showed that patients

with FD in England have an average of 9.4 consultations with healthcare professional per patient year, of which 5.6 were GP visits.

Table 55: Yearly follow-up visits per health state

Resource	Health state			
	Pain	Other symptoms	Single complication	Multiple complications
GP visit	2.1	3.5	3.7	4.8
Physiotherapist	5.4	5.6	18.5	8.8
Psychologist/ psychiatrist	3.7	1.5	0.1	0
Social worker	0.2	0.3	0.4	0.3
Key: GP, general practitioner.				

Table 56: Cost per visit

Resource	Cost	Ref
GP visit	£39.23	PSSRU (2021), 9.22 minute appointment
Physiotherapist	£41.00	PSSRU (2021), Band 5 physiotherapist
Psychologist/psychiatrist	£65.00	PSSRU (2021), Band 7 scientific and professional staff
Social worker	£52.00	PSSRU (2021)
Key: GP, general practitioner; PSSRU, Personal Social Services Research Unit. **Source**: HST4[120] (inflated to 2021 costs)		

The general management of FD, without considering any comorbidities that are more prevalent in patients with FD, is also associated with a health care resource burden. Resource use estimates were estimated from the results of a survey completed by clinical experts. The estimated annual resource use and the unit cost for each resource are presented in Table 57.

Table 57: Fabry related general annual HCRUs

Health care professional	Annual frequency	Unit cost (£)	Source
Full blood count	2.38	£3.63	NHS reference costs 20/21 DAPS05 haematology
Urine test	2.75	£5.72	NHS reference costs 20/21 DAPS01 Cytology
ECG	1.00	£182.00	NHS reference costs 20/21 - EY51Z
Liver function test	1.50	£5.72	NHS reference costs 20/21 DAPS01 cytology
Fasting lipid profile	1.00	£5.72	NHS reference costs 20/21 DAPS01 cytology
2D echocardiography with Doppler	0.63	£258.00	NHS National Tariff workbook EY50Z Complex Echocardiogram
Glomerular filtration rate	2.13	£1.85	NHS reference costs 20/21 DAPS04 clinical biochemistry
24 hour urine protein / creatinine	0.08	£5.72	NHS reference costs 20/21 DAPS01 cytology
Exercise testing	0.21	£182.00	NHS reference costs 20/21 - EY51Z
Renal USS	0.06	£66.00	NHS National Tariff workbook 130 Ophthalmology Service
MRI	0.23	£166.00	NHS National Tariff workbook RD02A Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over
Audiogram	0.63	£160.00	NHS reference costs 20/21 - 840 outpatient
Plasma Lyso-Gb3	0.18	£3.63	NHS reference costs 20/21 - DAPS05
Assay for alpha-galactosidase A Ab	1.33	£5.72	NHS reference costs 20/21 - DAPS01
GL-3G and Lyso-GL-3G	1.25	£5.72	NHS reference costs 20/21 - DAPS01
Holter	1.17	£182.00	NHS reference costs 20/21 - EY51Z
Antibody test & neutralizing assay	1.50	£5.72	NHS reference costs 20/21 - DAPS01

B.3.5.3. Adverse reaction unit costs and resource use

As discussed in Section B.3.3.5, AEs are not formally considered in the model base case. A scenario including the cost of managing AEs has been included. The inputs used to derive this scenario are included in Appendix O.

B.3.6. Severity

The inputs used to calculate whether this submission was eligible for a severity weighting are reported in Table 58 and Table 59. The total QALYs for FD patients receiving either agalsidase alfa or agalsidase beta are the deterministic results from the cost-utility scenario analysis reported in Section B.3.9.3.

Although PRX-102 does not meet the formal criteria for a severity weight, the symptoms of FD have a significant impact on patient HRQL and long-term survival, so there is real unmet need for additional treatment options to help improve outcomes.

Table 58: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	50/50	Patient characteristics section B.3.3.1
Starting age	40	Patient characteristics section B.3.3.1

Table 59: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment		QALY shortfall (absolute/proportional)
17.83	Agalsidase alfa	[redacted]	[redacted]
17.83	Agalsidase beta	[redacted]	[redacted]

B.3.7. Uncertainty

As described in Section B.3.3, FD is characterised by a lifetime of slow progression into different symptomatic health states and clinical complications. Given the rarity of FD, which leads to low patient numbers in these trials and the limited length of

follow-up, trials considering treatments for FD are often not powered to capture the long-term patient outcomes of interest. These challenges make it difficult to estimate long-term treatment efficacy directly from the PRX-102 clinical trials and for efficacy data to be used in the model, which aims to capture lifetime outcomes and costs.

However, multiple studies demonstrate that the endpoints collected in PRX-102 trials are relevant surrogate outcomes in FD for predicting long-term events.[84-91] Results show improvements in eGFR and LVMI observed in the PRX-102 clinical trials are likely to translate into significant reductions in the incidence of long-term clinical events. The evidence also indicates that equivalence between PRX-102 and ERTs in eGFR and LVMI outcomes is likely to translate to equivalence in the rate of experiencing clinical events. Although the available data has its limitations, uncertainty is minimised because of the availability of studies that demonstrate key surrogacy relationships, and because of consistent feedback from UK clinical experts on their belief that PRX-102 is at least as efficacious as existing ERTs.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A summary of the variables and distributions applied in the economic model is presented in Appendix O including references to the corresponding sections in the submission where each one is explained in more detail.

B.3.8.2. Assumptions

Table 60 details the key assumptions used in the economic model and provides a justification for each one, as well as the references to the corresponding sections in the submission where each one is explained in more detail.

Table 60: Summary of model assumptions

Topic	Assumption	Justification
Model structure	Treatment with ERT or PRX-102 decreases the probability of transitioning to a worse disease state	Since ERT or PRX-102 cannot reverse end-organ damage that has already occurred, and clinical data show ERT can stabilise organ function; it is expected that patients being treated with ERT will not improve and thus will not transition back to a healthier disease state (also in line with evidence from Rombach et al [2013a]).[28]
Clinical equivalence between treatments	PRX-102 has equivalent clinical effectiveness to both ERTs	Data from PRX-102 trials show non-inferiority between PRX-102 and agalsidase beta. Clinical feedback from an advisory board confirmed that clinicians believe, based on the available evidence, that PRX-102 is at least as efficacious compared with agalsidase beta, and by extension agalsidase alfa (due to precedent from HST4 and data in the literature, including long-term real-world cohort studies (Arends))[92]
Treatment discontinuation	Patients discontinue from all treatments at a rate of 0.05% and then experience untreated transition probabilities	Clinical opinion[49] suggested that treatment discontinuation is likely overestimated in clinical trials compared with clinical practice, as the reasons for discontinuation (e.g. infusion reactions) can typically be managed in practice. Clinicians indicated that patients would discontinue from PRX-102 and ERTs at the same rate.
Efficacy source generalisability	The Netherland prospective study for FD is assumed to be representative of UK clinical practice	Clinicians noted that as this study is focused on a single centre and included all patients (i.e. is a 100% case series which incorporated all data) that this is the most robust data available to inform the transition probabilities between health states
Mortality risk	Average life expectancy for Fabry patients is 58.2 years for males and 74.7 years for females	This is based on data from Waldek[102], consistent with the preferred analysis conducted by the ERG in HST4.[98] These values were validated by UK clinical experts in an advisory board
Baseline characteristics	Data from the Malottki et al.[8] study and the Fabry registry provide the best source of patient baseline characteristics	This is consistent with the preferred approach in NICE HST4[98] where the ERG preferred the use of data collected from patients treated in clinical practice, rather than data from the primary trials
Key: ERT, enzyme replacement therapy; FD, Fabry disease.		

B.3.9. Base case results

As noted in Section B.3.5.1.1, agalsidase alfa and agalsidase beta are both subject to a confidential simple PAS. As the information related to the size of the discount is not publicly available, the results presented are based on the reported list price for the comparators, but the proposed simple PAS of [redacted] is applied for PRX-102.

B.3.9.1. Base case incremental cost-comparison results

Base case results of the cost-comparison between PRX-102 E2W and agalsidase alfa and agalsidase beta are presented in Table 61. Results show that PRX-102 E2W is a cost-saving option when compared to both ERTs separately and as a blended ERT comparator (assuming 30% of patients receive agalsidase alfa and the remaining 70% receive agalsidase beta). Base case cost comparison results show cost-savings per patient over a lifetime horizon (60 years) of £564,502 with PRX-102 E2W when compared with blended ERT. As Table 62 highlights, these results are driven by lower total drug acquisition costs of PRX-102 compared to both existing ERT regimens and lower administration costs of PRX-102 compared to agalsidase beta.

Table 61: Base case results (PAS price)

Costs	PRX-102 E2W	Agalsidase alfa	Agalsidase beta	Blended comparator
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]	-£477,580	-£601,754	-£564,502
Key: PAS, patient access scheme.				

Table 62: Base case disaggregated results (PAS price)

Costs	PRX-102 E2W	Agalsidase alfa	Agalsidase beta	Blended comparator (70% alfa, 30% beta)
Drug acquisition				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]
Healthcare resource use				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	£0.00	£0.00	£0.00
Key: PAS, patient access scheme				

B.3.9.2. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted where all inputs were varied simultaneously over 1,000 iterations, based upon their distributional information. The mean incremental costs from PRX-102 E2W vs. agalsidase alfa and agalsidase beta are displayed in Table 63. The mean results of the PSA align closely to the deterministic results, suggesting the results are not significantly impacted by second order uncertainty. The range in costs for each treatment arm across the 1000 iterations show that even in the iteration that generated the highest costs for PRX-102, there still would have been a cost saving versus any comparator.

Table 63: Mean probabilistic sensitivity analysis results (PAS price)

Costs	PRX-102 E2W	Agalsidase alfa	Agalsidase beta	Blended comparator
Mean total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]	-£477,352	-£601,480	-£564,241
Range in costs	[redacted]	[redacted]	[redacted]	[redacted]
Key: PAS, patient access scheme.				

B.3.9.3. Scenario analysis

To further explore the uncertainty around the modelled results in respect of key inputs and assumptions, a series of scenario analyses with alternative modelling assumptions were performed, including a cost utility analysis in line with the NICE reference case. All performed scenario analyses are briefly summarised in Table 64, below.

Table 64: Scenarios explored in cost effectiveness model (PAS price)

No.	Scenario analysis	Scenario description	Total costs			Incremental costs (PRX-102 Vs)	
			PRX-102	Agalsidase alfa	Agalsidase beta	Agalsidase alfa	Agalsidase beta
Base case			[redacted]	[redacted]	[redacted]	*-£477,580*	*-£601,754*
1	Time horizon	40 years	[redacted]	[redacted]	[redacted]	-£458,915	-£578,259
2		20 years	[redacted]	[redacted]	[redacted]	-£342,049	-£431,148
3		10 years	[redacted]	[redacted]	[redacted]	-£218,052	-£275,059
4	Discounting	No discounting	[redacted]	[redacted]	[redacted]	-£874,671	-£1,101,616
5		5% discount	[redacted]	[redacted]	[redacted]	-£391,625	-£493,554
6	HCRU frequency source	Hughes et al 2013	[redacted]	[redacted]	[redacted]	-£477,580	-£601,754
7	FD complication distribution source	KOL survey	[redacted]	[redacted]	[redacted]	-£477,580	-£601,754
8	Utility source	Rombach 2013	[redacted]	[redacted]	[redacted]	-£477,580	-£601,754
9		Arends 2018, no adjustment for BALANCE	[redacted]	[redacted]	[redacted]	-£477,580	-£601,754
10		Rombach 2013, no adjustment for BALANCE	[redacted]	[redacted]	[redacted]	-£477,580	-£601,754
11	Wastage	No wastage	[redacted]	[redacted]	[redacted]	-£477,580	-£601,754
12		Full	[redacted]	[redacted]	[redacted]	-£478,269	-£600,494
13	AE management	Include AE management costs	[redacted]	[redacted]	[redacted]	-£477,805	-£601,979
14	PRX-102 dosing (E2W or E4W)	25% E4W PRX-102 dosing	[redacted]	[redacted]	[redacted]	-£495,850	-£620,025
15		50% E4W PRX-102 dosing	[redacted]	[redacted]	[redacted]	-£514,121	-£638,295
16		75% E4W PRX-102 dosing	[redacted]	[redacted]	[redacted]	-£532,391	-£656,566
17		100% E4W PRX-102 dosing	[redacted]	[redacted]	[redacted]	-£550,662	-£674,836

Key: AE, adverse events; HCRU, health care resource use; FD, Fabry disease; KOL, key opinion leader

B.3.9.3.1. Cost-utility analysis

A scenario exploring the economic consequences of implementing PRX-102 E2W using a cost-utility approach was also performed in line with the NICE reference case. The deterministic results of this scenario are reported in Table 65. The scenario shows PRX-102 E2W is economically dominant compared to agalsidase alfa and agalsidase beta, providing equal health outcomes at a reduced price. Detailed results of the cost-utility analysis including incremental results, full incremental analysis, one-way sensitivity analysis and probabilistic results are reported in Appendix J.

Table 65: Deterministic results of cost-utility analysis scenario

Technology	Total LYs	Total QALYs	Total costs (£)	Inc. LYs	Inc. QALYs	Inc. Costs	ICER (£/QALY)
PRX-102 E2W	19.815	[redacted]	[redacted]	-	-	-	-
Agalsidase alfa	19.815	[redacted]	[redacted]	**0.000**	**0.000**	-£477,580	**PRX-102 Dominant**
Agalsidase beta	19.815	[redacted]	[redacted]	**0.000**	**0.000**	-£601,754	**PRX-102 Dominant**

B.3.10. Benefits not captured in the QALY calculation

PRX-102 offers clinicians and patients additional flexibility with regards to the frequency of treatment administration, with the option for treatment to be provided E4W. This dosing schedule has the potential to reduce the annual cost of treatment administration, and have a significant impact on patients' HRQL, and could potentially reduce the annual infusion frequency by 13 days per year. The E4W administration schedule also provides benefits related to sustainability. Fewer administrations would reduce travel and the number of homecare nurse visits required to maintain patient's dosing schedules and also a reduction in plastic waste.

Additionally, as highlighted in Section B.2.9.1.6, the BALANCE trial showed that PRX-102 demonstrated lower levels of immunogenicity in terms of IgG ADAs and neutralising antibodies compared with agalsidase beta. These observations of low treatment-emergent immunogenicity and increased tolerability are important from a

safety and an efficacy perspective, as antibodies developed against an ERT product, especially neutralising antibodies, would be expected to inhibit the treatment's activity and potentially adversely affect the clinical outcome. Clinician experts at an advisory board highlighted that the reduction in ADAs signals the possibility of limited reduction in long-term efficacy, which could potentially improve long-term renal and cardiac outcomes.[49]

B.3.11. Validation

B.3.11.1. Validation of cost-effectiveness analysis

The following key aspects of the model methods and inputs were validated by health economic and clinical experts following a virtual advisory board:

- The model structure and its appropriateness to reflect the clinical pathway
- Assumptions in the efficacy inputs to compare PRX-102 with ERTs, given difficulties in performing ITC analyses
- The patient populations from the PRX-102 trials and how they compare with the NICE scope
- Data sources considered to inform resource use costs
- Clinical validity of modelled utilities

The model was finalised before being validated by internal and external modellers. A programmer who did not build the model reviewed all formulae and labelling in the model. Following this first validation step, an extreme value analysis was conducted. This involved inputting sensible upper and lower bounds (e.g. £0 for costs, but not negative costs) into the model, one parameter at a time, and observing the corresponding changes in the results. Where it was not sensible to vary only one parameter or the expected effect on the results was not straightforward, a related group of parameters was varied simultaneously. The results were checked against their expected impact or the predicted direction of change for the varied parameter(s). As an example, setting all healthcare resource use costs to zero would result in £0 for healthcare resource use across all treatment arms.

B.3.12. Interpretation and conclusions of economic evidence

The economic analysis of PRX-102 E2W is based on a previous model submitted to NICE (HST4)[98] for the treatment of FD. This analysis was considered acceptable for decision-making and addresses the critiques outlined in the HST4 submission to ensure it aligns with the ERG and Committee feedback. In the absence of data on long-term clinical outcomes from the PRX-102 clinical trials, data from Rombach et al. have been used to be consistent with the approach adopted in HST4. These data inform the transitions between health states, assuming equal efficacy between PRX-102 and agalsidase alfa based on the findings of the PRX-102 trials, the literature, and extensive clinical feedback.[70-73].

The results of the economic analysis consistently demonstrate that PRX-102 is a cost-saving therapy option compared with existing ERTs. A supplementary cost-utility analysis shows that these cost-savings come with no loss in health outcomes, making PRX-102 an economically dominant intervention compared to agalsidase alfa and agalsidase beta. The base case results are also considered to be underestimates of the true economic benefit of PRX-102 E2W, which is supported by a series of scenario analyses that explore plausible alternative assumptions to estimate the QALYs and costs associated with PRX-102 and both ERT regimens. The base case analysis assumes that all patients receive the E2W regimen, when in clinical practice, a significant proportion of patients may receive the E4W regimen. This leads to greater cost savings because of reduced treatment administration frequency, and can also give patients an additional 13 days per year of infusion-free time.

The results are largely insensitive to parameters and assumptions tested in deterministic sensitivity analyses and scenario analysis, with PRX-102 remaining the lowest cost treatment option in all cases. The assumptions implemented in the base case analysis have been extensively validated by the clinical trial data, the published literature and UK clinical expert opinion.

A key limitation of the analysis is the inability to model long-term clinical outcomes directly using the PRX-102 trial data. This is because of the rarity of the disease and

the fact that these clinical events can take many years to occur. However, BALANCE clearly demonstrates the equivalence of PRX-102 E2W and agalsidase beta across multiple clinical endpoints. The literature on surrogacy relationships and extensive clinical feedback has also confirmed that PRX-102 will be at least as effective as existing ERTs in reducing the speed or progression through the modelled health states.

PRX-102 provides clear benefit in patients with FD by offering a highly effective, cost-saving treatment option for patients and the healthcare system. PRX-102 provides both patients and clinicians with greater choice and the potential to minimise the burden of treatment administration on patients and carers.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]

Summary of Information for Patients (SIP)

January 2023

File name	Version	Contains confidential information	Date
ID3904_PRX 102 NICE SIP_FINAL_25Jan2023_redacted.	1	Yes	25 January 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the Summary of Information for Patients (SIP)?

The SIP is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

UK approved name: Pegunigalsidase alfa (PRX-102) **Brand name:** Elfabrio®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population is adult patients with Fabry disease (FD) who would usually be treated with enzyme replacement therapy (ERT) such as agalsidase alfa (Replagal®) or agalsidase beta (Fabrazyme®). ERT is a type of therapy where patients receive a functioning enzyme via intravenous infusion (via injection into a vein) to replenish or replace malfunctioning or deficient enzyme caused as a result of their condition.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is

pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation has been applied for via the European Commission (EC) decision reliance procedure. Committee for Medicinal Products for Human Use approval is expected on [redacted], and Market Authorisation Application (MAA) approval is expected on [redacted].[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

We do not have any current partnerships or any conflicts of interest with patient groups related to the medicine. We have made several arms length donations and grants to patient groups over the last few years, but we do not consider these to be relevant conflicts of interest to this appraisal.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
FD is a rare, inherited condition caused by mutations in a gene responsible for the production of an enzyme called alpha-galactosidase A.[2-6] This enzyme is needed to break the fatty substance called globotriaosylceramide (Gb3) and to remove it from cells. In patients with FD, Gb3 builds up in the cells of various body tissues, which can lead to serious disease in vital organs.[3-6] FD gets worse over time and can affect many part of the body including the kidneys, heart, brain, nervous system and gastrointestinal system. There are two types of FD – classic and non-classic disease. Patients with classic disease have no or little alpha-galactosidase A and experience symptoms in early childhood, which affect multiple organs and get progressively worse.[5, 7] Patients with non-classic FD

have low levels of alpha-galactosidase A, experience symptoms later in life, and have a milder disease affecting fewer organs. Classic disease tends to be more common in males than in females.[4, 5, 7]

FD is a rare disease, with a recent study reporting 535 diagnosed patients with FD in England in 2019.[8] The survival rate of patients in this study was 95.3% over 5 years and 87.8% over 10 years.[8] Patients with FD experience a wide range of symptoms because of the multiple organs involved.[9,8] FD has also been found to be associated with depression and anxiety.[10, 11] Consequently, patients with FD have a lower quality of life compared with the general population, and quality of life decreases with increasing age, organ problems and disease severity.[12,13]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients with FD experience a wide range of symptoms, so diagnosis can be challenging.[5] The main diagnostic test is confirmation of a mutation in a gene called *GLA* known to cause FD.[14] However, for patients with certain *GLA* gene variants, diagnosis may be uncertain and further tests may be needed. Tests may include biopsy of the affected organ (e.g. kidney or heart) followed by studying the tissue under an electron microscope to confirm whether it contains signs of FD; magnetic resonance imaging to detect characteristics of FD of the heart muscle; and measurement of the Fabry marker, lyso-Gb3, in blood plasma.[14] No additional diagnostic tests will be needed to be treated with PRX-102.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP
- Please also consider:

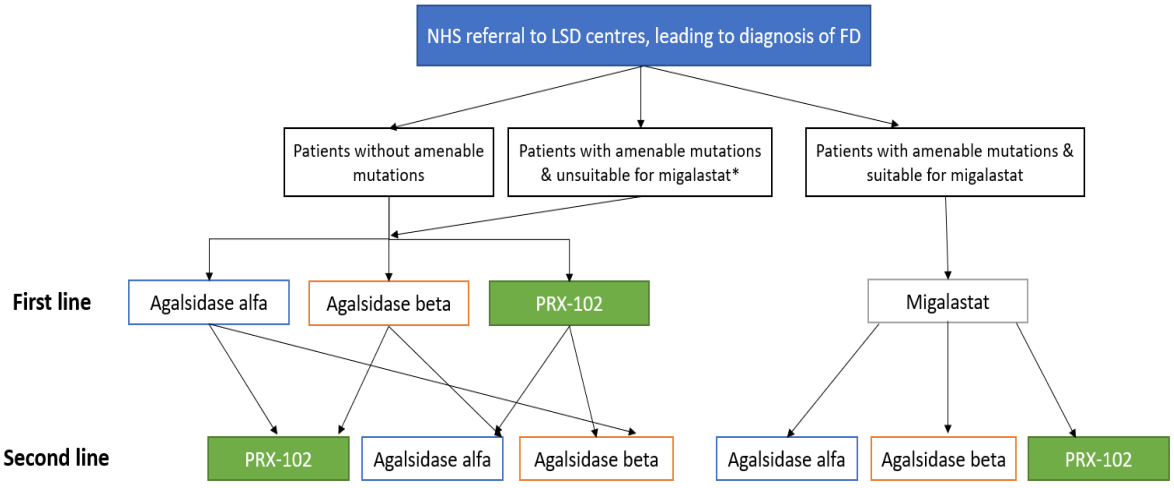
- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are

Figure 1 shows the sequence of treatments offered to patients with FD based on treatment guidelines from the British Inherited Metabolic Disease Group (BIMDG).[14] Adult patients who are suitable for treatment with ERT are offered a choice of two therapies that are both administered by intravenous infusion (via a vein) every 2 weeks: agalsidase beta 1 mg/kg (Fabrazyme®) or agalsidase alfa 0.2 mg/kg (Replagal®).

Patients (≥ 16 years) are also tested to check what type of *GLA* mutation they have; if the mutation is the type that responds to treatment (known as an 'amenable mutation'), then additional treatment with oral migalastat tablets can also be offered. Migalastat tablets are taken every other day with a 4-hour fasting window (no food 2 hours before and after taking migalastat).[14]

The new therapy PRX-102 will be offered to patients as another ERT treatment option. It will be available for adults with FD who would usually be treated with an ERT. This includes: 1) patients without amenable mutations who have never received any Fabry treatment; 2) patients with amenable mutations who are unsuitable for treatment with migalastat for any reason (because of issues with adherence, intolerance, patient /clinician choice or any other reason); and 3) patients who have been previously treated with currently available therapies (agalsidase alfa, agalsidase beta or migalastat). The decision about which ERT is most suitable for use (PRX-102, agalsidase alfa or agalsidase beta) would be made by the clinician and the patient (Figure 1).

Figure 1: Proposed position of PRX-102 within the current treatment pathway



Key: FD, Fabry disease; LSD, lysosomal storage disorder.
Note: * Unsuitable due to issues with adherence, tolerance, due to patient or clinician choice, or any other reason.
Source: BTMDG, 2020[14]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Because FD impacts the whole body it can cause substantial burden to patients, and reduce physical and mental function and patient quality of life.[12] Quality of life can also decrease with increasing age. In one study, over half of patients with FD experienced pain/discomfort (51.7%), 39.5% experienced problems with conducting usual activities, almost one-third (33.2%) experienced anxiety/depression and over a quarter reported mobility problems (27.6%).[15] In a UK study, 46% of patients with FD reported clinically significant depression and 28% had severe clinical depression, which is higher than that of the general population.[16]

Patients with FD experience substantial limitations on daily activities and ability to work because the disease affects multiple aspects of their lives. In one study, patients with FD aged under 50 years were significantly limited in their ability to conduct vigorous activities compared with healthy people.[17] Other daily activities (lifting/carrying groceries; climbing several flights of stairs; bending, kneeling or stooping; walking more than a mile) were also affected.[17] Another study highlighted the link between the pain of FD and the impact this has on daily life.[18] Most of the patients in the study (79.3%) reported moderate or severe Fabry-specific pain and over half (54.2%) reported consistent and frequent pain. Furthermore, as pain intensity increased, so did the impact on daily life, in terms of daily activities, enjoyment of life, mood, work, sleep, relationships and walking. Fabry disease also affects patients' work. One study reported a 57% employment rate in patients with FD, while almost one fifth had never had a job because of their diagnosis.[19] Studies have shown that most patents with moderate/severe Fabry-related pain report moderate/severe interference with work; in one study, more than two thirds needed time off work.[18 19]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

PRX-102 is a new type of long-acting ERT used to treat FD.[1] Patients with FD do not have enough alpha-galactosidase A, the enzyme responsible for breaking down the substances Gb3 and lyso-Gb3. Without enough of the enzyme, these two substances accumulate and can cause a range of symptoms and potentially organ failure. PRX-102 is used as a long-term ERT to supplement or replace the low level of this enzyme in adult patients who have confirmed FD who would otherwise receive another ERT. PRX-102 has been designed to be more stable in the body and remain active for longer compared with existing ERTs, and therefore has the potential for fewer infusions, with the options of dosing every 2 weeks or every 4 weeks.[1, 20, 21] PRX-102 also leads to a lower level of anti-drug antibodies, which is

an advantage compared with other ERTs given that these types of antibodies may reduce a drug's effectiveness.[22, 23]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- ~~Yes /~~ No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

PRX-102 is not intended to be used in combination with any other medicines.[1]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

PRX-102 is provided as a solution which is first diluted before being given as a drip (infusion) into a vein over at least 90 minutes.[1] Treatment should be managed by a healthcare professional with experience in treating patients with FD. To begin with, PRX-102 should be given in a hospital; for patients who tolerate the treatment well, and if recommended by the healthcare professional, infusions can be given at home by the patient themselves with a responsible adult present, or by a caregiver, or with the help of a homecare nurse. Proper training must be given before patients or caregivers can administer the treatment themselves, and self-administration should be closely monitored by the responsible healthcare professional. Patients should be monitored for any reactions related to the infusion for 2 hours after infusion. Patients having infusion-related reactions during home infusion or self-administration must immediately reduce the infusion rate or stop the infusion depending on the severity of the reaction and should contact a healthcare professional.

The recommended dose of PRX-102 is 1 mg/kg of body weight once every 2 weeks, although some patients can be offered a reduced dosing schedule of 2 mg/kg of body weight once every 4 weeks.[1] Therefore, PRX-102 is the only ERT which can be dosed at this lower administration frequency.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates, etc. Please provide references to further information about the trials or publications from the trials.

Table 1 gives an overview of the BALANCE trial, a pivotal randomised controlled trial (RCT) that directly compared PRX-102 with a currently available ERT, agalsidase beta, in adults with FD with declining kidney function who had previously received agalsidase beta. Other non-comparative clinical trials have been completed. These studies investigated PRX-102 in a broader patient population (i.e. not just those with declining kidney function), as follows: BRIDGE studied PRX-102 1 mg/kg every 2 weeks in patients switched from agalsidase alfa; BRIGHT studied PRX-102 2 mg/kg every 4 weeks in patients switched from ERTs every 2 weeks; and a series of Phase I/II studies investigated PRX-102 in patients who had never received an ERT, with including long-term data after treatment with PRX-102 for up to 6 years.

Table 1: Summary of BALANCE RCT

Study	BALANCE (NCT02795676); Phase III, double-blind, multinational, randomised controlled trial over 2 years
Location	29 sites across 12 countries, including 4 sites in the UK
Population	Symptomatic patients with FD aged 18–60 years
Patient group size	PRX-102 1 mg/kg every 2 weeks: n=52; agalsidase beta 1 mg/kg every 2 weeks: n=25
Completion dates	Completed; date of last visit for last patient: 12 October 2021
Primary publication	Wallace et al., 2022[23]

Key: eGFR, estimated glomerular filtration rate; $eGFR_{CKD\text{-}EPI}$, eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation; NYHA, New York Heart Association.

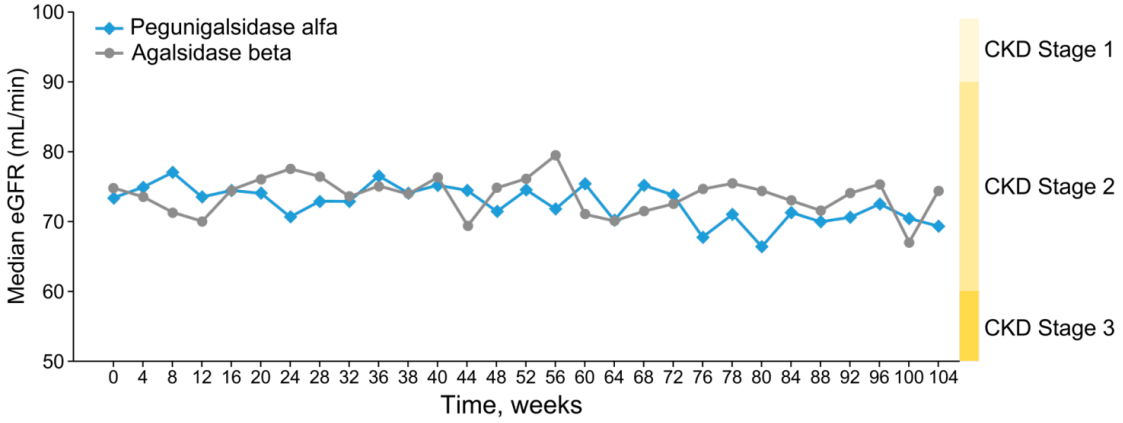
3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the BALANCE trial, PRX-102 was shown to be non-inferior (i.e. no less effective) to agalsidase beta in treating adults with FD with declining kidney function for 2 years, based on a key measure of FD progression as measured by kidney function (the median estimated glomerular filtration rate [eGFR] annualised slope, the study's primary endpoint).[23] At 2 years, eGFR slope was similar between the treatments (Figure 2). These results demonstrated no significant difference in efficacy between the treatments, and results were confirmed to be robust in supportive analyses.

Figure 2: Median eGFR values over time in the BALANCE trial: ITT population



Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{CKD\text{-}EPI}$, eGFR Chronic Kidney Disease Epidemiology Collaboration equation; ITT, intention to treat.
Source: Wallace et al. 2022.[23]

Patients in BALANCE remained stable for other measurements including additional markers of kidney function (urine protein–creatinine ratio and achievement of kidney function goals); markers of heart function (left ventricular mass index, echocardiogram readings), and markers of FD activity (e.g. plasma lyso-Gb3 level and the Mainz Severity Score Index).[22, 23] Stability was also reported in terms of pain experienced by patients as measured by the Brief Pain Inventory, and in terms of number of pain medications being taken.

In BRIGHT, patients were switched to PRX-102 for 1 year at the less-frequent dosing schedule of every 4 weeks, following at least 2 years of treatment with agalsidase alfa every 2 weeks or agalsidase beta every 2 weeks. After PRX-102 treatment, patients remained stable in terms of kidney function and in the FD marker plasma lyso-Gb3, as well as having improved or stable heart function, compared with baseline measurements.[24]

In BRIDGE, patients were switched to PRX-102 every 2 weeks following at least 2 years of treatment with agalsidase alfa every 2 weeks.[25] After 1 year on PRX-102, patients showed improvements in kidney function, sustained reductions in the FD marker plasma lyso-Gb3) and stable heart function

Results from studies in patients who have never received any ERT showed that 1 year of treatment with PRX-102 led to stable kidney and heart function.[26] [27, 28]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used, does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?
Please outline in plain language any quality of life related data such as **patient-reported outcomes (PROs).**
Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The EuroQol 5 Dimension 5 Level (EQ-5D-5L) is a generic questionnaire for measuring quality of life in the categories of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression was used in the PRX-102 studies. In BALANCE, most patients in both treatment arms reported improvement or no change in quality of life on all domains after 2 years of treatment.[22] Changes in the overall health score measured by the EQ-5D-5L over the study were small, with a slightly greater improvement with PRX-102 compared with agalsidase beta. BALANCE also reported an improvement or no change in pain severity in a greater proportion of patients receiving PRX-102 compared with those receiving agalsidase beta (73.3% vs 63.6%); additionally, a smaller proportion of patients receiving PRX-102 needed pain medication compared with patients receiving agalsidase beta (73.1% vs 88.0%). The Mainz Severity Score Index (MSSI)[29] was used within BALANCE to provide scores for general, neurological, cardiovascular, kidney, and overall assessments of symptom severity. In BALANCE, scores remained stable, with a minor

improvement in patients receiving PRX-102 and a minor worsening in patients receiving agalsidase beta (-2.1 vs +2.0).[22] Similar improvements in symptoms and quality of life were reported with PRX-102 in BRIGHT and BRIDGE.[30] [31]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies, etc.

PRX-102 has been studied in a comprehensive clinical trial programme in 142 patients with FD, including 117 patients receiving PRX-102 at a therapeutic dose (1 mg/kg or 2 mg/kg). The most common side effects were hypersensitivity, nausea and infusion-related reactions.[1] PRX-102 was well-tolerated in BALANCE, with no new safety concerns. Compared with agalsidase beta, the overall proportion of patients with side effects emerging during treatment was slightly lower, and the rate of events, when treatment exposure was accounted for, was notably lower. No side effects led to dose interruptions or changes within BALANCE, and there were no deaths. In particular, injection site reactions were less common with PRX-102 compared with agalsidase beta and all resolved without any aftereffects. Reactions related to infusion were also less common with PRX-102 than with agalsidase within 2 hours of completing the infusion. PRX-102, also led to a lower rate of anti-drug antibody production than agalsidase beta, which is an advantage because such antibodies may reduce a drug's effectiveness.[22, 23] Of the patients who had anti-drug antibodies after 2 years of treatment, patients receiving PRX-102 had a lower rate of neutralising antibodies compared with agalsidase beta (63.6% vs.100.0%). The Phase III trials BRIDGE and BRIGHT in the wider population and the Phase I/II trials in patients who had never received an ERT all reported a safety profile consistent with that seen in BALANCE.[22, 30, 31] [22, 23] [25] [24]

If you experience any side effects, you should talk to your doctor.[1]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

PRX-102 has been designed to be more stable in the body compared with existing ERTs, with a longer half-life (~80 hours vs up to 2 hours for agalsidase alfa/beta).[20-23, 26 32-34] PRX-102 has shown be non-inferior to the existing ERT, agalsidase beta, in the head-to-head BALANCE trial in terms of the kidney function measure, eGFR, which is an important measure of disease progression.[23] PRX-102 also showed similar efficacy to agalsidase beta in terms of another kidney function measure, proteinuria; the heart function measure, LVMI; markers of FD severity (plasma lyso-Gb3 and MSSI); and quality of life. PRX-102 showed a similar, well-tolerated safety profile to agalsidase beta in the BALANCE trial.[23] However, PRX-102 had a lower rate of infusion-related reactions than agalsidase beta, which is encouraging given that patients had previously received agalsidase beta for a long time, and these reactions are a major concern with ERTs and expected to be more common when starting a new biologic treatment.[23] Additionally, compared with existing ERTs, PRX-102 leads to a lower rate of anti-drug antibodies.[35, 36 23] Because these antibodies lower the drug's activity and potentially its clinical benefit, the ability of PRX-102 to reduce production of these antibodies may lead to improvements in long-term kidney and heart function in patients with FD.[22, 37]

Results from the BRIGHT study demonstrated that PRX-102, at the lower dose frequency (every 4 weeks instead of every 2 weeks), was well-tolerated with no safety issues and led to stable kidney function and plasma lyso-Gb3, a marker of FD, and resulted in improved or stable heart function.[24 30] PRX-102 is a suitable option for many patients, when used at the therapeutic dose (1 mg/kg or 2 mg/kg), having demonstrated efficacy and safety in 117 patients within clinical trials, including those with and without declining kidney function, and those with and without previous ERT treatment.[23 24 25 26 27, 28 38]

This less frequent dosing option of PRX-102 compared with other ERTs (every 4 weeks instead of every 2 weeks), may provide a convenience benefit for patients and caregivers alike, with the potential to provide patients with an additional 13 infusion-free days per year. The less frequent dosing administration may also have sustainability benefits,

including potential reductions in the need for travel of homecare nurses, and in plastic waste.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

There are no anticipated disadvantages of PRX-102 compared with the existing ERTs, agalsidase alfa and agalsidase beta. However, PRX-102, along with the other existing ERTs, does present the usual drawbacks associated with all infusions, when compared with the oral therapy migalastat. These include inconvenience to patients in having to potentially travel for treatment, potential for discomfort, pain and injection site reactions, and fear of the infusion process.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects FD

The cost-effectiveness model captures the progressive nature of FD by including health states for symptoms experienced in the early phase of the disease including pain, followed by health states for end-stage kidney disease, cardiac conditions and stroke. The model captures the fact that patients with FD are at an increased risk of experiencing these complications, which can have a significant impact on patients' quality of life, mortality risk and on healthcare resource use.

Health outcomes

PRX-102 has been shown to be a highly effective alternative treatment option, with the results from the BALANCE trial demonstrating that there are no significant difference in the efficacy and safety outcomes between the PRX-102 and agalsidase beta. PRX-102 has the potential to improve patients' quality of life with BALANCE showing that patients receiving the treatment had a slightly lower risk of experiencing treatment-related adverse events and infusion-related reactions. Additionally, there is the potential for patients to be offered the option to follow a dosing regimen that involves infusions every 4 weeks, which would allow patients to gain 13 additional infusion-free days per year.

Cost outcomes

Patients with FD are at a greater risk of experiencing significant complications such as end-stage kidney disease, strokes and cardiac complications, which result in high disease management costs. Therefore, the availability of an additional effective treatment option could result in cost savings for the health service, as well as improved quality of life and survival outcomes for patients. The potential for patients to receive an infusion every 4 weeks would significantly reduce the annual costs associated with treatment administration and free up additional NHS resources.

Uncertainty

Given the duration of the clinical trials was short, there is uncertainty regarding the long-term effectiveness of treatment in its ability to reduce the risk of patients developing long-term complications. However, multiple studies demonstrate that improvements in eGFR, as were observed in the PRX-102 clinical trials, are a strong indicator that the risk of long-term complications will be reduced.[39] The BALANCE trial also demonstrates that patients receiving PRX-102 have a lower risk of developing anti-drug antibodies, which have the potential to lessen the effectiveness of treatments over time.

Results

The results indicate that PRX-102 is no less effective than existing therapies. PRX-102 provided on a twice-weekly dosing regimen is anticipated to result in no additional costs to the NHS. The every-4-week dosing regimen could offer cost savings by reducing the resource burden of treatment administration. This dosing regimen is also associated with quality of life benefits for patients, halving the number of administration days per year.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative, please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see Section 3f).

PRX-102, when compared with existing ERTs, has been designed to be more stable in the body, remain active for longer, have an improved distribution in the body, and a lower risk of immune reactions leading to anti-drug antibodies.[20-23, 26] PRX-102 has demonstrated a lower rate of infusion-related reactions than agalsidase beta, which are a major concern with ERTs and expected to be more common when starting a new biologic treatment.[23] PRX-102 has also led to a lower rate of anti-drug antibodies than existing ERTs[35, 36 23], which may lead to better functioning of the kidney and heart over the long term.[22, 37] Because PRX-102 has a much longer half-life than other ERTs (mean of ~80 hours compared with up to 2 hours)[32-34], PRX-102 may be given less often than existing ERTs – every 4 weeks instead of every 2 weeks - offering improved patient convenience and the

potential to give patients an extra 13 infusion-free days per year. The innovative nature of PRX-102 has been endorsed in the UK by the Medicines and Healthcare products Regulatory Agency: PRX-102 received an Innovation Passport in August 2021 and is being assessed through the Innovative Licensing and Access Pathway.[40]

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme.

Find more general information about the Equality Act and equalities issues here.

No equality issues are expected.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials, etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE

- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: Guidance on Patient Involvement in HTA - EUPATI Toolbox
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: Health technology assessment: an introduction to objectives, role of evidence, and structure in Europe (who.int)

Further information on FD:

- British Inherited Metabolic Disease Group (BIMDG) Guidelines for the treatment of Fabry Disease
- Orphanet: Fabry disease

Information on PRX-102:

- BALANCE (head-to-head study versus agalsidase alfa in patients with declining kidney function who previously received agalsidase beta): Slide 1 (publicnow.com)
- BRIGHT (PRX-102 at less frequent dose [every 4 weeks] in patients with/without declining kidney function who previously received agalsidase alfa/beta): eP149: Safety and efficacy of pegunigalsidase alfa, every 4 weeks, in Fabry disease: Results from the phase 3, open-label, BRIGHT study - ScienceDirect
- BRIDGE (PRX-102 at standard dose [every 2 weeks] in patients with/without declining kidney function who previously received agalsidase alfa: PowerPoint Presentation (gcs-web.com); page 316 of Abstracts (wiley.com)
- Phase I/II studies (PRX-102 in patients with/without declining kidney function who had not previously received ERT): Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year Phase 1/2 clinical trial (wiley.com)
- Long-term Phase I/II study: eP148: Long-term safety and efficacy of pegunigalsidase alfa: A multicenter extension study in adult patients with Fabry disease - ScienceDirect
- Pooled safety study: Slide 1 (gcs-web.com)

4b) Glossary of terms

- ERT, enzyme replacement therapy: treatment manufactured to replace the naturally occurring alpha-galactosidase A enzyme, used in patients with FD who have limited or no alpha-galactosidase A. Current ERTs for FD are agalsidase and agalsidase beta; PRX-102 is a new ERT option
- Gb3, globotriaosylceramide: a fatty substance that builds up in cells in patients with FD, potentially leading to serious disease in vital organs; Gb3 is a marker of FD
- *GLA* gene: responsible for producing the enzyme alpha-galactosidase A, responsible for breaking down Gb3
- Infusion-related reaction: side effect of the ERT infusion; these include a wide range of symptoms but may include hypersensitivity, tingling, dizziness, headache, sneezing, chest pain, itchiness, nausea, etc.
- Anti-drug antibody: antibodies that the body produces as a reaction to a biologic drug (e.g. an ERT), which can limit effectiveness of the treatment
- eGFR, estimated glomerular filtration rate: an estimated measure of how well the kidneys are filtering; a low eGFR represents a greater extent of kidney impairment
- LVMI, left ventricular mass index: the calculated amount of left ventricular wall thickness and cavity size as assessed by an echocardiogram, and can be used as an indicator of heart function. High LVMI can lead to an increased risk of cardiac events (e.g. heart attack or stroke)
- EQ-5D-5L, EuroQol 5 Dimension 5 Level: questionnaire designed to measure quality of life, on domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text.

1. Chiesi. Summary of product characteristics. Elfabrio 2 mg/ml. 2022.
2. Orphanet. Fabry disease. 2022. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=324. Accessed: December 2022.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Fabry disease - pegunigalsidase alfa [ID3904]

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
ID3904 pegunigalsidase alfa for treating Fabry disease_clarification questions [AIC]	0.2	Yes	17 February 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Comparators

A1. Priority Question. The EAG's clinical experts consider the treatment choice in patients with an amenable mutation would not only be migalastat, instead agalsidase alfa and agalsidase beta may also be considered and used as treatment options. In addition, the EAG's clinical experts reported that they would expect pegunigalsidase alfa to be a treatment option for patients eligible for migalastat. The EAG therefore considers migalastat should also be included as a comparator to pegunigalsidase alfa. The EAG's clinical experts reported that the efficacy of pegunigalsidase alfa or ERTs would not be expected to differ based on mutation status and that they would consider migalastat, pegunigalsidase, and ERTs to be relevant treatment options in a population with an amenable mutation. Please provide an appropriate analysis to compare the treatment effectiveness of pegunigalsidase alfa with migalastat. Please provide results of this analysis for all efficacy and safety outcomes listed in the NICE final scope.

[Company: please enter your answer to this question here]

A2. Priority Question. Please provide further justification and analysis to support the strong assumption in the company submission that the treatment effectiveness of agalsidase beta and agalsidase alfa are equivalent (for example, by considering and interpreting the results of the head-to-head studies of these two treatments listed in Table 24 of the company submission). Please also provide a numerical estimate of the uncertainty around this assumption for the outcomes specified in the NICE final scope.

[Company: please enter your answer to this question here]

Pegunigalsidase alfa dose

A3. Priority Question. Please provide an analysis comparing the treatment effectiveness and safety of the 2 weekly (E2W) pegunigalsidase alfa treatment regimen with the 4 weekly (E4W) treatment regimen.

[Company: please enter your answer to this question here]

A4. Priority Question. Please explain any clinical rationale for using the E2W pegunigalsidase alfa treatment regimen rather than the E4W treatment regimen.

[Company: please enter your answer to this question here]

Subgroups

A5. Priority question. The EAG considers that the imbalance between males and females in the two trial arms of BALANCE could be important given feedback from the EAG's clinical experts about the severity of disease in these two groups. Please provide baseline and follow-up results for these two subgroups (per arm and the difference between groups) for the following additional outcomes:

a) **eGFR slope**

b) **LVMI as a measure of cardiac function**

c) **Exercise tolerance (stress test)**

d) **Pain severity (measured on BPI)**

e) **Frequency of pain medication use**

f) **MSSI scores**

g) **Occurrence of FCEs**

h) **Quality of life on the EQ-5D**

i) **Adverse events**

[Company: please enter your answer to this question here]

A6. Priority question. Subgroups based on sex and type of Fabry disease (classic vs non-classic) are also of interest because of potential imbalance across treatment arms in BALANCE and the potential difference between these subgroups in disease severity. Please provide baseline and follow-up results for these four subgroups (men with classic FD, women with classic FD, men

with non-classic FD and women with non-classic FD) for the following outcomes (per arm and the difference between groups):

a) **eGFR slope**

b) **LVMI as a measure of cardiac function**

c) **Exercise tolerance (stress test)**

d) **Pain severity (measured on BPI)**

e) **Frequency of pain medication use**

f) **MSSI scores**

g) **Occurrence of FCEs**

h) **Quality of life on the EQ-5D**

i) **Adverse events**

Applicability of BALANCE, BRIGHT and BRIDGE to relevant population

A7. The EAG notes that the evidence included in the submission for pegunigalsidase alfa is in people already using treatments and that treatment-naïve patients are not captured in the trials. Please comment on how generalisable the results of BALANCE, BRIGHT and BRIDGE are to treatment-naïve patients in the UK.

[Company: please enter your answer to this question here]

A8. The EAG notes that the BALANCE trial only includes people with deteriorating renal function and that this may not be a feature that all patients with FD have (e.g., those with the cardiac variant). Please comment on how this may impact the applicability of the BALANCE trial results to the whole population that would be eligible for pegunigalsidase alfa in clinical practice in the UK if it were to be recommended.

[Company: please enter your answer to this question here]

Systematic literature review and indirect comparison feasibility assessment

A9. Priority Question. Please provide a list of the 3 included RCTs identified in the clinical systematic literature review (SLR) that were deemed not relevant to the scope and missing from the Company submission Appendix D.1 Table 8 including the rationale for why they were deemed not to be relevant.

[Company: please enter your answer to this question here]

A10. Please provide a list of the 164 included studies for the clinical SLR that was performed based on searches in Appendix D.1 of the company submission, highlighting which studies were included in the company submission and providing the reason for exclusion of each of the remaining studies not included in the company submission. Please include in this list any migalastat studies that were identified but excluded.

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("Controls" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Comparators

B1. Priority question: As outlined in clarification question A1, clinical expert opinion provided to the EAG suggests that migalastat is not the only treatment option for patients with an amenable mutation. The EAGs clinical experts considered that ERTs and pegunigalsidase alfa would be considered

appropriate treatment options for patients with Fabry disease independent of amenable mutation status. As ERTs can therefore be seen as alternatives for migalastat by clinicians and vice-versa, the EAG believes that migalastat should be included in the submission as an additional comparator. Therefore, based on the response to A1, please conduct a cost utility analysis including migalastat as a comparator to pegunigalsidase alfa and agalsidase alpha and beta, utilising the committee's preferred assumptions in HST4. The EAG notes that a disutility for infusions was deemed reasonable by committee, which should be included in the company's cost-utility analysis

[Company: please enter your answer to this question here

Baseline characteristics

B2. The EAG's clinical experts advised that by age 40, there will be a proportion of FD patients who will have had multiple complications. Please clarify why the baseline health state distribution of patients in the model did not include the multiple complication health states?

[Company: please enter your answer to this question here]

B3. Priority question: Please provide the baseline health state distribution of patients from BALANCE, including patients with multiple complications, and implement these data in a scenario analysis.

[Company: please enter your answer to this question here]

B4. Priority question: Please provide the mean weight from BALANCE and provide a scenario analysis using these data.

a) **Please provide the overall mean weight from a pooled assessment of BALANCE, BRIDGE and BRIGHT and provide a scenario analysis using these data.**

[Company: please enter your answer to this question here]

B5. Priority question: Please clarify what severity of pain is assumed for the pain health state on the BPI scale.

[Company: please enter your answer to this question here]

Treatment effectiveness

B6. Priority question: As the company has submitted pegunigalsidase alfa for appraisal as an STA, the base case should be a cost utility analysis and a cost-minimisation should be presented as a scenario. Furthermore, when adopting a cost-utility approach, probabilistic sensitivity analysis should assess the impact of uncertainty in all parameters used in the model.

The EAG is concerned that the economic model fails to incorporate any of the uncertainty captured in the pivotal BALANCE trial. For example, the transition probabilities included in the economic model do not explicitly include a treatment effect that can be adapted to include the treatment effect observed in BALANCE. Thus, uncertainty around the treatment effect for pegunigalsidase alfa cannot be captured in the economic model via the probabilistic sensitivity analysis (PSA). These transition probabilities have also not been included in the PSA.

The NICE methods guide recommends that the committee's preferred cost-effectiveness estimate should be derived from a probabilistic analysis when possible, unless the model is linear. Therefore, this failure of the model to account for the uncertainty in the trials is directly impactful to decision making. As such, the EAG considers the PSA results provided by the company do not robustly capture the uncertainty associated with the fundamental assumption of clinical equivalence of ERTs in the model. Please consider adapting the model such that the uncertainty around the treatment effect from BALANCE is included in the model and the PSA.

[Company: please enter your answer to this question here]

Transition probabilities

B7. Priority question: The costs for health state events (Table 54) includes the assumption that 27% of FD patients will receive a renal transplant; however,

the economic model doesn't allow for transition from any ESRD related health state to any non ESRD related health state.

a) **Please discuss the clinical validity of applying the HRQoL values associated with ESRD to 27% of patients in the model who have had a kidney transplant.**

b) **Please adjust the model to allow for transition to non-ESRD health states following renal transplants.**

[Company: please enter your answer to this question here]

B8. Priority question: Clinical expert opinion provided to the EAG is that Fabry disease is a progressive condition which leads to the accumulation of symptoms before death. The economic model outlines a disease epidemiology where although transition to a more progressive and complex health state is possible, it is severely limited (all probabilities are less than 0.01).

a) **Please comment on the clinical validity of these transition probabilities given the nature of the disease as a progressive disorder.**
b) **As a scenario analysis please calculate and utilise transition probabilities estimated from the newer registry studies as highlighted by the company in the CS (p.132).**

[Company: please enter your answer to this question here]

Adverse events

B9. Priority question. Infusion reactions have not been included in the list of adverse events (AEs) in Table 29. Please outline the number of infusion reactions in each arm of the BALANCE trial and incorporate it into the economic model.

[Company: please enter your answer to this question here]

Health-related quality of life

B10. Priority question: The NICE decision support unit (DSU) recommends that general population utilities adjusted for age and sex are derived from the HSE

2014 dataset. Please update the model to use general population utility values adjusted for age and sex based on the HSE 2014 dataset.

[Company: please enter your answer to this question here]

B11. Priority question: In Section B.3.4.1 of the company submission, the company describes the BALANCE regression analysis used to estimate health state utility values for the model, but does not provide further information on the final regression model nor the results of the analysis.

a) **Please provide the final regression model used to estimate health state utility values from BALANCE.**

b) **Please provide the results and health state utility values estimated from the final regression model and implement these data in a scenario analysis. When adapting the model for the scenario, please ensure variance around the utility estimates from BALANCE can be explored using the model PSA. Where utility values cannot be calculated for specific health states due to missing or incomplete data please use the utilities from the company's base case.**

[Company: please enter your answer to this question here]

B12. Priority question: Expert clinical opinion provided to the EAG details that HRQoL values for those in health states associated with three symptoms (i.e. stroke, cardiac complications and pain) would be lower than those in two symptom health states. In addition, there would be HRQoL differences between the two symptom health states, as seen in the differences between the single symptom health states. Please recalculate the health state utility values (HSUVs), providing a scenario analysis where the three-symptom health state has the lowest utility value and there is a difference in HSUVs between the health states with two symptoms.

[Company: please enter your answer to this question here]

B13. Priority question: For the scenario exploring AEs, only costs have been included, aligned with the base case approach of cost-minimisation analysis.

As part of the cost-utility analysis, please provide a scenario where disutilities associated with AEs are included.

[Company: please enter your answer to this question here]

Mortality

B14. Priority question: The CS describes how in HST4 the background mortality applied in the model was too low, leading to patients having an unrealistically high life expectancy. The company has therefore adjusted the transition probabilities to death to account for the reduced life expectancy of those with Fabry disease. Please;

a) **Describe how mean life expectancy of male and females in the economic model has been calculated as the EAG has been unable to validate the company's estimates as outlined in the CS.**
b) **Describe how the transition probabilities to death have been adjusted from the values reported in Rombach *et al.* to decrease life expectancy.**

[Company: please enter your answer to this question here]

Resource use and costs

B15. In Table 54 of the company submission, please clarify why no weighting is given for patients with CKD stages 1-4.

[Company: please enter your answer to this question here]

B16. Priority question: The EAG's clinical experts considered that for the E4W pegunigalsidase alfa regimen, the number of infusions at the initial duration should be the same as the E2W (six infusions) as it is related to safety and not frequency of administration. As such, please supply an alternative scenario for the E4W regimen, where the number of infusions at the initial duration is six.

[Company: please enter your answer to this question here]

B17. Priority question: The EAG's clinical experts advised that the majority of patients require nurse assistance to administer their infusions at home and few patients would be fully independent when administering their infusion.

Please run a scenario where 90% of patients require a nurse to administer their infusions at home and 10% self-administer treatment.

[Company: please enter your answer to this question here]

B18. Priority question: Expert clinical opinion provided to the EAG suggests that the assumed yearly Health Care Professional follow-up figures (Table 55 in the CS) may not reflect UK clinical practice. In particular, the 18.5 annual physiotherapist visits for those with other complications (ESRD and stroke), the 5.4 physiotherapist sessions for pain and the inclusion of social workers which would not be provided by the NHS. The CS highlights a recent linked database analysis by Malottki *et al.* conducted in 2022, which identified that the average FD patient in England will have 9.4 consultations with health care professionals per year, of which 5.6 would be GP appointments. This information contradicts the data presented in Table 55 of the CS, which reports 3.5 GP appointments each year and 5.5 visits with other health care professionals. Given the information from the study please;

a) **Justify the underestimated yearly GP appointments, overestimation of follow up from other healthcare professionals, the grouping of ESRD and stroke under the single complications column and inclusion of social workers.**
b) **Conduct a scenario analysis using the mean yearly follow-up figures as outlined in Malottki *et al.* and remove resource associated with social workers.**

[Company: please enter your answer to this question here]

B19. The EAG consulted with its clinical expert regarding the weighting of health state events (Table 54 in the CS), they highlighted differences to what they would expect in UK clinical practice. As a scenario analysis, please change the weighting for patients requiring a pacemaker to 5%, myocardial infarction to 10%, cardiac congestion requiring hospitalisation to 10%, percutaneous coronary intervention to 5%, and implantable cardiac defibrillator to 5%.

[Company: please enter your answer to this question here]

B20. Priority question: The EAG consulted with its clinical experts regarding FD management resource use assumptions included in the model. In particular, it was noted that plasma Lyso-Gb3, assay for alpha-galactosidase A Ab, GL-3G and Lyso-GL-3G and antibody test & neutralizing assays are not provided by the NHS. Please provide two scenarios using the following FD management resource use assumptions provided in the below table.

Health care professional	Annual frequency (scenario 1)	Annual frequency (scenario 2)
Full blood count	2.38	1.00
Urine test	2.75	1.00
ECG	1.00	1.00
Liver function test	2.00	1.50
Fasting lipid profile	2.00	1.00
2D echocardiography with Doppler	0.63	0.63
Glomerular filtration rate	2.13	0.5
24 hour urine protein / creatinine	0.08	0.08
Exercise testing	0.21	0.21
Renal USS	0.06	0.06
MRI	0.50	0.23
Audiogram	0.63	0.63
Plasma Lyso-Gb3	0.00	0.00
Assay for alpha-galactosidase A Ab	0.00	0.00
GL-3G and Lyso-GL-3G	0.00	0.00
Holter	1.17	0.50
Antibody test & neutralizing assay	0.00	0.00

[Company: please enter your answer to this question here]

B21. Priority question: Complication follow up costs have been included in the model ("HCRUs", cells C113:K117) but the assumptions underpinning the costs have not been described in the company submission. Please describe the complication follow up costs that have been included in the model, justifying any assumptions that have been made.

[Company: please enter your answer to this question here]

B22. Priority question: Terminal care costs have been included in the model but the assumptions underpinning the costs have not been described in the company submission. Please describe the terminal care costs that have been included in the model, justifying any assumptions that have been made.

[Company: please enter your answer to this question here]

Probabilistic sensitivity analysis

B23. Priority question: Please clarify why health state transition probabilities were not varied in the PSA. Please include the transition probabilities in the PSA.

[Company: please enter your answer to this question here]

B24. Priority question: Please justify the exclusion of health state utility values from the PSA. Please provide PSA results where health state utilities are included in the analysis.

[Company: please enter your answer to this question here]

B25. Priority question: A Dirichlet distribution has been used in the PSA for the baseline patient distribution input parameters in the model. However, the formula for the lower and upper bounds are the same. Please clarify if the Dirichlet has been implemented correctly, as the formula for alpha in the model is mean*n + 0.05 and beta hasn't been calculated.

[Company: please enter your answer to this question here]

Systematic literature review

B26. The company reports that the cost-effectiveness, HRQoL and cost evidence searches were run in May 2021. Please justify why an update search was not performed for the economic information systematic literature reviews (SLRs).

[Company: please enter your answer to this question here]

B27. Priority question: ERT as a blended comparator was an exclusion criteria for the cost-effectiveness SLR as such, the study by Rombach *et al*. 2013 was used to inform the transition probabilities was not identified.

a) **Please clarify how many studies were excluded based on blended ERT as the intervention?**
b) **Please discuss if any of these studies met the remaining inclusion criteria and provide title and abstract for those studies.**
c) **Please discuss if any of the studies that met the remaining inclusion criteria were published more recently than Rombach *et al.* 2013 and, if relevant, more recent data may be available to inform transition probabilities in the model.**

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

C1. In the company submission (pg. 127), it is stated that the market share for agalsidase alfa and agalsidase beta is 70% and 30%, respectively. However, in the economic model, the market share for agalsidase alfa and agalsidase beta is 30% and 70%, respectively. Please clarify if the model has the correct market share values and amend where necessary.

[Company: please enter your answer to this question here]

C2. In the economic model, the source for mean weight (tab “controls”, cell J36) is BALANCE, BRIGHT & BRIDGE. However, in Table 38 of the company submission, the source of mean weight is Malottki *et al.* Please clarify if Malottki *et al.* is the correct source of mean weight.

[Company: please enter your answer to this question here]

C3. The standard deviation (SD) of mean weight in Malottki et al is 20.4 but in the model 18.5 is used (with the source listed as BALANCE, BRIDGE & BRIGHT). Please clarify if the mean weight SD in the model is correct and amend if necessary.

[Company: please enter your answer to this question here]

C3. In Table 34 and 38 of the company submission, it is stated that the average life expectancy of females with Fabry disease is 74.7 years, sourced from Waldek *et al.* 2009. However, in the publication, it states that the female life expectancy is 75.4 years. Please correct the model as necessary.

[Company: please enter your answer to this question here]

C4. The EAG considers that the data for proportion males and baseline health state distribution presented in Table 38 of the company submission have been sourced from the ERG report for HST4 (Table 46, original source: Eng *et al.* Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis. 2007; 30(2): 184-92). Please clarify if the cited source (Waldek *et al.* 2009) is correct.

[Company: please enter your answer to this question here]

C5. In Table 45 of the company submission, the baseline utility from BALANCE is 0.762, but in the model a value of 0.74 has been used. Please clarify if the baseline utility value in the model is correct and amend if necessary.

[Company: please enter your answer to this question here]

C6. In Table 54 of the company submission, the total annual cost of “other symptoms” is £1,793 but in the model is £2,463. Please clarify if the company submission is correct and amend if necessary.

[Company: please enter your answer to this question here]

C7. Table 15 of the company submission suggests that the difference in means between PRX-102 and agalsidase beta is identical for males and females,

regardless of whether hypertrophy is present at baseline. Should the values for those without hypertrophy at baseline (given below as in the submission) be corrected?

PRX-102 – agalsidase beta: difference in means (95% CI), males: [redacted]
PRX-102 – agalsidase beta: difference in means (95% CI), females: [redacted]

[Company: please enter your answer to this question here]

C8. In Table 28 of the company submission:

a) The number of patients with mild or moderate TEAEs in BALANCE [redacted] the number of patients with any TEAEs, in both treatment arms [47 (90.4) vs 24 (96)]. Is this correct or should this be amended?
b) The same is also observed for the number of patients with any treatment-related AEs and mild or moderate treatment-related AEs in this table [21 (40.4) vs 11 (44.0)]. Please confirm if this is correct.

[Company: please enter your answer to this question here]

C9. The EAG notes that the baseline values for the BALANCE trial presented in the company submission (Table 8) for the following outcomes do not match baseline values reported in the CSR (Table 11.3). Please clarify why these values differ or correct as appropriate:

a) mean eGFR slope at baseline (both arms and overall);
b) mean eGFR score at baseline (both arms and overall).

[Company: please enter your answer to this question here]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Fabry disease – pegunigalsidase alfa [ID3904]

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
ID3904 PRX-102 for treating FD_clarification questions_03March2023_[ACIC]_readacted	0.3	Yes	7 March 2023

Notes for company

Highlighting in the template

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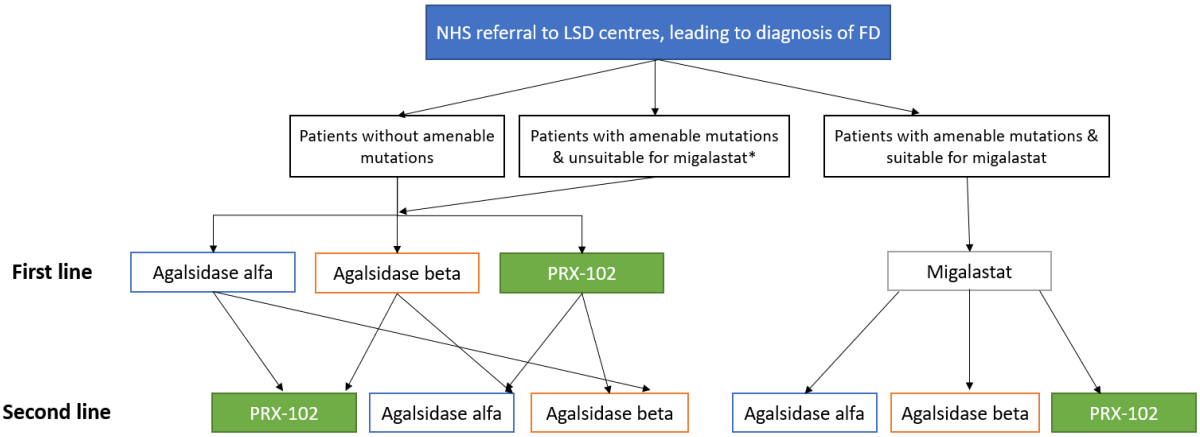
Section A: Clarification on effectiveness data

Comparators

A1. Priority Question. The EAG's clinical experts consider the treatment choice in patients with an amenable mutation would not only be migalastat, instead agalsidase alfa and agalsidase beta may also be considered and used as treatment options. In addition, the EAG's clinical experts reported that they would expect pegunigalsidase alfa to be a treatment option for patients eligible for migalastat. The EAG therefore considers migalastat should also be included as a comparator to pegunigalsidase alfa. The EAG's clinical experts reported that the efficacy of pegunigalsidase alfa or ERTs would not be expected to differ based on mutation status and that they would consider migalastat, pegunigalsidase, and ERTs to be relevant treatment options in a population with an amenable mutation. Please provide an appropriate analysis to compare the treatment effectiveness of pegunigalsidase alfa with migalastat. Please provide results of this analysis for all efficacy and safety outcomes listed in the NICE final scope.

As noted within B.1.3.4.2 and Figure 1 of the submission (and presented below), PRX-102 is positioned as an additional treatment option for adults with FD *who would be treated with an ERT*. This would include patients who are treatment-naïve who would usually be treated first-line with agalsidase alfa or agalsidase beta, and those previously treated with currently available therapies, as second-line to agalsidase alfa, agalsidase beta or migalastat. The eligible patient population would therefore include patients without an amenable mutation, and also those with an amenable mutation, but only if those amenable patients were unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). For the small number of patients who are suitable but choose not to receive migalastat, their current choice of treatment is therefore only ERT (agalsidase alfa or agalsidase beta), and the introduction of PRX-102 would provide these patients with an additional ERT treatment option.

Figure 1: Proposed place of PRX-102 in the treatment pathway



Key: FD, Fabry disease; LSD, lysosomal storage disorder.
Notes: *, unsuitable due to issues with adherence, tolerance, patient/clinician choice, or any other reason.

This positioning was agreed by the clinical experts from 4 of the 5 treating specialist LSD centres in the UK who attended the advisory board carried out during the development of the PRX-102 submission.[1] In addition, this positioning was independently validated by 3 UK clinical experts who were consulted by the Commercial Medicines Directorate at NHS England during the development of their budget impact analysis, as their report noted that "*The clinical community consider patients on agalsidase alfa or agalsidase beta would be eligible to switch to pegunigalsidase alfa, this is because they are enzyme replacement treatments. Patients on migalastat would not be considered for switching to pegunigalsidase alfa due to mutation type and no additional benefit of moving from an oral to intravenous treatment. New diagnosed Fabry disease patients requiring enzyme replacement treatment would be offered pegunigalsidase alfa first line ahead agalsidase alfa and agalsidase beta where clinically appropriate*"[2]

The clear clinical positioning of PRX-102 in patients who would usually be treated with an ERT means that migalastat is no longer considered a comparator in this appraisal, and as such clinical and economic analyses comparing PRX-102 with migalastat are not presented.

A2. Priority Question. Please provide further justification and analysis to support the strong assumption in the company submission that the treatment effectiveness of agalsidase beta and agalsidase alfa are equivalent (for example, by considering and interpreting the results of the head-to-head studies of these two treatments listed in Table 24 of the company submission). Please also provide a numerical estimate of the uncertainty around this assumption for the outcomes specified in the NICE final scope.

As stated in Section B2.9.3 in Document B, we assume that PRX-102 E2W demonstrates equivalent efficacy to both agalsidase alfa and agalsidase beta, as follows:[3, 4]

- BALANCE provides head-to-head data vs. agalsidase beta showing non-inferiority of PRX-102 E2W to agalsidase beta E2W
- BRIDGE provide supportive switch-over evidence that shows patients treated with PRX-102 E2W after switching from agalsidase alfa and beta show stable renal function
- The assumption of clinical equivalence between agalsidase beta and agalsidase alfa is further supported by several SLRs and meta-analyses that provide no evidence that one of the existing ERTs is superior to the other[5-7]
- Furthermore, an independent international retrospective cohort study of 387 patients (192 females) found no difference in Fabry clinical events or eGFR slope in patients treated with agalsidase alfa or beta with a median follow-up of 4.9 years (range, 0.8–14.4 years)[8]
- The NICE HST4 appraisal accepted the assumption of clinical equivalence of agalsidase beta and agalsidase alfa
- In addition, a naïve comparison between BALANCE and BRIDGE suggested there were no significance differences in PRX-102 efficacy for key outcomes of interest between the studies, adding further evidence that the efficacy demonstrated in BALANCE was reflective of the efficacy of PRX-102 in other studies (see Appendix D.1.3.1), although the analyses are limited due to small patient populations and differing baseline characteristics such as sex and age
- In an advisory board, the 4 UK clinical experts consulted considered that the non-inferiority conclusion from BALANCE and the precedent in HST4 would be

supportive of clinical equivalence of PRX-102 to the existing comparator treatments.[1]

The two studies listed in Table 24 of Document B that provide head-to-head comparisons of agalsidase alfa and agalsidase beta are Vedder 2007[9] and Sirrs 2014.[10] In addition, the independent international retrospective cohort study mentioned above (Arends et al, 2018) also reported outcomes for agalsidase alfa or beta. The studies reported the following:

- Sirrs et al, 2014: A total of 92 patients who ERT naïve were randomised to either agalsidase alfa 0.2 mg/kg E2W or agalsidase beta 1.0 mg/kg E2W. The study observed no statistical difference in endpoints between the agalsidase alfa and agalsidase beta arms (HR alfa versus beta 1.29; p=0.67) but the power was noted to be limited. There was no significant difference in the proportion of patients receiving agalsidase alfa or agalsidase beta (19.4% vs 13.3%; p=0.57) that met the composite clinical endpoint (renal events [development of end-stage renal disease OR decline in GFR of 50% or greater, sustained for 30 days and excluding other causes], cardiovascular events [pacemaker or other intracardiac device, coronary artery bypass grafting, valve replacement surgery, coronary angioplasty or stent, cardioversion, hospitalization or emergency room visit for unstable angina/acute coronary syndrome, myocardial infarction, congestive heart failure, tachy- or brady-arrhythmia, heart block, cardiac arrest], cerebrovascular event [TIA or stroke documented by a physician or acute hearing loss], or death)
- Vedder et al, 2007: A total of 34 patients with FD were randomised to either agalsidase alfa 0.2 mg/kg E2W or agalsidase beta 0.2 mg/kg E2W within an open-label trial. The authors concluded that the study revealed no difference in reduction of LVM or other disease parameters after 12 and 24 months of treatment with either agalsidase alfa or beta at a dose of 0.2 mg/kg E2W. Treatment failure occurred frequently in both groups and seemed to be related to age and severe pre-treatment disease.
- Arends et al, 2018: In an independent international retrospective cohort study, 387 patients were treated with agalsidase alfa 0.2 mg/kg E2W or agalsidase beta 1.0 mg/kg E2W. The study reported no difference in Fabry clinical events or eGFR

slope in patients treated with agalsidase alfa or beta with a median follow-up of 4.9 years.

Although we do not have a specific numerical estimate of uncertainty around the assumption of equivalence between agalsidase alfa and beta within the current appraisal, the estimates of uncertainty when comparing agalsidase alfa and beta within the aforementioned studies for the outcomes specified in the NICE final scope are presented in Table 1. Note that Sirrs et al, 2014 did not provide any estimates of uncertainty for the agalsidase alfa and beta comparison.

Table 1: Comparisons of agalsidase alfa and agalsidase beta from published literature on various outcomes

Comparison between agalsidase alfa vs agalsidase beta		
Outcome	**Vedder et al, 2007**	**Arends et al, 2018**
LV mass	Median change in LV mass: -11% vs -15% (p=0.3) after 12 months; data were consistent for 24 months	Not reported
LVMI	Not reported	Change in LVMI in patients with LVH: $\beta_{alfa\text{-}beta}$: −2.26 g/m$^{2.7}$ (95% CI: −5.39 to 0.87); P=0.15
eGFR	Change in median eGFR: 5 ml/min vs 5 ml/min (p-value not reported)	Difference in eGFR slope between alfa and beta: • For patients with baseline eGFR ≥60: −0.12mL/min/1.73m^2/year (95%CI −0.76 to 0.51); P=0.70 • For patients with baseline eGFR <60: −0.85mL/min/1.73m^2/year (95%CI −2.31 to 0.62); P=0.26
Urinary protein (proteinuria)	• Change in urinary protein after 12 months: from 0.25 g/24h to 0.30 g/24h vs from 0.24 g/24h to 0.20 g/24h (p-value for change between groups: 0.16) • Change in urinary protein after 24 months: from 0.25 g/24h to 0.27 g/24h vs from 0.24 g/24h to 0.15 g/24h (p-value for change between groups: 0.33)	Not reported
Fabry clinical events	Not reported	26% vs 27%; event rate for alfa vs beta stratified for sex and phenotype and adjusted for age at initiation of ERT and baseline eGFR: HR: 0.96 (95%CI 0.59 to 1.57); P=0.87 Sensitivity analyses: • Addition of a decrease in eGFR of ≥33% and increase in LVMI of ≥20% to the definition of clinical events: HR 0.84 (95%CI 0.55 to 1.29); P=0.44 • Impact of inclusion of LVMI as covariate: HR 0.94 (95%CI 0.55 to 1.59); P=0.81 • Impact of exclusion of patients with a renal event before treatment initiation: HR 0.84 (95% CI: 0.50 to 1.40); P=0.50

Comparison between agalsidase alfa vs agalsidase beta		
		• Cox regression analysis in which 188 patients were matched 1:1: HR 0.98 (95%CI 0.55 to 1.77); P=0.95
Pain	Reduction of pain score (BPI-3) after: • 12 months: 0 vs -1.5 • 24 months: same as for 12 months	Not reported
Urinary GL3	Median decrease in GL-3 in patients with elevated baseline levels after 12 months: 284 nmol/24h vs 265 nmol/24h (p = 0.65)	Not reported
Plasma GL-3	Decrease in plasma GL-3 in patients with elevated baseline levels after 12 months: 2.56 vs 1.84 (p = 0.46)	Not reported
Lyso Gb3	Not reported	Decrease in lysoGb3 after adjustment for baseline lysoGb3 concentration, sex and phenotype: • Males with classic FD: ($\beta_{alfa\text{-}beta}$: −18.06nmol/L (95%CI −25.81 to −10.03); P<0.001 • Other patients (females and non-classic males),: $\beta_{alfa\text{-}beta}$: −1.07nmol/L (95% CI −2.04 to −0.11); P=0.03
Antibodies	• Antibodies in males: 4/8 (50%) vs 6/8 (75%) (p = 0.3) • Antibodies in females: none • Antibody titres at 6 months in treated males: 1/64 to 1/32768 vs 1/256 to 1/16384 • Patients with a decline in antibody titre after 12 months: 0 vs 2/6 (33.3%)	Patients with persistent antibodies for alfa vs beta: 11/39 (28%) vs 22/42 (52%); OR 2.8 (95% CI 1.02 to 7.88); P=0.041
IRRs	IRRs in antibody positive males: 1/4 (25%) vs 2/6 (33.3%)	Not reported
AEs	AEs: 2/18 vs 5/16 (risk ratio reported in secondary analysis in El Dib, 2016: 0.36 [95% CI 0.08 to 1.59)[5] SAEs: 1/18 vs 3/16 (risk ratio reported in secondary analysis in El Dib, 2016: 0.30 [95% CI 0.03 to 2.57]) [5] Mild-moderate AEs: low, did not differ between groups	Not reported

Comparison between agalsidase alfa vs agalsidase beta		
Cardiac events	Reported within secondary publication by El Dib, 2016: [5] 1/15 vs 2/14: risk ratio 0.47 (95% CI: 0.05, 4.6)	Not reported
Death	Reported within secondary publication by El Dib, 2016:[5] 1/18 vs 0/18: risk ratio 3 (95% CI: 0.13, 69.09)	Not reported

Additionally, 3 systematic reviews and meta-analyses reported comparisons of agalsidase alfa and beta as follows:

- El Dib et al, 2016:[5] this systematic review and meta-analysis reported that there was no evidence identifying that the alfa or beta form is superior (note that results from the analyses are reported as secondary analyses of the Vedder, 2007 paper in Table 1 above)
- Lidove et al, 2010:[6] This literature review did not reveal any clear differences in clinical responses among patients treated with agalsidase alfa or agalsidase beta
- Pisani et al, 2017:[11] This systematic review and meta-analysis studies the impact of the switch from agalsidase beta to agalsidase alfa, given a shortage of agalsidase beta, thereby allowing a comparison of the two drugs. The study concluded that switching to agalsidase alfa does not worsen renal and cardiac function or FD-related symptoms, at least in the short term. Quantitative synthesis was conducted for the following endpoints with results of the impact of the switch from agalsidase beta to alfa (mean change from baseline) as follows:
  - eGFR (n=7 studies): −0.52ml/min/1.73 m^2 (95% CI: −3.22 to 2.19); p=0.708
  - Urine albumin-to-creatinine ratio (n=3 studies): −7.67 (95% CI: −49.66 to 34.31); p= 0.721
  - LVMI (n=6): −4.2g/m^2 (95% CI: −8.66 to −0.25); p<0.034
  - Left ventricular posterior wall dimension (LVPWD; n=3 studies): −0.69mm (95% CI: −1.02 to -0.36); p<0.001
  - Ejection fraction (n=3 studies): −3.51 (95% CI: −6.55; −0.48); p=0.023

Pegunigalsidase alfa dose

A3. Priority Question. Please provide an analysis comparing the treatment effectiveness and safety of the 2 weekly (E2W) pegunigalsidase alfa treatment regimen with the 4 weekly (E4W) treatment regimen.

PRX-102 received a positive opinion from the EMA CHMP on 23 Feb 2023 for the long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase). At this time, only the 1mg kg E2W dose is included in the posology section of the label.[12] The inclusion of an alternative E4W posology in the label will be addressed in the post-approval setting,

in accordance with regulatory procedure. As such the E4W posology is no longer in scope of this appraisal. The final SmPC is included for your reference.

A4. Priority Question. Please explain any clinical rationale for using the E2W pegunigalsidase alfa treatment regimen rather than the E4W treatment regimen.

See response to A3.

Subgroups

A5. Priority question. The EAG considers that the imbalance between males and females in the two trial arms of BALANCE could be important given feedback from the EAG's clinical experts about the severity of disease in these two groups. Please provide baseline and follow-up results for these two subgroups (per arm and the difference between groups) for the following additional outcomes:

a) **eGFR slope**

b) **LVMI as a measure of cardiac function**

c) **Exercise tolerance (stress test)**

d) **Pain severity (measured on BPI)**

e) **Frequency of pain medication use**

f) **MSSI scores**

g) **Occurrence of FCEs**

h) **Quality of life on the EQ-5D**

i) **Adverse events**

Table 2 includes data outcomes listed in question A5 for the sub-groups of males and females. However, it should be noted that whilst subgroup analyses can be a valuable tool, there are certain circumstances in which they may not be appropriate. One such circumstance is when randomization is not stratified by relevant subgroups

of interest, such as sex in the BALANCE trial. Without proper randomization, the distribution of confounding factors between treatment groups can become uneven, leading to biased estimates of treatment effects. Moreover, the validity of subgroup analyses is also dependent on having a sufficiently large sample size within each subgroup. However, in the BALANCE trial, there are only a small number of patients when split by treatment group and sex (all groups have less than 30 patients). This small sample size can result in statistical instability and imprecise estimates of treatment effects, rendering subgroup analyses unreliable.

Table 2: BALANCE: clinical outcomes in males and females[13]

	PRX-102		**Agalsidase beta**	
Gender	**Male**	**Female**	**Male**	**Female**
a) eGFR Slope (mL/min/1.73 m^2/year)				
N	29	23	18	7
Baseline				
n	29	23	18	7
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint (using quantile regression for the median)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
b) LVMI (g/m^2) for patients with hypertrophy at baseline				
Baseline				
n	8	4	7	2
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint: Week 104				
n	5	4	5	2
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]

	PRX-102		Agalsidase beta	
Gender	**Male**	**Female**	**Male**	**Female**
Change from baseline: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
b) LVMI (g/m^2) for patients without hypertrophy at baseline				
N	29	23	18	7
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
b) LVMI (g/m^2) for patients with missing evaluation at baseline				
Endpoint: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
c) Exercise tolerance test (Normal stress test): Overall impression				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]

	PRX-102		Agalsidase beta	
Gender	**Male**	**Female**	**Male**	**Female**
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
d) Pain severity (measured as BPI)				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
e) Frequency of pain medication use: Number of subjects with at least one pain medication				
Endpoint: At any time during the study				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
f) Mainz severity score index (MSSI): Overall score				
Baseline				
n	26	23	18	7
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]

	PRX-102		Agalsidase beta	
Gender	**Male**	**Female**	**Male**	**Female**
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
g) Occurrence of Fabry clinical events (FCEs)				
Endpoint: At any time during the study				
Any FCE				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac Events				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular Events				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Renal Events				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac related Death				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
h) Quality of life on the EQ-5D				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint: Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

	PRX-102		Agalsidase beta	
Gender	**Male**	**Female**	**Male**	**Female**
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
i) Treatment emergent adverse events				
Endpoint: Week 104				
Any adverse event				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any drug related adverse event				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any severe adverse event				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any drug related severe adverse event				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any serious adverse event				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any drug related serious adverse event				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Keys: BPI, Brief pain inventory; CI: Confidence interval; eGFR, estimated glomerular filtration rate; LVMI, Left ventricular mass index; Min, minimum; Max, maximum; NA, not applicable; SD, Standard deviation; SE, Standard error

Note: 1. Percentages were calculated on the number of subjects (N).

2. For the number of patients with at least one Fabry Clinical Event, patients who had more than one type was counted only once

3. Patients with event classified as “Very Severe” per CTCAE severity in eCRF are presented in the category “Severe”.

Source: Chiesi Data on File - Additional Analyses from BALANCE[13]

A6. Priority question. Subgroups based on sex and type of Fabry disease (classic vs non-classic) are also of interest because of potential imbalance across treatment arms in BALANCE and the potential difference between these subgroups in disease severity. Please provide baseline and follow-up results for these four subgroups (men with classic FD, women with classic FD, men with non-classic FD and women with non-classic FD) for the following outcomes (per arm and the difference between groups):

a) **eGFR slope**

b) **LVMI as a measure of cardiac function**

c) **Exercise tolerance (stress test)**

d) **Pain severity (measured on BPI)**

e) **Frequency of pain medication use**

f) **MSSI scores**

g) **Occurrence of FCEs**

h) **Quality of life on the EQ-5D**

i) **Adverse events**

Within the BALANCE study, all female patients in the trial were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic: 27/29 (93.1%) in PRX-102 arm and 14/18 (77.8%) in the agalsidase beta arm. Thus, the additional data included for all-comer female patients presented in response to question A5 can be generalised to 'non-classic female population'. In addition, the sub-groups of classic or non-classic within the male population was not a prespecified endpoint in BALANCE; the number of non-classic male population was too limited to warrant a comparison against classic male Fabry disease patients, i.e., 2 in PRX-102 arm and 4 in agalsidase beta arm. Given this, the limitations described in response to question A5 will be magnified and any if any results were generated, they should not be interpreted.

Applicability of BALANCE and BRIDGE to relevant population

A7. The EAG notes that the evidence included in the submission for pegunigalsidase alfa is in people already using treatments and that treatment-naïve patients are not captured in the trials. Please comment on how generalisable the results of BALANCE and BRIDGE are to treatment-naïve patients in the UK.

Treatment-naïve patients were captured in the Phase I/II trials as described in Section B.2.6.4 and Section B.2.10.4 in Document B. Table 3 presents key outcomes after 12 months of treatment with PRX-102 reported in the Phase I/II trial, PB-102-F01 conducted in treatment-naïve patients compared with results from

BALANCE and BRIDGE. As per the response to A3, the BRIGHT study of the Q4W posology is no longer in scope of this appraisal and is not discussed further.

Although BALANCE was conducted in a renally impaired population only, comparison between all of the trials demonstrated that treatment-naïve patients treated with PRX-102 E2W for 12 months exhibited similar results in regards to the efficacy outcomes investigated. Clinical experts are in general agreement that the results from BALANCE would be generalisable to the full FD population,[1] and given the similarities between the PB-102-F01 and BALANCE efficacy results, this generalisability is assumed to also apply in the treatment naïve population.

Table 3. Comparison of change in outcomes after 12 months of PRX-102 treatment in the Phase I/II trial PB-102-F01 and the Phase III trials, BALANCE and BRIDGE

	Mean (SD) change after 12 months		
	PB-102-F01	**BALANCE**	**BRIDGE**
eGFR mL/min/1.73 m^2	-1.6 (2.4)	-0.69 (7.53)	-2.56 (9.59)
eGFR slope mL/min/1.73 m^2	-1.8	-2.38 (8.9)	-1.19 (7.9)
LVMI g/m^2	-0.3	0.3 (7.33)	4.1 (12.2)
UPCR category	After 12 months of PRX-102 E2W treatment, only 2 patients had an abnormal UPCR compared to 4 at baseline	Normal to mildly increased UPCR: 4 patients Moderately increase UPCR: 0 patients Severely increased UPCR: 0 patients	Normal to mildly increased UPCR: 0 patients Moderately increase UPCR: -3 patients Severely increased UPCR: 2 patients
Mean LVM (g)	Males: 0.2 mg/kg: -5.7 1.0 mg/kg: -9.6 2.0 mg/kg: 9.6 Females 0.2 mg/kg: 1.7 1.0 mg/kg: 4.4 2.0 mg/kg: 6.3	0.510	-
LVMi (g/m^2)	-0.3	0.065	-2.5
Mainz Severity Score Index	• Total general score: -1.8 • Total neurological score: -2.6	• Total general score: -0.33 • Total neurological score: -0.28	• Total general score: -0.1 • Total neurological score: -1.2 • Total cardiovascular score: 0.3

	Mean (SD) change after 12 months		
	PB-102-F01	**BALANCE**	**BRIDGE**
	• Total cardiovascular score: -0.8 • Total renal score: -1.0	• Total cardiovascular score: -0.40 • Total renal score: -0.28	• Total renal score: 0.0
Plasma GB3 (% change)	Males: 0.2 mg/kg: -23.8% 1.0 mg/kg: -42.7% 2.0 mg/kg: -50.2% Females: 0.2 mg/kg: -6.4% 1.0 mg/kg: -6.7% 2.0 mg/kg: -4.9%	4.57% (38.63)	-9.8%
Plasma lyso GB3 (% change)	Males: 0.2 mg/kg: -61.8% 1.0 mg/kg: -67.7% 2.0 mg/kg: -50.2% Females: 0.2 mg/kg: -6.6% 1.0 mg/kg: -44.5% 2.0 mg/kg: -37.2%	10.28% (22.79)	-31.46%
BPI (pain at its worse over the last 24 hours)	• 0.2 mg/kg, 1.1 from baseline • 1.0 mg/kg, -0.2 from baseline • 2.0 mg/kg, -0.7 from baseline	0 (2.4)	0.4 (1.6)
Key: eGFR; estimated glomerular filtration rate; FD, Fabry disease; Gb3, globotriaosylceramide; LVMI, left ventricular mass index; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging; ;MMSI, Mainz severity score index SE, standard error; UPCR, urine protein to creatinine ratio.			

A8. The EAG notes that the BALANCE trial only includes people with deteriorating renal function and that this may not be a feature that all patients with FD have (e.g., those with the cardiac variant). Please comment on how this may impact the applicability of the BALANCE trial results to the whole population that would be eligible for pegunigalsidase alfa in clinical practice in the UK if it were to be recommended.

The company conducted a naive comparison to compare outcomes across Phase III trials in order to determine how similar the outcomes were for the population in BALANCE compared with the differing population of BRIDGE, as described in Section B2.9 of Document B and detailed in the Appendices (Appendix D.1.3.1). Briefly, the naïve comparison was attempted but the analyses were very limited due to small patient populations and differing baseline characteristics between trials such as sex and age. However, despite the limitations of the analyses, results of the naïve comparisons suggested that there are no significant differences in efficacy of PRX-102 for key outcomes of interest between BALANCE (PRX-102 E2W in renally impaired population) and BRIDGE (PRX-102 E2W in non-renally impaired population).

Additionally, UK clinical experts consulted at an advisory board were asked specifically about the demographics of the participants in BALANCE and whether they are representative of the FD population in the UK. The experts noted a few variations in terms of generalisability to UK clinical practice. The age of patients was considered slightly lower than seen in practice and younger patients, especially younger female patients, maybe associated with better renal function. There was also a slightly higher proportion of classical patients in BALANCE compared to clinical practice, although it was considered not to be too relevant However, it was noted that there was no biological rationale for a difference in the function of ERT in the full FD population versus the renally-impaired FD population and as such there was general agreement that the results from BALANCE would be generalisable to the full FD population.[1]

Systematic literature review and indirect comparison feasibility assessment

A9. Priority Question. Please provide a list of the 3 included RCTs identified in the clinical systematic literature review (SLR) that were deemed not relevant to the scope and missing from the Company submission Appendix D.1 Table 8 including the rationale for why they were deemed not to be relevant.

Table 4 includes a list of 3 RCTs that were included in the clinical systematic literature review that were not relevant for the company submission. The list includes two studies of migalastat and one study of lucerastat. Both these interventions are not included in the scope of the appraisal are not relevant comparators to PRX-102. (See response to A1 for PRX-102 positioning)

Table 4: RCTs included in review but not relevant to the scope of submission

RCTs details	Intervention versus comparator	Rationale for not including RCTs in the company submission
Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. *New England Journal of Medicine* 2016; 375: 545-555	Migalastat versus placebo	In UK clinical practice it is anticipated that migalastat would continue to be used in patients with amenable mutation due its targeted nature and established use. PRX-102 is an ERT and has been compared with other available ERT options (agalsidase alfa and agalsidase beta) in the market. Hence, migalastat has not been considered as a relevant comparator to this submission.
Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *Journal of Medical Genetics* 2017; 54: 288-296.	Migalastat versus ERT (agalsidase alfa or agalsidase beta)	
Guérard N, Oder D, Nordbeck P, et al. Lucerastat, an Iminosugar for Substrate Reduction Therapy: Tolerability, Pharmacodynamics, and Pharmacokinetics in Patients with Fabry Disease on Enzyme Replacement. *Clin Pharmacol Ther* 2018; 103: 703-711	Lucerastat + ERT therapy versus ERT therapy	PRX-102 is an ERT and has been compared with other available ERT options (agalsidase alfa and agalsidase beta) in the market. Lucerastat does not have marketing authorisation in the UK. Hence, lucerastat (a substrate reduction therapy) has not been considered as a relevant comparator to this submission.

A10. Please provide a list of the 164 included studies for the clinical SLR that was performed based on searches in Appendix D.1 of the company submission,

highlighting which studies were included in the company submission and providing the reason for exclusion of each of the remaining studies not included in the company submission. Please include in this list any migalastat studies that were identified but excluded.

In total, 2,947 records were retrieved from all the electronic databases searched as part of the SLR. Following the removal of 221 duplicates, 3,726 records were screened at primary screening, of which 1,758 records were excluded. Further, 968 records were screened for eligibility at the full-text stage of which 165 studies from 414 publications were included in the review. Of 165 included studies, 13 RCTs were deemed relevant, of which 5 RCTs were dose-ranging studies only and hence were not included. In addition, 3 RCTs assessed migalastat or lucerastat as an intervention and hence were not included in the analysis since these are not comparators of interest for PRX-102 (see response to A9).

A further 149 studies were non-randomised or observational studies and hence were not included. In addition, the BRIGHT study is no longer relevant for the submission as the PRX-101 E4W dose is not currently licenced (see response to A3). The PRISMA flow diagram representing the flow of studies through the clinical SLR has been included below (Figure 2). Additionally, the excel sheet attached below presents a list of studies included in the clinical SLR. The list has been divided into studies deemed relevant for submission and studies excluded along with reasons for their exclusion.

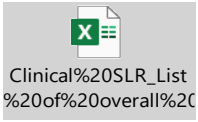
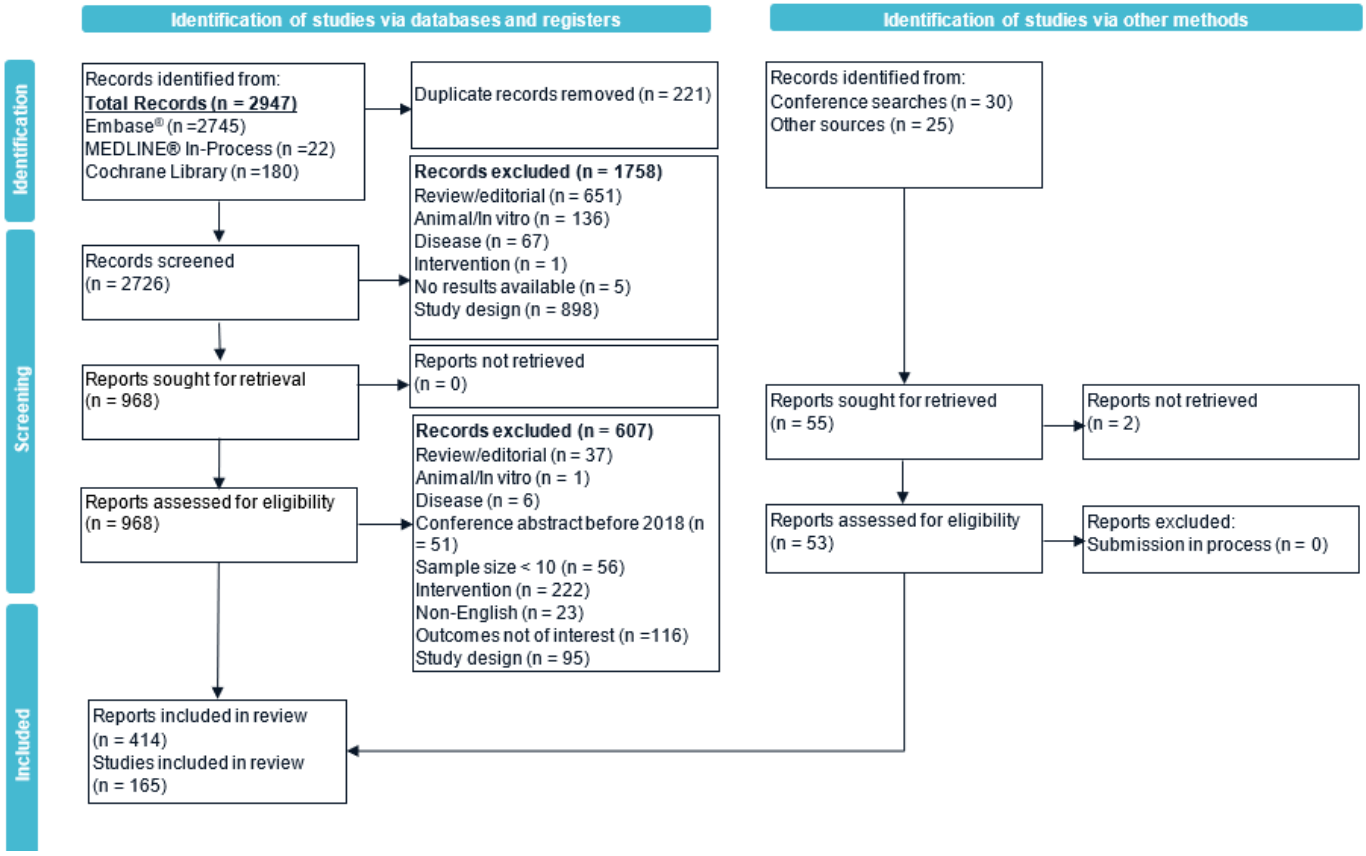


Figure 2: PRISMA diagram for the overall clinical



An additional context for number of studies processed at each stage of the clinical SLR has been included to address a minor error in the PRISMA flow included in the company submission. The only minor change that has been made is the total number of observational studies included in the clinical SLR, and to which one additional study has been added. Thus, a total of 165 studies were included in the review. Please note that the number of studies relevant for the submission, i.e., RCTs has not changed and this minor update does not impact on any results/ interpretation presented.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("Controls" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the

revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Comparators

B1. Priority question: As outlined in clarification question A1, clinical expert opinion provided to the EAG suggests that migalastat is not the only treatment option for patients with an amenable mutation. The EAGs clinical experts considered that ERTs and pegunigalsidase alfa would be considered appropriate treatment options for patients with Fabry disease independent of amenable mutation status. As ERTs can therefore be seen as alternatives for migalastat by clinicians and vice-versa, the EAG believes that migalastat should be included in the submission as an additional comparator. Therefore, based on the response to A1, please conduct a cost utility analysis including migalastat as a comparator to pegunigalsidase alfa and agalsidase alpha and beta, utilising the committee's preferred assumptions in HST4. The EAG notes that a disutility for infusions was deemed reasonable by committee, which should be included in the company's cost-utility analysis

As set out in response to A1, migalastat is not a comparator of interest for this appraisal, as PRX-102 is anticipated to be used as a treatment option for patients with symptomatic FD who would be offered ERT. The eligible patient population would only include patients with an amenable mutation, in those who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). Therefore, a cost-utility analysis comparing PRX-102 to migalastat is not relevant for this appraisal.

Baseline characteristics

B2. The EAG's clinical experts advised that by age 40, there will be a proportion of FD patients who will have had multiple complications. Please clarify why the baseline health state distribution of patients in the model did not include the multiple complication health states?

The health state distribution was based on data from the Fabry Registry and is consistent with the ERG's preferred distribution from HST4.[14] Patients with ESRD would not be considered to start a new therapy, meaning that only the stroke and cardiovascular event health state could be populated. There is no evidence available to determine this percentage of patients with CV and stroke from the literature and as such would be associated with uncertainty.

B3. Priority question: Please provide the baseline health state distribution of patients from BALANCE, including patients with multiple complications, and implement these data in a scenario analysis.

The information required to estimate these inputs was not formally gathered in BALANCE and it is difficult to allocate patients to a specific health state based on the data that was collected in the trial. The Fabry registry provides robust estimates of these parameters that have already been considered appropriate by NICE and therefore represent the most relevant source to use for a UK population.[1, 14]

B4. Priority question: Please provide the mean weight from BALANCE and provide a scenario analysis using these data.

a) **Please provide the overall mean weight from a pooled assessment of BALANCE, BRIDGE and BRIGHT and provide a scenario analysis using these data.**

The mean patient weights from each of the relevant trial along with a pooled weight, are presented in Table 5. Data from BRIGHT has been included to supplement the analysis as it provide additional information on the weight of patients with Fabry Disease, despite it no longer being within the scope of the decision problem. The economic results when using the pooled trial mean weight are reported in Table 13. It should be noted that the analysis in Malottki et al. 2022 was based on a larger sample size of 535 Fabry disease patients, meaning it is likely to be a better reflection of UK Fabry disease patients and most relevance to this submission.

Table 5: Patient weights from PRX-102 trials

Trial	Weight	SD	N
BALANCE	78.9 kg	17.54	77
BRIDGE	74.8 kg	15	22
BRIGHT	82.4 kg	22.7	30

Pooled	79.0 kg	18.3 kg	129

B5. Priority question: Please clarify what severity of pain is assumed for the pain health state on the BPI scale.

The severity of pain was not discussed in Rombach et al., the source for the transition probabilities. Arends et al. 2018, which is the preferred source of health state utility values, reported a BPI average pain of 2.0 in all patients at first EQ-5D measurement.[8] This value is closely aligned with the BPI average pain at baseline in BALANCE, which was 2.2 in both arms of the trial.

Treatment effectiveness

B6. Priority question: As the company has submitted pegunigalsidase alfa for appraisal as an STA, the base case should be a cost utility analysis and a cost-minimisation should be presented as a scenario. Furthermore, when adopting a cost-utility approach, probabilistic sensitivity analysis should assess the impact of uncertainty in all parameters used in the model.

The EAG is concerned that the economic model fails to incorporate any of the uncertainty captured in the pivotal BALANCE trial. For example, the transition probabilities included in the economic model do not explicitly include a treatment effect that can be adapted to include the treatment effect observed in BALANCE. Thus, uncertainty around the treatment effect for pegunigalsidase alfa cannot be captured in the economic model via the probabilistic sensitivity analysis (PSA). These transition probabilities have also not been included in the PSA.

The NICE methods guide recommends that the committee's preferred cost-effectiveness estimate should be derived from a probabilistic analysis when possible, unless the model is linear. Therefore, this failure of the model to account for the uncertainty in the trials is directly impactful to decision making. As such, the EAG considers the PSA results provided by the company do not robustly capture the uncertainty associated with the fundamental assumption of clinical equivalence of ERTs in the model. Please consider

adapting the model such that the uncertainty around the treatment effect from BALANCE is included in the model and the PSA.

The approach to economic modelling was founded on the conservative assumption of no difference in health outcomes between PRX-102, agalsidase alfa and agalsidase beta. As noted in the response to A2, a large body of evidence and clinical opinion supports the assumption of clinical equivalence and that the outcomes of the BALANCE trial, which demonstrated non-inferiority between PRX-102 and agalsidase beta (which can be extrapolated to agalsidase alfa). Non-inferiority was a semi-quantitative outcome, pre-determined as the attainment of the lower bound of the confidence interval for the treatment difference (PRX-102 minus agalsidase beta) was greater or equal to -3.0 mL/min/1.73 m^2/year. Evidence directly linked to the slowing of disease progression and inhibiting the onset of long-term comorbidities associated with FD were not captured due to the 2-year duration of the trial. Therefore, there is no explicit uncertainty around the treatment effect identified in BALANCE that can be varied within the probabilistic sensitivity analysis.

There were minor differences in the safety profile of the two treatments in BALANCE, which were expected to have negligible impact on a patient's health-related quality of life and were therefore excluded for simplicity. Following clarification question B13 these have been included in the model. Besides this, no difference in health outcome was expected and as a result a cost-comparison, or a cost-utility with no incremental QALYs was compiled.

It was not feasible to derive transition probabilities from BRIDGE or BALANCE. The trials did not follow a large enough population over sufficient follow-up to generate a set of robust transition probabilities required for this model structure. Therefore, the company used the transitions derived from the study by Rombach et al., a source that has already been accepted by NICE as appropriate for modelling the progress of FD.

The transitions were previously omitted from probabilistic analysis, as uncertainty parameters had not been identified. Given the assumption of equal efficacy, with all three treatments using the same transition matrix, this was not expected to impact the probabilistic results significantly. Uncertainty characteristics for the transition probabilities have been identified in the form of 95% confidence intervals assuming a

beta distribution. These are used in the one-way sensitivity analysis. The alpha and beta parameters informing the beta distribution were not reported. These were calculated using SOLVER to derive the standard deviation that provides alpha and beta values that most closely match the upper and lower bounds .

Probabilistic results including the varied transition probabilities have been presented in Section B2: New base case and scenario results

Transition probabilities

B7. Priority question: The costs for health state events (Table 54) includes the assumption that 27% of FD patients will receive a renal transplant; however, the economic model doesn't allow for transition from any ESRD related health state to any non ESRD related health state.

a) **Please discuss the clinical validity of applying the HRQoL values associated with ESRD to 27% of patients in the model who have had a kidney transplant.**

b) **Please adjust the model to allow for transition to non-ESRD health states following renal transplants.**

The assumption is associated with limitations as the health states represent a simplification of the management of ESRD. There is no known data of the outcomes of FD patients following renal transplant. This means that any amendments would be based on assumed inputs. The uncertainty of the current input is partially mitigated by the assumption of equal efficacy between treatments, meaning it does not impact economic outcomes.

A backward transition would not accurately reflect the experiences of these patients. The management of a patient who has successfully received a renal transplant differs significantly from the costs that would be captured by returning a patient to a previous state. Health-related quality of life for these patients is also likely to differ due to exposure to immunosuppressants. To truly capture this event a separate health-state would be required. However, this level of detail cannot be modelled in a robust way given the lack of data to underpin any assumptions. Therefore, the transition probabilities have not been altered to address this question.

B8. Priority question: Clinical expert opinion provided to the EAG is that Fabry disease is a progressive condition which leads to the accumulation of symptoms before death. The economic model outlines a disease epidemiology where although transition to a more progressive and complex health state is possible, it is severely limited (all probabilities are less than 0.01).

a) **Please comment on the clinical validity of these transition probabilities given the nature of the disease as a progressive disorder.**
b) **As a scenario analysis please calculate and utilise transition probabilities estimated from the newer registry studies as highlighted by the company in the CS (p.132).**

The transition probabilities inherently reflect the slow, progressive nature of FD by the fact that once a patient progresses to a health state, reflecting the incidence of a new symptom or comorbidity, they cannot return to a previous healthier state. The magnitude of each probability does not reflect whether or not the transition matrix describes a progressive disease.

The transition probabilities reported in Rombach were used in this model after being identified as the most appropriate dataset available in the literature on FD following a clinical and economic SLR. Rombach was deemed the most appropriate source at an advisory board, with no alternative datasets known to the experts. An alternative set of transition probabilities developed using the Clinical Practice Research Datalink has not at present been published.

Adverse events

B9. Priority question. Infusion reactions have not been included in the list of adverse events (AEs) in Table 29. Please outline the number of infusion reactions in each arm of the BALANCE trial and incorporate it into the economic model.

There were 17 (32.7%) incidences of mild or moderate IRRs within 24 hours of infusion in the PRX-102 arm, with 8 (32%) in the agalsidase beta arm. Accounting for duration of follow-up, this results in an annual probability of IRR of 17% on PRX-102 and 20% on agalsidase beta. The cost of managing an IRR was assumed to be zero

as they are typically managed by reducing the dose at the time of infusion and administration of anti-histamines, which are associated with negligible cost.

Health-related quality of life

B10. Priority question: The NICE decision support unit (DSU) recommends that general population utilities adjusted for age and sex are derived from the HSE 2014 dataset. Please update the model to use general population utility values adjusted for age and sex based on the HSE 2014 dataset.

The economic model has been updated to include the expected EQ-5D-3L utility values estimated using the methodology outlined in Hernandez-Alava et al. 2022.[15] The new base case results include this approach to age- and sex- adjusted utilities.

B11. Priority question: In Section B.3.4.1 of the company submission, the company describes the BALANCE regression analysis used to estimate health state utility values for the model, but does not provide further information on the final regression model nor the results of the analysis.

a) **Please provide the final regression model used to estimate health state utility values from BALANCE.**

b) **Please provide the results and health state utility values estimated from the final regression model and implement these data in a scenario analysis. When adapting the model for the scenario, please ensure variance around the utility estimates from BALANCE can be explored using the model PSA. Where utility values cannot be calculated for specific health states due to missing or incomplete data please use the utilities from the company's base case.**

To determine which covariates should be included within the regression equation stepwise variable selection was performed. Due to the relatively small sample size in BALANCE, forward selection was preferred over backwards selection. Forward variable selection is a pragmatic approach to identifying the covariates within the regression model. Within this approach covariates were added to a base model and AIC/BIC are used to determine whether the model fit improves. This was repeated until the addition of further covariates does not improve the model fit further. To

explore forcing specific covariates into the regression model the following base models were considered:

- Baseline utility only
- Baseline utility + treatment
- Baseline utility + age + sex
- Baseline utility + pain-related adverse events
- Baseline utility + Fabry clinical events

The covariates which were considered within the stepwise regression were:

- Baseline utility (this is included in all base models)
- Treatment
- Age
- Sex (note, due to high correlation between sex and Fabry disease type, only sex was considered within the stepwise regression)
- eGFR
- UPCR
- Pain-related adverse events
- Neuropathic pain adverse events
- Serious adverse events
- Fabry clinical events

The results of the forward variable selection are presented in Table 6. Following the forward selection process, the preferred regression was baseline utility + Fabry clinical events (Table 7). Assessed statistically, the model was within 5 units of the

best fitting model based on AIC but had substantially improved BIC over the same model.

Table 6: Utility analysis – stepwise variable selection results

Base model[a]	Model selection based on AIC			Model selection based on BIC		
	Covariates	AIC	BIC	Covariates	AIC	BIC
Baseline utility only	Baseline utility FCE	**-398.9**	[redacted]	Baseline utility FCE	**-398.9**	[redacted]
Baseline utility + treatment	Baseline utility FCE Treatment	**-398.5**	**-375.1**	Baseline utility FCE Treatment	**-398.5**	**-375.1**
Baseline utility + age + sex	Baseline utility FCE Age Sex Baseline UPCR Baseline eGFR	**-398.2**	-355.4	Baseline utility FCE Age Sex	**-395.3**	-368.1
Baseline utility + pain-related adverse events	Baseline utility FCE Pain-related AEs Baseline UPCR Baseline eGFR	[redacted]	-361.8	Baseline utility FCE Pain-related AEs	**-397.4**	-374.1

Key: eGFR, Estimated Glomerular Filtration Rate; FCE, Fabry clinical events; UPCR, Urine Protein Creatinine Ratio.
Notes, Yellow cells indicate best fitting models based on AIC and BIC; bold text indicates models within five units of the best fitting model; [a] The base model including FCE, is not presented as it gives the same covariates as the baseline utility only model

Table 7: Base case utility regression model

Coefficient	Coefficient value	Standard error	p-value
Intercept	[redacted]	0.039	< 0.001
Baseline utility	[redacted]	0.049	< 0.001
FCE: yes (reference: no)	[redacted]	0.033	0.005

Key: FCE, Fabry clinical event

Due the population size and follow-up duration for BALANCE, there were a limited number of clinical events and no incidents of modelled comorbidities occurring during the trial. This means that only the 'pain' and 'other symptom' health states could be modelled with data from BALANCE. The other symptoms health state was derived assuming the prevalence of Fabry Clinical events.

Table 8: Health state values estimated from BALANCE

Health state	Utility value
Pain	[redacted]
Clinical symptom or organ involvement	[redacted]

These utility values were implemented as a scenario in the economic model, with the remaining health states utilities being populated with values from Arends 2018. The multiplicative approach previously described in Document B has also been updated to scale all of the Arends health state utility values that are used for the later health states.

There was an error in the multiplicative utility adjustment approach described in Document B, with the coefficient for baseline utility used to adjust literature utilities rather than the baseline utility from BALANCE. This has been updated and is incorporated in the new base case. The new base case still uses utility values from Arends 2018[8] for all health states. Results from this adjustment are reported in Table 12.

B12. Priority question: Expert clinical opinion provided to the EAG details that HRQoL values for those in health states associated with three symptoms (i.e. stroke, cardiac complications and pain) would be lower than those in two symptom health states. In addition, there would be HRQoL differences between the two symptom health states, as seen in the differences between the single symptom health states. Please recalculate the health state utility values (HSUVs), providing a scenario analysis where the three-symptom

health state has the lowest utility value and there is a difference in HSUVs between the health states with two symptoms.

As the health state utility values were taken from the literature, we are not in a position to recalculate a specific value. A multiplier has been applied to the 3-complication health state utility value to address the question. The multiplier was derived by calculating the percentage change on moving from a single complication state to a double complication state, for the utility values reported in Arends et al. 2018 this was approximately 29%.[8] This was then applied to the three complication health state, reducing the utility from 0.53 to 0.37. This approach was implemented as a scenario in the model, with the results reported in Table 13. Given the assumption of equal efficacy between PRX-102 and ERTs, this change does not impact the base case results.

B13. Priority question: For the scenario exploring AEs, only costs have been included, aligned with the base case approach of cost-minimisation analysis. As part of the cost-utility analysis, please provide a scenario where disutilities associated with AEs are included.

Utility decrements associated with each adverse event have been calculated by identifying annual utility decrements from the literature and applying them for the mean duration of each adverse event in BALANCE. Results from this scenario are presented in Table 13. Table 9 presents the utility values sourced from the literature and associated durations from BALANCE.

Table 9: Adverse event disutility

Adverse event	Utility decrement	Duration (Days) BALANCE	Source
Sinusitis	-0.19	19.09	Stein 2017[16]
Viral infection	-0.19	1.80	Stein 2017[16]
Fatigue	-0.13	9.00	Nafees 2008,[17] Swinburn 2010[18]
Pain	-0.07	10.00	Doyle 2008[19]
Infusion related reaction	-0.01	1.00	Boye 2011, study valuated diabetes population[20]

Adverse event	Utility decrement	Duration (Days) BALANCE	Source
Paraesthesia	-0.07	71.00	Assume same as pain in extremity
Nausea	-0.05	1.36	Nafees 2008[17]
Diarrhoea	-0.05	27.71	Nafees 2008[17]
Pain in extremity	-0.07	72.13	Doyle 2008[19]
Cough	-0.19	53.11	Assume same as sinusitis
Oropharyngeal pain	-0.07	2.00	Doyle 2008[19]
Dyspnoea	-0.09	21.00	Sullivan et al. (2011)[21]
Nasopharyngitis/flu	-0.16	6.80	Derived from total QALY loss of 0.00222 (CRD/CHE Technology Assessment Group, 2008; Turner et al., 2003) - NICE HST4[22]
Headache	-0.08	5.23	Sullivan et al. (2011)[21]
Upper respiratory tract infection	-0.02	1.80	Sullivan et al. (2011)[21]
Urinary tract infection	-0.07	11.50	Armstrong 2009[23]
Gastritis	-0.13	67.00	Sullivan et al. 2011[21]
Bronchitis	-0.16	23.90	Derived from total QALY loss of 0.00222 (CRD/CHE Technology Assessment Group, 2008; Turner et al., 2003)- NICE HST4[22]
Abdominal pain	-0.05	11.75	Assume same as diarrhoea
Pyrexia	0.00	3.38	Assumption
Blood creatine phosphokinase increased	-0.07	52.00	Assume same as pain
Myalgia	-0.07	0.50	Assume same as pain

Adverse event	Utility decrement	Duration (Days) BALANCE	Source
Back pain	-0.07	10.00	Assume same as pain

Mortality

B14. Priority question: The CS describes how in HST4 the background mortality applied in the model was too low, leading to patients having an unrealistically high life expectancy. The company has therefore adjusted the transition probabilities to death to account for the reduced life expectancy of those with Fabry disease. Please;

a) **Describe how mean life expectancy of male and females in the economic model has been calculated as the EAG has been unable to validate the company's estimates as outlined in the CS.**
b) **Describe how the transition probabilities to death have been adjusted from the values reported in Rombach *et al.* to decrease life expectancy.**

The functionality to calibrate the life year estimates was not included in the model provided to NICE in error. The functionality aligns the undiscounted life years in the model with an estimate for the population based on the Waldek et al. estimates of Fabry disease life expectancy. Given 50% of patients were modelled as male, Waldek's estimates would suggest the life expectancy in the model would be 66.80 years. The unadjusted life expectancy estimate in the model was 76.37.[24]

The functionality uses Goal Seek to estimate a standard mortality ratio that is applied to the general population mortality and aligns the models undiscounted life year estimates with the values from Waldek et al. This, in theory, compensates for some of the known limitations of the Markov model approach such as the mortality probabilities not increasing with time. A scenario using the estimated SMR has been reported in Table 13 and shows that after calibration PRX-102 is still cost saving.

Resource use and costs

B15. In Table 54 of the company submission, please clarify why no weighting is given for patients with CKD stages 1-4.

This is an error in the economic model. This resource use table was developed in line with the approach taken in HST4, where the cost of managing CKD stages 1-4 were applied to 0.3% of patients. This input is amended as a scenario and the results are captured in Table 13.

B16. Priority question: The EAG's clinical experts considered that for the E4W pegunigalsidase alfa regimen, the number of infusions at the initial duration should be the same as the E2W (six infusions) as it is related to safety and not frequency of administration. As such, please supply an alternative scenario for the E4W regimen, where the number of infusions at the initial duration is six.

See response to A3.

B17. Priority question: The EAG's clinical experts advised that the majority of patients require nurse assistance to administer their infusions at home and few patients would be fully independent when administering their infusion. Please run a scenario where 90% of patients require a nurse to administer their infusions at home and 10% self-administer treatment.

This scenario has been implemented in economic model. This alteration led to a minor increase in costs in all three treatment arms. The results with this assumption implemented are presented in Table 13.

B18. Priority question: Expert clinical opinion provided to the EAG suggests that the assumed yearly Health Care Professional follow-up figures (Table 55 in the CS) may not reflect UK clinical practice. In particular, the 18.5 annual physiotherapist visits for those with other complications (ESRD and stroke), the 5.4 physiotherapist sessions for pain and the inclusion of social workers which would not be provided by the NHS. The CS highlights a recent linked database analysis by Malottki *et al.* conducted in 2022, which identified that the average FD patient in England will have 9.4 consultations with health care professionals per year, of which 5.6 would be GP appointments. This information contradicts the data presented in Table 55 of the CS, which reports

3.5 GP appointments each year and 5.5 visits with other health care professionals. Given the information from the study please;

a) **Justify the underestimated yearly GP appointments, overestimation of follow up from other healthcare professionals, the grouping of ESRD and stroke under the single complications column and inclusion of social workers.**
b) **Conduct a scenario analysis using the mean yearly follow-up figures as outlined in Malottki *et al.* and remove resource associated with social workers.**

The health care resource use reported and accepted in HST4 was used as the baseline for inputs in the economic model for PRX-102. These inputs were then validated as part of an advisory board, with none of the attending clinical experts raising any objections.

The scenario using the data reported in Malottki et al. has been implemented as a scenario in the economic model, with the results reported in Table 13.

B19. The EAG consulted with its clinical expert regarding the weighting of health state events (Table 54 in the CS), they highlighted differences to what they would expect in UK clinical practice. As a scenario analysis, please change the weighting for patients requiring a pacemaker to 5%, myocardial infarction to 10%, cardiac congestion requiring hospitalisation to 10%, percutaneous coronary intervention to 5%, and implantable cardiac defibrillator to 5%.

This scenario has been implemented in the economic model, the results of the scenario have a minor impact on total costs in each treatment arm, as can be seen in Table 13.

B20. Priority question: The EAG consulted with its clinical experts regarding FD management resource use assumptions included in the model. In particular, it was noted that plasma Lyso-Gb3, assay for alpha-galactosidase A Ab, GL-3G and Lyso-GL-3G and antibody test & neutralizing assays are not

provided by the NHS. Please provide two scenarios using the following FD management resource use assumptions provided in the below table.

Health care professional	Annual frequency (scenario 1)	Annual frequency (scenario 2)
Full blood count	2.38	1.00
Urine test	2.75	1.00
ECG	1.00	1.00
Liver function test	2.00	1.50
Fasting lipid profile	2.00	1.00
2D echocardiography with Doppler	0.63	0.63
Glomerular filtration rate	2.13	0.5
24 hour urine protein / creatinine	0.08	0.08
Exercise testing	0.21	0.21
Renal USS	0.06	0.06
MRI	0.50	0.23
Audiogram	0.63	0.63
Plasma Lyso-Gb3	0.00	0.00
Assay for alpha-galactosidase A Ab	0.00	0.00
GL-3G and Lyso-GL-3G	0.00	0.00
Holter	1.17	0.50
Antibody test & neutralizing assay	0.00	0.00

This scenario has been implemented in the economic model. Results from these scenarios are presented in Table 13.

B21. Priority question: Complication follow up costs have been included in the model ("HCRUs", cells C113:K117) but the assumptions underpinning the

costs have not been described in the company submission. Please describe the complication follow up costs that have been included in the model, justifying any assumptions that have been made.

These HCRU estimates are in line with the estimates included in HST4. In the case of Cardiac and Stroke follow-up costs, where costs were sourced from the literature, the price was inflated to the 2022 price level. The cost of a single appointment to manage ESRD was sourced from the National Schedule of Reference costs in HST4, the equivalent cost has been sourced from the latest version of this document.

B22. Priority question: Terminal care costs have been included in the model but the assumptions underpinning the costs have not been described in the company submission. Please describe the terminal care costs that have been included in the model, justifying any assumptions that have been made.

All patients were assumed to incur a three-month palliative care cost before death. This included costs related to hospital care in the 90 days before dying, based on Georghiou and Bardsley (2014)[25], including a district nurse, nursing and residential care, hospital care and Marie Curie nursing costs. A one-off terminal care cost of £8,524, after adjustment for inflation, was applied to patients upon entry to the death health state.

Probabilistic sensitivity analysis

B23. Priority question: Please clarify why health state transition probabilities were not varied in the PSA. Please include the transition probabilities in the PSA.

As referenced in response to B6, this comment has now been addressed and the updated probabilistic results capture the uncertainty around the transition probabilities.

B24. Priority question: Please justify the exclusion of health state utility values from the PSA. Please provide PSA results where health state utilities are included in the analysis.

The uncertainty around the utility values included in the model were varied in the PSA in rows *183-202* within the parameter sheet.

B25. Priority question: A Dirichlet distribution has been used in the PSA for the baseline patient distribution input parameters in the model. However, the formula for the lower and upper bounds are the same. Please clarify if the Dirichlet has been implemented correctly, as the formula for alpha in the model is mean*n + 0.05 and beta hasn't been calculated.

Regarding the upper and lower bound, they do use the same formula but the control in column Y is linked to the random number in column T. This means that whenever the lower or upper bound is used in the one-way sensitivity analysis the correct value is in place.

The Dirichlet distribution is a family of continuous multivariate probability distributions parameterized by a vector (alpha, column R) of positive real numbers. The distribution does not require a beta value, thus the column is blank. The Dirichlet distribution cannot process inputs of 0, so it is common practice to add a small value to make all variables non-zero.

Section B2: New base case and scenario results

The economic model base case has been updated following the clarification process. The new base case includes the following changes:

- Transition probabilities into probabilistic sensitivity analysis,
- A correction to the multiplicative approach for adjusting literature sourced utilities to align with BALANCE
- General population utilities using the preferred method by Hernandez Alava et al. 2022[15]
- Updated pack costs for agalsidase beta

Table 10 displays the deterministic base case provided in the original submission. Table 11 displays deterministic results from the updated base case and Table 12 from the updated PSA. Table 13 presents the results from model updates and scenarios requested by the EAG at the clarifications stage and describes model changes and key drivers of results.

Table 10: Original base case pairwise results

Technologies	Total Lys	Total QALYs	Total costs (£)	Incremental Lys	Incremental QALYs	Incremental Costs	ICER (£/QALY)	INMB
PRX-102	19.815	[redacted]	[redacted]	-	-	-	-	-
Agalsidase alfa	19.815	[redacted]	[redacted]	0.000	0.000	-£496,926	PRX-102 Dominant	£496,926
Agalsidase beta	19.815	[redacted]	[redacted]	0.000	0.000	-£601,765	PRX-102 Dominant	£601,765

Table 11: Updated base case pairwise results

Technologies	Total Lys	Total QALYs	Total costs (£)	Incremental Lys	Incremental QALYs	Incremental Costs	ICER (£/QALY)	INMB
PRX-102	19.815	[redacted]	[redacted]					
Agalsidase alfa	19.815	[redacted]	[redacted]	0.000	0.000	-£477,580	PRX-102 Dominant	£477,580
Agalsidase beta	19.815	[redacted]	[redacted]	0.000	0.000	-£472,159	PRX-102 Dominant	£472,159

Table 12: Updated probabilistic results - pairwise comparison

Technologies	Costs	LYs	QALYs	Inc Costs	Inc LYs	Inc QALYs	ICER
PRX-102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**PRX-102 Dominant**
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**PRX-102 Dominant**

Figure : Cost-effectiveness Plane

Table 13. Clarification question economic scenarios

Clarification		Model changes	Scenario results	Notes
B4	Provide a scenario analysis using mean weight pooled from BALANCE, BRIDGE and BRIGHT	'Controls' tab in the model now contains a switch to select mean weight from BALANCE, BRIDGE or BRIGHT or using pooled weight from all three trials	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	The mean weight pooled across BALANCE, BRIDGE and BRIGHT is higher than the base case analysis, driven mainly by the higher mean weight from BRIDGE. As all ERTs included in the model are weight based, the increase in costs across all treatments is driven by higher drug acquisition costs
B9	Incorporate the number of IRR's into the economic model	N/A – Economic model already considers IRR		
B11	Use health state utility values estimated from BALANCE as a scenario	A switch on the 'controls' tab was added to allow the user to select BALANCE regressions for initial health states	Total QALYs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	Data availability from BALANCE only allowed for the calculation of utility values for the 'pain' and 'other symptoms' health states. The remainder of HSUVs used data from Arends[8]. This scenario resulted in approximately 1 fewer QALY for all treatments
B12	Allow for utility values in the 3 complication health state to be worse than the 2 complication state and allow for differences between the 2 complication states	A multiplier was calculated using data from Arends[8] after moving from a single complication to a double complication state. A switch can be toggled on the 'controls' tab to apply the multiplier	Total QALYs PRX-102: [redacted] agalsidase alfa [redacted] agalsidase beta: [redacted]	As a very small proportion of patients enter this health state in the model, the reduction in QALYS from reducing utility in the 3 complication state is marginal compared to the base case. This change did not influence costs.
B14	Model corrected to include functionality to adjust mortality rates using a standardised mortality ratio with data from Waldek[26]	Model 'controls' tab now contains a switch to apply SMR to mortality rates	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta [redacted]	In the original submission using unadjusted mortality rates from Rombach[27], life expectancy was 76.37. Applying the SMR calculated from Waldek reduced this to 66.8 years and thus causes a reduction in costs for all treatments as patients stay on treatment for life.

B15	Clarify why no weighting is given to CKD 1-4 HCRU	Model input corrected to apply rate of 0.3%	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	Given the small magnitude of increase to the HCRU input, the results are almost identical to the updated base case results.
B17	Increase the proportion of patients requiring nurse assistance for infusions to 90%	Inputs in the 'Drug and admin costs' tab relating to administration type distribution were changed to 90% from 50%	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	Increasing the proportion of patients requiring a nurse assistance for home infusions increases costs for all treatments, with agalsidase beta having the largest increase due to having the largest infusion duration out of the 3 treatments at the reduced rate. The increase is driven by this value multiplied by the cost of a nurse visit being multiplied by a greater proportion in this scenario
B18b	Change the HCRU rates for healthcare professional visits to align with data from Malottki (2022)	A switch added to the 'controls' tab allows the user to apply HCRU follow up visits using Rombach (2013) or Malottki (2022) data. Malottki data was applied as 5.6 GP visits and 3.8 physiotherapist and psychology visits split equally to reach the 9.4 average visits reported in Malottki. As social worker visits are not provided by the NHS, this is set to 0 when the Malottki input is selected	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	Using the inputs from the Malottki (2022) study causes an increase in the number of GP visits in all states versus base case but significantly reduces the utilisation of physiotherapists and psychologists in the pain state. This represents a cost saving for all treatments versus the base case and given resource use is assumed equivalent across treatments, this cost saving is identical across all treatments
B19	Change the weighting of cardiac events experienced by patients to values preferred by the EAG.	A switch added to the 'controls' tab allows the user to change the input for 'FD cardiac complication weighting source' to either HST4 values or EAG preferred values	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	Changing the weighting of cardiac events has a minimal impact on the model results. This small incremental change is driven by a lower number of patients making up health states that include cardiac involvement

B20	Change the annual frequency of FD management resource use to better reflect services offered by the NHS	A switch was added to the 'controls' tab which allows the user to select different sources for the 'HCRU FD frequency source', reflecting both of the scenarios preferred by the EAG	Total costs scenario 1 PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	For this scenario, the EAG preferred values doubled the annual frequency of MRI scans, driving the most of the cost increase compared to the base case analysis, as well as increased liver function tests and fasting lipid profiles
			Total costs scenario 2 PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	For this scenario, the EAG preferred values represented a blanket reduction in frequencies across most of the categories, leading to the overall incremental cost reduction seen in this scenario
Cost Utility results				
B13	Including AE associated disutility into the cost utility analysis	For all AE's that had a cost included in the model a disutility was also sourced from the literature. A switch on the 'Controls' tab can be toggled to include AE disutility	Total costs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted] Total QALYs PRX-102: [redacted] agalsidase alfa: [redacted] agalsidase beta: [redacted]	As AE costs were already included in the original economic model, total costs remain the same as the original scenario for all treatments. Due to the favourable AE profile of PRX-102 compared to agalsidase alfa and agalsidase beta, applying AE disutility to the model results in PRX-102 having a greater number of total QALYs than ERTs. Therefore PRX-102 strictly dominates the other treatments due to lower total costs and higher total QALYs.
Key: AE, adverse events; EAG, evidence assessment group ERT, enzyme replacement therapy; FD, Fabry disease; HCRU, health care resource use; HSE, health survey England; HSUV, health state utility value, IRR, infusion related reaction; QALY, quality adjusted life year; SMR, standardised mortality ratio				

Systematic literature review

B26. The company reports that the cost-effectiveness, HRQoL and cost evidence searches were run in May 2021. Please justify why an update search was not performed for the economic information systematic literature reviews (SLRs).

As noted within the submission, a comprehensive economic SLR was carried out in May 2021. The update to the NICE methods in Section 3.3.26, states that the "*Search for economic evaluations using transparent and reproducible approaches until sufficient appropriate and relevant evidence has been identified. Reviews may not be exhaustive if additional studies identified would merely provide further support that is consistent with the already-identified evidence*". Therefore, given the robustness of the original economic SLR, we tested key evidence incorporated within the economic model was tested with key clinical experts at an advisory board and no additional evidence recommended for use within the economic modelling.[1]

B27. Priority question: ERT as a blended comparator was an exclusion criteria for the cost-effectiveness SLR as such, the study by Rombach *et al*. 2013 was used to inform the transition probabilities was not identified.

a) **Please clarify how many studies were excluded based on blended ERT as the intervention?**
b) **Please discuss if any of these studies met the remaining inclusion criteria and provide title and abstract for those studies.**
c) **Please discuss if any of the studies that met the remaining inclusion criteria were published more recently than Rombach *et al.* 2013 and, if relevant, more recent data may be available to inform transition probabilities in the model.**

Responses to the above questions are included as below

a) It can be confirmed that only one study, Rombach et. al. 2013 was excluded from the review for previously published economic models for assessing ERT as a blended comparator

b) The study by Rombach et. al. did meet all other review inclusion criteria apart from being assessing ERT as a blended comparator

c) As mentioned previously, no alternative data would have been identified in the SLRs. As a result, Rombach et al. 2013 remains the most appropriate data source for informing the transitions in the model.

We confirm that we could not identify any study in economic SLR except Rombach et al. 2013 which was excluded on blended intervention .

Section C: Textual clarification and additional points

C1. In the company submission (pg. 127), it is stated that the market share for agalsidase alfa and agalsidase beta is 70% and 30%, respectively. However, in the economic model, the market share for agalsidase alfa and agalsidase beta is 30% and 70%, respectively. Please clarify if the model has the correct market share values and amend where necessary.

Agalsidase alfa has a 70% market share. The model has been corrected to reflect this.

C2. In the economic model, the source for mean weight (tab “controls”, cell J36) is BALANCE, BRIGHT & BRIDGE. However, in Table 38 of the company submission, the source of mean weight is Malottki *et al.* Please clarify if Malottki *et al.* is the correct source of mean weight.

Malottki et al. is the correct source for mean patient weight.

C3. The standard deviation (SD) of mean weight in Malottki et al is 20.4 but in the model 18.5 is used (with the source listed as BALANCE, BRIDGE & BRIGHT). Please clarify if the mean weight SD in the model is correct and amend if necessary.

The SD for the mean weight reported in Malottki has been updated.

C3. In Table 34 and 38 of the company submission, it is stated that the average life expectancy of females with Fabry disease is 74.7 years, sourced from Waldek *et al.* 2009. However, in the publication, it states that the female life expectancy is 75.4 years. Please correct the model as necessary.

75.4 has been used in the response to clarification of B14.

C4. The EAG considers that the data for proportion males and baseline health state distribution presented in Table 38 of the company submission have been sourced from the ERG report for HST4 (Table 46, original source: Eng *et al.* Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis. 2007; 30(2): 184-92). Please clarify if the cited source (Waldek *et al.* 2009) is correct.

Eng et al. 2007 is the correct source for these inputs.

C5. In Table 45 of the company submission, the baseline utility from BALANCE is 0.762, but in the model a value of 0.74 has been used. Please clarify if the baseline utility value in the model is correct and amend if necessary.

0.762 is the correct baseline utility. This has been amended in the model and is included in the updated base case.

C6. In Table 54 of the company submission, the total annual cost of “other symptoms” is £1,793 but in the model is £2,463. Please clarify if the company submission is correct and amend if necessary.

The model presents the correct value.

C7. Table 15 of the company submission suggests that the difference in means between PRX-102 and agalsidase beta is identical for males and females, regardless of whether hypertrophy is present at baseline. Should the values for those without hypertrophy at baseline (given below as in the submission) be corrected?

PRX-102 – agalsidase beta: difference in means (95% CI), males:	[redacted]
PRX-102 – agalsidase beta: difference in means (95% CI), females:	[redacted]

The values for the respective section (patients without hypertrophy at baseline) of Table 15 should be corrected to the following:

PRX-102 – agalsidase beta: difference in means (95% CI), males: [redacted]
PRX-102 – agalsidase beta: difference in means (95% CI), females: [redacted]

C8. In Table 28 of the company submission:

a) The number of patients with mild or moderate TEAEs in BALANCE [redacted] the number of patients with any TEAEs, in both treatment arms [47 (90.4) vs 24 (96)]. Is this correct or should this be amended?

These are the correct values as stated within the CSR of BALANCE. These were likely instances of the same patient having mild/moderate/severe AEs.

b) The same is also observed for the number of patients with any treatment-related AEs and mild or moderate treatment-related AEs in this table [21 (40.4) vs 11 (44.0)]. Please confirm if this is correct.

These are the correct values as stated within the CSR of BALANCE. These were likely instances of the same patient having mild/moderate/severe AEs.

C9. The EAG notes that the baseline values for the BALANCE trial presented in the company submission (Table 8) for the following outcomes do not match baseline values reported in the CSR (Table 11.3). Please clarify why these values differ or correct as appropriate:

a) mean eGFR slope at baseline (both arms and overall);
b) mean eGFR score at baseline (both arms and overall).

These values should be corrected to align with the CSR as follows:

Mean (SD) eGFR score at baseline: PRX-102 1 mg/kg E2W, 73.46 (20.21); agalsidase beta 1 mg/kg E2W, 74.16 (20.97); Overall, 73.69 (20.32)

Mean (SD) eGFR slope at baseline: PRX-102 1 mg/kg E2W, -8.42 (6.96); agalsidase beta 1 mg/kg E2W, -7.79 (4.74); Overall, -8.22 (6.30)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Pegunigalsidase alfa for treating Fabry disease [ID3904]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Society for Mucopolysaccharide and Related Diseases (MPS Society)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MPS Society is the only organisation in the UK that provides support to patients diagnosed with one of 25 MPS or related lysosomal disorders (including Fabry Disease). The organisation supports over 1,500 children, adults and families. The MPS Society was established in 1982, with the aim of providing support, information, and advice to affected individuals and families. We offer specialist support, information and advocacy, working in partnership with individuals, families, health, statutory services and other relevant professionals, ensuring that the individual and their needs always remains our main priority and that they have access to the specialist care, services and treatment that they need. The MPS Society does not receive any statutory funding in England, therefore the MPS Society relies upon a rolling programme of grant applications to Trusts and Foundations, together with monies raised by members and the public through fundraising. The MPS Society receive grants from pharmaceutical companies to support the different activities it provides.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant	The MPS Society has received funding from; Chiesi- £30k for its advocacy and mental health services and website development Takeda -£30k for its patient services Sanofi - £5k for its 40th anniversary video (deferred from 2021) Amicus- £27k for its advocacy service, cost of living support, 40th anniversary video (deferred from 2021)

companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patient/care giver/specialist centre surveys (1) Review of known adult patients across 5 UK (England) Specialist Centres. MPS Society (May 2022) - unpublished (2) Living with Fabry Disease, A market research study (2014). MPS Society (funded and supported by Shire Pharmaceuticals and Cello Health Insight). (3) MPS Society – Understanding the impact symptoms have on Quality of Life in people with Fabry disease – unpublished (4) Living with Fabry Disease is like…. (2013) Fabry patient feedback part of study (2) – unpublished

Living with the condition **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?**	Fabry disease (also known as Anderson Fabry disease) is an inherited lysosomal storage disease caused by mutations in the GLA gene which encodes the enzyme alpha-galactosidase A. Mutations in the GLA gene change the enzyme's structure and function and prevent it breaking down a fat called Gb3. Progressive Gb3 in the cells leads to a wide range of symptom. Progressive accumulation of Gb3 often starts in childhood and is frequently evident in adolescence. Although symptoms generally appear in childhood they often go unrecognised (due to their unspecific nature) until adulthood. At this stage irreversible organ damage may have already occurred. Early diagnosis is particularly important in Fabry disease as the condition is progressive and life threatening. In England the diagnosis of Fabry disease is rarely made in children under 12 years of age unless there is a known family history. However, we are aware anecdotally (through interaction with our Fabry membership cohort) that even in cases where there is a known family history of Fabry disease; diagnosis can be delayed due to difficulties in accessing appropriate referrals for family screening. The largest majority of our adult members have endured decades of living with Fabry disease before being diagnosed. Premature death due to Fabry disease is prevalent in this group of patients. **<u>Fabry disease in children</u>** The most frequent early clinical manifestations of Fabry disease in children are neurological including acroparathesia, altered temperature sensitivity and inability to sweat. Between 60 – 80% of children report gastrointestinal symptoms including altered bowel habits and abdominal pain. Tinnitus, vertigo, fatigue and angiokeratoma were reported in 40% of children under the age of 18 years. *(Acta Paediatr 2006 Jan; 95 (1): 86 – 92 Clinical Manifestations of Children – U Ramaswami)* Caregivers of children with Fabry Disease report that these symptoms have an impact on access to education and have a detrimental impact of social integration (2). *'Hard socially as they can't do the same activity as friends' (3)* *'Anxiety and mental health due to not being able to keep up with peers' (3)* Some children experience major complications during their paediatric years; including serious renal and cardiac manifestations, stage 2 or 3 chronic kidney disease, arrhythmia, and left ventricular hypertrophy

	(Paediatr Res 2008 Nov;64 (5):550-5 Characterisation of Fabry disease in 352 patients in the Fabry Registry – Hopkin RJ et al) **Fabry disease in adults** By the time a person with Fabry disease reaches adulthood, significant build-up in Gb3 in the cells may have occurred, and new signs and symptoms related to organ damage may have occurred. From early adulthood many have developed renal disease and renal failure resulting in the need for dialysis and /or kidney transplant, cardiac disease and frequent TIAs and strokes often resulting in severe physical and mental disability and death. Hearing loss, tinnitus, the skin rash angiokeratoma, gastrointestinal problems, acroparathesia, corneal opacities, heat and cold intolerance and fatigue are the other clinical manifestations of Fabry disease that contribute to a thoroughly debilitating existence as an adult with progressive Fabry disease. Both the Living with Fabry Study (2) and Understanding the impact symptoms have on Quality of Life in people with Fabry disease study (3) identified that Fabry Disease has a significant impact on four areas of an individual's life: **Physical** - The type and severity of physical symptoms of Fabry vary widely. Symptoms reported in this study mirror those listed above. Pain in hands/feet and fatigue/exhaustion were the most commonly reported symptoms and were describes as 'severe' and 'crippling'. Some people reported being asymptomatic or having only mild symptoms (such as mild fatigue). However, around half of those enrolled in the study reported severe symptoms which place limitations on their lives (limited mobility, loss of earnings and dependency of caregivers). *'I have difficulty with all kinds of mobility. Painful / stiff joints, breathlessness. Physical activity brings on Fabry crisis and extreme fatigue. Makes me overheat etc'* *'Legs become heavy and painful after short periods of anything physical'* *'I am unable to do physical activity, I suffer swelling and pain, get hotter and pain crisis starts. Im not as mobile, I get too fearful of the pain it causes'*

	Emotional - The emotional impact of Fabry correlates with disease burden. Respondents reported feeling isolated, alone, depressed, distressed and worried about the future and their life expectancy. Anecdotally the MPS Society recognise a particular correlation between significant mental health issues and the severity of Fabry related pain. *'Yes, feeling pain affects my emotional wellbeing, makes me more snappy and if in crisis my emotions are more stressed'* *'Pain and exhaustion can make you feel very low'* **Practical** – Respondents reported Fabry having an impact on their ability to access education and employment. Time off due to illness, unpredictability of symptoms, inability to plan ahead and variation of pain/energy levels all had a negative impact of ability to work/attend places of education. Planning time for hospital appointments, treatments also had an impact of school/work attendance. The financial impact of this was particular noted by respondents. *'I work part time unable to manage full time'* *'Exhaustion impacts on work as does treatment and pain'* *'Lost some jobs due to hospital visits'* *'Yes, I had time off school, wasn't able to engage in university life and not as sociable at work'* **Social** – Respondents commented that maintaining relationships with friends or partners can be difficult, particularly if fatigue prevents socialising. Respondents report being unable to socialise for a variety of reasons, including: Exacerbation of pain and fatigue (needing to stay in bed); being unable to eat in restaurants due to gastrointestinal symptoms, avoiding areas where they may become too hot/cold, low mood, feeling misunderstood by the general public. *'I had to postpone many events over the years and now I decline invitations'* *'Often drop out of social activities due to different symptoms of the disease. Family now understand and work around me if needs be'* A respondent in a further MPS Society survey (3) commented specifically that Fabry Disease has a negative impact on intimate relationships. Which further intensifies feelings of guilt, shame and low self –esteem *'No relationship due to confidence issues with Fabry'*

Current treatment of the condition in the NHS **7. What do patients or carers think of current treatments and care available on the NHS?**	Review in May 2022 of adult patient numbers across 5 UK (England) Specialist centres (1) determined there was approximately 1200 Fabry Disease patients in England (40% male, 60% female). Approximately 50% of patients were on active treatment. The average number of newly diagnosed adult patients per year is 15. First line therapies available on the NHS include; **Enzyme replacement Therapy (ERT)** Replagal – Paediatric/Adult Fabrayzme – Paediatric/Adult **Chaperone** Migalastat – (Children from 12 years) Guidelines for the treatment of Fabry disease are available through the BIMDG https://www.bimdg.org.uk/site/guidelines-lsd.asp?t=1 Respondents to a survey conducted by the MPS Society (3) suggests that: On the licenced doses of ERT a majority of respondents report benefit from their once a fortnight Enzyme Replacement Therapy (ERT); reporting reduction in fatigue/gastrointestinal symptoms/pain. Respondents believe that early access to ERT will prevent/delay end organ damage. Reported advantages included: *'Hopefully keeping severe symptoms at bay'* *'Slows the progression of the disease'* *'not so tired'* *'Gastrointestinal symptoms do not continue whilst on treatment'* *'Only just started but headaches are less'*

	The symptoms most commonly reported to persist (at reduced severity) by those on ERT are Pain (tingling/burning), heat/cold intolerance. Headaches migraines. Patients have reported end organ damage that was unchanged while on treatment and the frequency of potentially life-threatening events such as stroke and Cardiac events were reduced. The invasive nature of a regular ERT infusion was noted by some respondents but for the majority, it is a small price to pay to prevent further Fabry disease progression. Those receiving a licensed dose of chaperone therapy reported a similar profile of symptoms persisting while on treatment. Clinicians have reported that chaperone therapy has shown improvements in cardiac symptoms (mainly reducing LVM) and has shown stabilization of Kidney function. This technology is only effective in Fabry patients with an amenable mutation. *'Hopefully it will help me not have any more strokes and heart attacks'* *'Much easier to administer'* Across all existing treatments participants reported Fabry Disease having a continuing impact on physical activity, work/education, relationships, emotional wellbeing.

8. Is there an unmet need for patients with this condition?	Approximately 50% of the UK Fabry disease population are untreated (1). **<u>Pain</u>** Both male and female patients with Fabry disease experience significant Fabry specific pain, which affects their quality of life. Morand O. et al reports that half of Fabry Disease patients experience frequent pain/moderate to severe pain/pain in their hands and feet. Pain frequency, intensity and location were similar for males and females. ***(Morand O et. al. Symptoms and Quality of Life in Patients with Fabry Disease: Results from an International Patient Survey Adv Ther 2019 36:2866–2880)*** Pain has been identified by the MPS Society as a symptom that often persists with or without treatment (3) and there is a correlation between pain severity and poor mental health/emotional wellbeing (2) *'I am unable to do physical activity, I suffer swelling and pain, get hotter and pain crisis starts. I'm not as mobile, I get too fearful of the pain it causes'* *'Limited ability to move around when in significant amount of pain. Don't leave the house regularly. Need a wheelchair if I know they'll be more than 10 mins of walking or standing for long periods. Can't use items in kitchen. Can't exercise anymore'* *'I get lots of pain in arms and legs when trying to exercise, carrying bags is incredibly painful on my hands, weakness is making it hard to lift things'* **<u>Gastrointestinal Symptoms</u>** Gastrointestinal symptoms have been identified as a group of symptoms that whilst showing some improvement with treatment, often persist to some degree (3) *'GI symptoms improved'* *'Slightly, not as many upset tummies, burning sensation not as bad as when young'* GI disturbance has been reported as a key disruptor to daily functioning and social integration (2).

	<u>Quality of life(QoL)</u> Andonian et. al. reports that individuals affected by Fabry disease reported an overall reduction in Quality of Life. Most frequently reported complaints occurred within the dimensions pain/discomfort (69.7%), daily activities (48.9%) and anxiety/depression (45.4%). ***(Andonian C, et.al Quality of life in patients with Fabry's disease: a cross-sectional study of 86 adults. Cardiovasc Diagn Ther 2022;12(4):426-435. doi: 10.21037/cdt-22-215.)*** This mirrors the results of MPS surveys (2,3) which have found that the vast majority of individuals with Fabry Disease report poor mental health, anxiety and poor emotional wellbeing that correlate with disease burden (most commonly pain/GI manifestations) *'Pain and exhaustion can make you feel very low'* *'Yes, I am unable to do physical activity, I suffer swelling and pain, get hotter and pain crisis starts. I'm not as mobile, I get too fearful of the pain it causes'* *'Yes, feeling pain affects my emotional wellbeing, makes me more snappy and if in crisis my emotions are more stressed. The stress to manage the symptoms has an effect and spontaneity is limited as plans have to be made to limit possible symptoms or events have to be cancelled because of not being well. I get anxious a lot, dreading the pain, but also dreading situations where pain could be brought on/ worsened'* Fear of early death and the increased likelihood of life-threatening events (stroke/cardiac events) was also reported as a significant stressor (3) Pain and Gastrointestinal symptoms (and the associated burden on QoL) are among the most commonly reported symptoms within both the treated and non-treated population.

Advantages of the technology **9. What do patients or carers think are the advantages of the technology?**	When surveyed, individuals receiving treatment for Fabry disease highlighted the following perceived and experienced advantages of treatment (3): Slow progression of symptoms * Improved health Preventing end organ damage * Keeping symptoms 'at bay' Reducing pain and fatigue Extend life expectancy. Reduced frequency of potentially life-threatening events such as stroke and Cardiac events *'Lessened severity/frequency of continuous pain'* *'Keeping the damage to my organs stable'* *'Reduces likelihood of long term effects of Fabry or at least slows down damage'* All ERT clinical trial respondents reported and improvement in GI symptoms and all but one reported an improvement in pain. * *'Slightly not as many upset tummies, burning sensation not as bad as when young'* *'About 40% less painful'* *'Reduced diarrhoea by half'* *'somewhat from 20 yrs ago but still difficult to manage'* Ruderfer et/ al. hypothesises that pegunigalsidase alfa has a potential to show superior efficacy versus the currently used enzyme replacement therapies in the treatment of Fabry disease patients due to improved pharmacokinetic and biodistribution qualities. [Clinical trail info] An MPS Society survey suggests that those enrolled in the clinical trial may experience improvement in disease areas poorly targeted by existing therapies (Pain/GI symptoms) (3) **(Ruderfer et.al. Development and Analytical Characterization of Pegunigalsidase Alfa, a Chemically Cross-Linked Plant Recombinant Human α Galactosidase A for Treatment of Fabry Disease. Bioconjugate Chem. 2018, 29, 1630−1639)** A case report of a 43 year old treated with Pegunigalsidase alfa demonstrated no histological signs of pathological accumulation in arterial and venous endothelium alongside stabilised kidney function and improved

	gastrointestinal symptoms, arthralgias, and peripheral pain. Suggesting a potential benefit of Pegunigalsidase alfa when compared to existing therapies. **(Dostálová G, Hulkova H, Linhart A. Anderson-Fabry disease: No histological signs of pathological accumulation in arterial and venous endothelium during pegunigalsidase alfa therapy. Kardiol Pol. 2021; 79(12): 1385–1386, doi: 10.33963/KP.a2021.0139.)**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	When surveyed, individuals receiving treatment for Fabry disease highlighted the following disadvantages of treatment (3): Time involved in scheduling drug delivery * Time involved in receiving treatment * Deterioration of veins and difficulties with cannulation * * Specifically noted by those enrolled in clinical trial

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Based on data from an MPS Society survey approx. 50% of Fabry patients are untreated. Of that 50% it can be assumed that a proportion did not meet the criteria for treatment at the time of the survey. https://bimdg.org.uk/site/guidelines-lsd.asp?t=1. However, it is anticipated that others will fall in to one of the following groups: • Untreated due to treatment related reactions to currently available therapies • Those who have defaulted on regular follow-up with a specialist centre Patients who have developed antibodies to existing therapies will reduced efficacy of treatment. Lender et. al describes the finding that pre-existing anti-drug antibodies in Fabry disease show less affinity for pegunigalsidase alfa. Patients who meet the eligibility criteria for treatment may therefore benefit from a therapy switch to PRX-102 to improve treatment outcomes. **(Lender M.et.al Pre-existing anti-drug antibodies in Fabry disease show less affinity for pegunigalsidase alfa Molecular Therapy: Methods & Clinical Development Vol. 26 September 2022)**

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	no comment

Other issues **13. Are there any other issues that you would like the committee to consider?**	Fabry Disease is a life limiting condition that carries with it a significant burden. Individuals diagnosed with Fabry often experience debilitating pain/fatigue/ GI symptoms that have been found to persist despite the use of existing therapies. The impact of disease burden on the mental health is well documented in the literature, has been highlighted by MPS Society/RDPA survey (2,3,4) and is witnessed by the MPS Society Support in interaction with the patient community. The impact of Fabry disease is however best described by patients themselves. These are just a few statements from MPS Society members about the impact of Fabry on their day to day lives: Fabry disease is like……(4) *'Dragging a weight around with you. You never know how heavy it is going to be from day to day'* *'A ticking time bomb'* *'A living hell. Honestly, if there is a hell then Fabry disease is what it is'* *'Living with a bit of a gremlin that will one day affect me but so far hasn't'* *'Living under a cloud'* *'You try to stay positive but… it's very emotional and it drains you'* *'Normal to me, because I don't know what living without Fabry disease is like'* *'Having no control over your life. Not being able to plan from one day to the next'* *'Living with a lifelong condition that has no cure. It's scary and overwhelming but with hope'*

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Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• 50% of Fabry Disease Community in the UK are untreated • Pain and gastrointestinal symptoms are poorly treated by existing therapies but have been reported to be more successfully targeted by Pegunigalsidase alfa • Patients who have developed antibodies to existing therapies may benefit from a switch to Pegunigalsidase alfa

Thank you for your time.

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Single Technology Appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Fabry disease or caring for a patient with Fabry disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 30 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with Fabry disease

Table 1 About you, Fabry disease, current treatments and equality

1. Your name	[redacted] (please keep confidential)
2. Are you (please tick all that apply)	☒ A patient with Fabry disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Fabry disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPS
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Fabry disease? **If you are a carer (for someone with Fabry disease) please share your experience of caring for them**	I was diagnosed with classic Fabry-Anderson disease in June 2009, and I was treated with ERT (Replagal) fortnightly until 2018. My participation in the Pegunigalsidase alfa trial (BRIDGE) started in January 2019, and I am now on the Extension phase of the trial. Since my initial diagnosis, I have included the ERT treatment in my daily routine without any problems. I have experience of living with Fabry both as a patient and as a member of a family considerably affected by the disease. I currently lead a full and independent life. So far, I can work full-time, engage in social and cultural activities, and I am physically active, although I have stopped some of the activities I once enjoyed (for example hiking). Nevertheless, I experience some of the physical symptoms and psychological effects associated with the condition, in mild form. Physically, my symptoms are mainly gastro-intestinal, including altered bowel habits and abdominal pain. Although I have found ways of managing these symptoms, they affect my quality of life from time to time. I also have very mild episodes of vertigos, and some angiokeratoma. In line with Fabry disease, some of my main organs have started to show the effects of the condition, and I now present with a-symptomatic arrythmia, related to cardiomyopathy (LVH), both closely monitored. Psychologically, I feel anxious about the progression of the disease and the uncertainty that lies ahead. My anxiety is compounded by seeing how the disease affected my brother and mother, who both suffered from kidney failure. My brother also developed vascular dementia due TIAs in the last few years of his life. The memory of their suffering has an enduring effect on my emotional well-being.

	Practically, living with Fabry has resulted in some difficulties in obtaining insurance and some work-related anxiety concerning whether and what information to disclose in the workplace.
7a. What do you think of the current treatments and care available for Fabry disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatments available on the NHS (ERT and Chaperone Therapy) are essential for patients living with Fabry; they slow progression of the disease and help in managing its effects, thus enhancing overall quality of life. Based on discussion I had with other patients in focus groups, there is consensus on the crucial role of treatment.
8. If there are disadvantages for patients of current NHS treatments for Fabry disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Any disadvantage of current NHS treatments for Fabry disease is, in my view, truly negligible if compared with the devastating effects of no treatment. I have personally not experienced any significant disadvantage with ERT. However, perhaps the administration of ERT requires some advance planning and logistical organisation.
9a. If there are advantages of Pegunigalsidase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Pegunigalsidase alfa help to overcome or address any of the listed disadvantages of current**	Pegunigalsidase alfa has had the crucial advantage of stabilizing my renal function, which was previously declining. This has been invaluable for my quality of life, both physically and emotionally, since, in addition to the physical benefits, it has given me reassurance and hope that the progression of the disease can be more significantly slowed down in some respects, if not halted entirely. I also understand that Pegunigalsidase alfa has positive effects in limiting the production of antibodies that restrict the efficacy of treatments, while also remaining in circulation in the system for longer than similar treatments.

treatment that you have described in question 8? If so, please describe these	The positive effect on my renal function is the most important advantage for me.
10. If there are disadvantages of Pegunigalsidase alfa over current treatments on the NHS please describe these. For example, are there any risks with Pegunigalsidase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have not experienced any disadvantages of Pegunigalsidase alfa. I have found the treatment to be safe, well-tolerated, with no negative effects to report and its administering well-organised clinically and logistically.
11. Are there any groups of patients who might benefit more from Pegunigalsidase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Any patient or group of Fabry patients with renal problems will benefit from Pegunigalsidase alfa. In addition, any group of people currently not treated might well benefit from it.
12. Are there any potential equality issues that should be taken into account when considering Fabry disease and Pegunigalsidase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I am not aware of any specific equality issue that might be noted when considering Fabry disease and Peguningalsidase alfa.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Introducing new treatments with potential additional benefits for Fabry patients is invaluable in offering clinical advancement while restoring hope in the possibility of limiting the devastating effects of the disease.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Although I currently lead a full and independent life, with no significant limitations, I experience some of the physical symptoms and psychological effects of Fabry, albeit in mild form. Physically, my symptoms are mainly gastro-intestinal, including altered bowel habits and abdominal pain; I also have some cardiac effects (LVH). Psychologically, I feel anxious about the progression of the disease and the uncertainty that lies ahead, specifically in relation to main organ deterioration.
- Any disadvantage of current NHS treatments for Fabry disease is, in my view, truly negligible if compared with the devastating effects of no treatment.
- Compared with my previous ETR, Pegunigalsidase alfa has had the crucial advantage of stabilising my renal function, which was previously declining. This has been invaluable in enhancing my quality of life, both physically and psychologically.
- I have not experienced any disadvantages of Pegnigalsidase alfa. I have found the treatment to be safe, well-tolerated, with no negative effects to report. Its administration has been well-organised both clinically and logistically. Click or tap here to enter text.
- Any patient or group of Fabry patients who experience renal decline will benefit from Pegunigalsidase alfa. In addition, any group of people currently not treated might well benefit from it.

Thank you for your time.

Your privacy

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Pegunigalsidase alfa for treating Fabry disease [ID3904]

STA Report

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Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Clinical Evidence Manager, BMJ-TAG, London Archie Walters, Health Economist, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMJ-TAG, London Nicole Downes, Senior Clinical Evidence Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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AE	Adverse event
ACEi	Angiotensin converting enzyme inhibitor
ADAs	Anti-drug antibodies
ARB	Angiotensin II receptor blocker
BIMDG	British Inherited Metabolic Disease Group
BPI	Brief Pain Inventory
CFB	Change from baseline
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
E2W	Every 2 weeks
E4W	Every 4 weeks
eGFR	Estimated glomerular filtration rate
E2W	Every 2 weeks
E4W	Every 4 weeks
EAG	External Assessment Group
EMA	European Medicines Agency
ERT	Enzyme replacement therapy
FCE	Fabry clinical event
FD	Fabry disease
Gb3	Globotriaosylceramide
GI	Gastrointestinal
IgG	Immunoglobulin G
IRR	Infusion-related reaction
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
LSD	Lysosomal storage disorders
LVMI	Left ventricular mass index
Lyso-Gb3	Globotriaosylsphingosine
MRI	Magnetic resonance imaging
MSSI	Mainz Severity Score Index
NICE	National Institute of Health and Care Excellence
OR	Odds ratio
PEG	Polyethylene glycol
PK	Pharmacokinetics
PP	Per-protocol

QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
UPCR	Urine protein to creatinine ratio

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	Exclusion of migalastat as a comparator	2.3.3
2	Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa	2.3.3
3	Transition probabilities lack external validity given disease epidemiology	4.2.3
4	The assumption of non-inferiority translating into clinical equivalence in the model given the key issue of non-inferiority	4.2.3
5	Cost effectiveness of ERTs	2.3.3

Abbreviations: ERT, enzyme treatment therapy.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is not modelled to affect QALYs as the company assumes equal treatment effectiveness between treatments.

The technology is modelled to affect costs as it has lower unit price than current treatments.

The modelling assumption that has the greatest effect on the incremental cost effectiveness ratio (ICER) is when adjusting the in-model average life expectancy to be reflective of Fabry disease (FD) patient life expectancy.

1.3 Summary of the EAG's key issues

Table 2. Issue 1. Exclusion of migalastat as a comparator

Report section	2.3.3
Description of issue and why the EAG has identified it as important	Migalastat was deemed not to be a relevant comparator by the company but, based on clinical expert advice, the EAG considers it to be a relevant comparator for patients with an amenable mutation. The EAG's clinical experts reported that for patients with an amenable mutation, migalastat or ERTs would be relevant treatment options and thus pegunigalsidase alfa would represent an additional treatment option for patients with an amenable mutation. The EAG therefore disagrees with the company's proposed exclusion of migalastat as a relevant comparator and considers clinical and economic evidence should be provided to enable a comparison of pegunigalsidase alfa with migalastat.
What alternative approach has the EAG suggested?	The inclusion of migalastat as a comparator with clinical effectiveness and cost-effectiveness results presented.
What is the expected effect on the cost-effectiveness estimates?	The extent of any impact on the ICER is unclear.
What additional evidence or analyses might help to resolve this key issue?	Clinical and cost-effectiveness analyses including migalastat as a treatment option for patients with an amenable mutation.

Abbreviations: EAG, external assessment group; ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio.

Table 3. Issue 2. Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa.

Report section	2.3.3
Description of issue and why the EAG has identified it as important	The EAG considers there to be a lack of robust clinical evidence to draw conclusions of clinical equivalence between pegunigalsidase alfa and any of the comparators in this appraisal. The EAG considers the key clinical effectiveness data of relevance to the NICE final scope to be from BALANCE which compared pegunigalsidase alfa with agalsidase beta. The EAG considers there to be differences in the population of the BALANCE RCT compared to the UK Fabry disease population limiting its generalisability; the inclusion and exclusion criteria for BALANCE restricted the population to previously treated patients with renal impairment. Additionally, there is a lack of head-to-head data comparing pegunigalsidase alfa with agalsidase alfa. The EAG is also concerned about the robustness of the company's claims of non-inferiority for pegunigalsidase alfa compared with agalsidase beta and notes that there was a change in the primary assessment endpoint of BALANCE as a result of a protocol amendment, from assessment of non-inferiority at 12-months to assessment of non-inferiority at 24-months. In the draft SmPC it is stated: "[redacted]". The EAG only had access to limited data from the 12-month analysis, which were provided in the draft SmPC, and [redacted] the primary analysis of the 24-month data in BALANCE was based on median values. The EAG considers this key issue likely to be unresolvable but notes that in HST4 the committee did not reject the assumption of equivalence for the comparison of migalastat with agalsidase alfa and agalsidase beta: "*The committee concluded that, despite some important uncertainties in the clinical evidence, migalastat may provide similar outcomes to ERT*."
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	The EAG considers this issue likely to be unresolvable based on the clinical evidence available at this time but the EAG considers results for mean and median eGFR and change from baseline should be consistently provided for both the 12 and 24 month time-points in BALANCE to enable comparison and support the company's conclusion of non-inferiority.

Abbreviations: EAG, external assessment group; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; HST, highly specialised technologies guidance; N/A, not applicable; NICE, National Institute of Health and Care Excellence; RCT, randomised controlled trial; SmPC, summary of product characteristics; UK, United Kingdom.

Table 4. Issue 3. Transition probabilities lack external validity given disease epidemiology

Report section	4.2.3
Description of issue and why the EAG has identified it as important	The EAG is concerned that given the EAG's independent clinical experts and CS outline Fabry disease as a progressive condition which is associated with the accumulation of symptoms, the transition probabilities used in the model instead reflect single symptom development and then death. A large component of the cost-effectiveness model is the progression of patients from single symptom health states to more complex health states; however, in the cycle with the highest volume of patients transitioning to other health states almost 98% of patients remain in their current health state with over 50% of those who do transition between health states moving from the Pain to Other symptoms health state. The EAG accepts that there is limited relevant information available to inform these probabilities but would like to draw attention to the lack of external validity and therefore potential generalisability of the patient journey outlined in the model.
What alternative approach has the EAG suggested?	At clarification, the EAG requested the company to use an alternative dataset, the existence of which was alluded to in the CS and use this to calculate alternative transition probabilities as a scenario. The company was unable to conduct the scenario as suggested, explaining that the dataset used in the base case was deemed the most appropriate by their panel of experts.
What is the expected effect on the cost-effectiveness estimates?	As the company's base case assumes that pegunigalsidase alfa and ERT treatments have the same treatment effectiveness, even if these treatment effects were more generalisable the conclusions drawn from the cost effectiveness analysis would likely be the same.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers an alternative dataset, preferably more contemporary and based on UK patients, would help confirm or alleviate the concerns the EAG has in the company's current approach. However, based on the company's response at clarification, these data may not be available.

Abbreviations: CS, company submission; EAG, external assessment group, ERT, enzyme replacement therapy, LY, life years; QALYS, quality adjusted life years.

Table 5. Issue 4. The assumption of non-inferiority translating to clinical equivalence in the model given the key issue of non-inferiority

Report section	4.2.3
Description of issue and why the EAG has identified it as important	The EAG notes that the same estimates of treatment effectiveness have been applied to pegunigalsidase alfa and other ERT treatments. As such any uncertainty around the difference in treatment effectiveness between treatments is not captured by the model, with this being especially true for the PSA for which the same random parameter variation is applied to each treatment. Given the uncertainty around the assumption of non-inferiority and therefore treatment effectiveness, the EAG considers that this uncertainty has not been addressed by the company and is critical for decision making.
What alternative approach has the EAG suggested?	At clarification the EAG asked the company to include transition probabilities in the PSA and to adapt the model such that the uncertainty around the treatment effect from BALANCE was included in the model and PSA.
What is the expected effect on the cost-effectiveness estimates?	It's expected that controlling for the uncertainty associated with treatment effectiveness between treatments would greatly influence and lead to a more accurate decision of cost effectiveness. This is due to the greater insight into the QALY difference between treatments, that under the company base case assumptions are the same. As such the decision of cost effectiveness lies in the difference in costs and not the difference in treatment effectiveness which is inherently uncertain.
What additional evidence or analyses might help to resolve this key issue?	An updated model which incorporates the uncertainty associated with the treatment effects in BALANCE.

Abbreviations: EAG, external assessment group; ERT, enzyme replacement therapy; PSA, probabilistic sensitivity analysis; QALY, qualitative life year.

Table 6. Issue 5. Treatment effects of ERTs

Report section	2.3.3
Description of issue and why the EAG has identified it as important	Similar to the issue raised in HST4, the EAG notes there are uncertainties associated with the treatment effect and cost-effectiveness of ERT treatments. The *Rombach et al.* study which this STA and HST4 draw many of their assumptions from outlines that even with a willingness to pay threshold of €1M / QALY, the probability of cost effectiveness is less than 0.1. As such, the EAG is concerned that pegunigalsidase alfa is being compared to treatments that are not cost-effective, with the inherent problems that causes for this appraisal and any subsequent appraisals (especially if pegunigalsidase alfa is approved).
What alternative approach has the EAG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that an evaluation of all treatments for Fabry disease, e.g. within an MTA, would be required to establish which, if any, of the available treatments represent good value for money for the NHS.
What additional evidence or analyses might help to resolve this key issue?	The EAG accepts that the required analysis is beyond the scope of this STA but considers it important to flag the potential impact decisions made within this STA could have for future appraisals of Fabry disease.

Abbreviations: EAG, external assessment group; ERT, enzyme replacement therapy, FD, Fabry disease, NICE, National Institute for Healthcare and Excellence, MTA, multiple technology assessment; QALY, quality adjusted life year.

1.4 Summary of EAG's preferred assumptions and resulting incremental costs

Outlined below are the EAG's preferred assumptions and the incremental costs between pegunigalsidase alfa and agalsidase alfa and agalsidase beta comparators. The assumption which had the greatest influence over incremental costs was adjusting the model so that patient life expectancy was reflective of that of Fabry disease (FD) patients.

Table 7. Summary of EAG's preferred assumptions and resulting ICER

Scenario	Incremental costs of pegunigalsidase alfa and agalsidase alfa	Incremental costs of pegunigalsidase alfa and agalsidase beta
Company corrected base case (post clarification)	-£475,181	-£471,243
Increase the proportion of patients requiring nurse assisted infusions to 90%	-£465,595	-£476,995
EAG estimation of acute complication costs	-£475,181	-£471,243
Removal of costs associated with social workers	-£475,181	-£471,243
Mortality adjusted to FD patient average life expectancy	-£394,741	-£391,520
EAG clinical expert assumptions for general management of FD	-£475,181	-£471,243

Abbreviations: EAG, external assessment group, FD, Fabry disease.

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 6.2

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of pegunigalsidase alfa (PRX–102, Elfabrio®; Chiesi) for treating adults with Fabry disease (FD). The company reports that they are positioning pegunigalsidase alfa for a narrower population compared to the NICE final scope[1] and the proposed European Medicines Agency (EMA) indication for pegunigalsidase alfa. The company's proposed positioning of pegunigalsidase alfa (PRX-102) is for adults with FD who would usually be treated with an enzyme replacement therapy (ERT) and the rationale for selecting this population is that it represents how pegunigalsidase alfa will be used in UK clinical practice. The EAG is concerned that the company deems migalastat not to be a relevant comparator and that no comparison between pegunigalsidase alfa and migalastat has been presented in the company submission (CS). The EAG's view of the treatment pathway and critique of the company's choice of comparators is detailed in Sections 2.2.1, 2.3, and 2.3.3.

2.2 Background

Within Section B.1 of the CS, the company provides an overview of:

- Fabry disease (FD) and its clinical signs and symptoms;
- The incidence and prevalence of FD;
- Mortality associated with FD; and
- The burden of FD and impact of enzyme replacement therapy (ERT).

In summary, FD is a rare,[2] progressive, X-linked lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-galactosidase A, due to a mutation in the galactosidase alpha (*GLA*) gene. FD results in the dysfunction of metabolic processes leading to progressive organ dysfunction and a reduced life expectancy. Patients with FD are usually first diagnosed as adults and experience a variety of clinical signs and symptoms that commonly include renal dysfunction, cardiovascular (CV) problems, neuropathic pain, cerebrovascular disease and gastrointestinal (GI) problems.[3-5]

The severity of FD depends on the extent of the α-galactosidase A deficiency and it is typically defined as classic FD or non-classic FD. The classic form tends to be more severe with earlier symptom onset, often in childhood and in multiple organs. The later-onset non-classic form is generally milder, with slower progression and more limited organ involvement.[5, 6] The *GLA* gene is located on the X chromosome and so all males carrying the mutation (i.e. hemizygous males) are

affected but females with either one or two affected X chromosomes can also be affected although the classic phenotype is more common in males.[3, 5, 6]

The company highlighted that there is uncertainty in the size of the FD population in the UK but estimated that the prevalent FD population in England is approximately 2,100 patients, with approximately 90 incident patients per year. Additionally, the company reported that of the prevalent FD population, only 50% are estimated to be diagnosed, resulting in an estimated 1,050 diagnosed FD patients in England.

2.2.1 Treatment pathway

In the NHS in England, clinical management of adults with FD is delivered through the lysosomal storage disorders (LSD) highly specialised service, provided by Highly Specialised LSD Centres.[7] The company reported that the clinical manifestations of FD are highly heterogeneous and there is no specific, clinically defined treatment pathway for FD, instead patients are treated on an individual basis.[4, 8]

FD may be treated with intravenous (IV) infusions of ERTs (agalsidase alfa or agalsidase beta) or if a patient has an amenable mutation, oral chaperone therapy with migalastat can be used.[7] UK clinical guidelines for the treatment of adults with FD published by the British Inherited Metabolic Disease Group (BIMDG) in 2020 recommend starting ERT, based on early clinical signs of renal, cardiac or neurological involvement.[9] The company reported that most males and approximately half of females meet these criteria when diagnosed. The BIMDG guidelines recommend IV infusions of ERT for adult patients (≥ 16 years) with a confirmed diagnosis of FD and meeting treatment initiation criteria,[9] specifically agalsidase beta 1 mg/kg every 2 weeks (E2W) (in some circumstance 0.3 mg/kg E2W) or agalsidase alfa 0.2 mg/kg E2W. Migalastat is recommended (123 mg capsule once daily on alternate days) as an alternative treatment option for FD patients with an amenable mutation and meeting treatment initiation criteria.

In 2017, NICE recommended migalastat as an option for treating FD in people over 16 years of age with an amenable mutation, only if migalastat is provided with the discount agreed in the patient access scheme (PAS), and only if ERT would otherwise be offered.[10] The EAG notes that neither agalsidase alfa or agalsidase beta have been formally evaluated by NICE. Estimates from the published literature suggest that migalastat is eligible for use in between 35 to 50% of the global FD population.[11] However, the company highlight that not all eligible patients will be suitable for treatment because of issues with tolerance or adherence, as migalastat requires a 4-hour fasting

window to be effective (2 hours before and after administration).[12] The EAG notes that tolerance and adherence may also be issues with ERTs but for different reasons.

Agalsidase alfa and agalsidase beta are administered intravenously every two weeks (E2W) and can induce the production of neutralising anti-drug antibodies (ADAs), which may reduce their long-term benefit.[13, 14] In addition, ERTs may be associated with infusion-related reactions (IRRs), defined as hypersensitivity or anaphylactoid reactions occurring during or after (delayed infusion reactions [DIR]) IV administration.[15] IRRs and DIRs may be managed through the use of pre-medication such as antihistamines and prolongation of infusion times to reduce their occurrence.

The company reported that clinicians attending a UK advisory board stated that ERT treatment is usually initiated with agalsidase alfa as it has a shorter infusion time, and if there is evidence of organ damage progression, patients would be switched to agalsidase beta due to its higher dose of ERT.[16] The EAG's clinical experts reported that this is not the case and the choice of ERT is based on multiple factors.

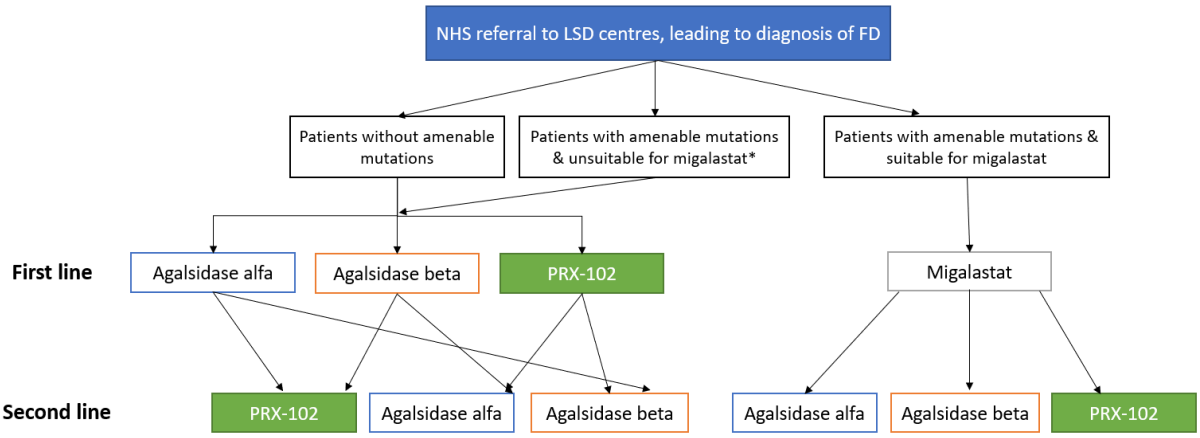
The EAG notes that pegunigalsidase alfa is indicated for long-term ERT in adult patients with a confirmed diagnosis of FD.[17] The company propose that pegunigalsidase alfa will be used as a treatment option for patients with symptomatic FD who would usually be offered ERT in line with BIMDG guidelines,[9] including treatment-naïve patients and those previously treated with currently available therapies. The company further specify that the eligible patient population would only include patients with an amenable mutation who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). The EAG considers that this restriction on eligibility for patients with an amenable mutation for potential treatment with migalastat is not clear-cut and disagrees with the company's pictorial representation of the current treatment pathway for FD patients (Figure 1).

Based on clinical expert advice and the NICE highly specialised technologies (HST) guidance in HST4[10], the EAG considers that ERTs are also a treatment option for patients with an amenable mutation and suitable for treatment with migalastat. The EAG's clinical experts also advised that treatment for FD is not typically classified as first-line and second line, instead all current treatments (ERT or migalastat) would be considered in treatment naïve patients meeting the criteria for treatment with the only restriction being that migalastat is only an option for patients with an amenable mutation. The EAG therefore considers that not all patients with an amenable mutation and suitable for migalastat will necessarily receive migalastat and as such ERTs are a relevant treatment option for some patients with an amenable mutation. The EAG notes that the company

are defining eligibility for pegunigalsidase alfa for patients with an amenable mutation as being restricted to only those patients in whom migalastat is deemed to be unsuitable. The EAG therefore considers there is potentially a population of patients who have an amenable mutation and are suitable for migalastat or ERT but won't be eligible for pegunigalsidase alfa due to the restricted positioning proposed by the company.

The EAG also notes that the company's proposed positioning of pegunigalsidase alfa in the treatment pathway is narrower than the marketing authorisation and that the company consider their proposed position to be representative of how pegunigalsidase alfa will be used in UK clinical practice. However, clinical experts have advised the EAG that for patients with an amenable mutation, migalastat or ERTs would be relevant treatment options. In the EAG's clinical experts view, pegunigalsidase alfa could be an additional treatment option for use in patients with an amenable mutation. The EAG therefore recommends that migalastat is maintained as a comparator for pegunigalsidase alfa as per the NICE final scope. Further critique of the comparators is provided in Section 2.3.3.

Figure 1. Proposed place of pegunigalsidase alfa (PRX-102) in the treatment pathway (Reproduced from CS, Figure 1)



Key: FD, Fabry disease; LSD, lysosomal storage disorder.

Notes: *, unsuitable due to issues with adherence, tolerance, patient/clinician choice, or any other reason.

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE,[1] together with the company's rationale for any deviation from this, is provided in Table 8. Key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow below, but the EAG notes that in general the decision problem specified by the company matches the NICE final scope

well, with the main difference being the absence of migalastat as a comparator in both the review of clinical effectiveness and the economic model.

Table 8. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with FD	Adults with FD who would usually be treated with an ERT	Treatment choice in FD is individualised; however, in UK clinical practice it is anticipated that migalastat would continue to be used in patients with amenable mutations due its targeted nature and established use. The focused positioning of this submission is representative of how pegunigalsidase alfa (PRX-102) will be used in UK clinical practice.	The EAG is concerned that the company's definition of the population does not align with their proposed positioning for pegunigalsidase alfa because there is a population of patients who have an amenable mutation and are suitable for migalastat but who may be treated with an ERT instead. See Section 2.3.3 below for further discussion. The EAG is also concerned about the generalisability of the results from the BALANCE RCT to clinical practice in the UK due to the restricted eligibility criteria including the requirement for patients to have renal impairment and to have received prior ERT. See Section 2.3.1 below for further discussion.
Intervention	Pegunigalsidase alfa, Elfabrio®	Pegunigalsidase alfa (PRX-102), Elfabrio®	As per NICE scope	The treatment regimen for pegunigalsidase alfa in the BALANCE RCT is consistent with pegunigalsidase alfa's anticipated marketing authorisation. The EAG notes that the mean weight of patients in BALANCE may differ to the UK Fabry disease population. As it is a weight-based treatment, the mean treatment dose may differ in UK

				clinical practice. However, based on subgroup analyses from BALANCE, the EAG does not consider weight to be a treatment-effect modifier. See Section 2.3.2 below for further discussion.
Comparator(s)	• Agalsidase alfa • Agalsidase beta • Migalastat (for those aged over 16 years with an amenable mutation)	• Agalsidase alfa • Agalsidase beta	Treatment choice in FD is individualised; however, in UK clinical practice it is anticipated that migalastat would continue to be used in patients with amenable mutation due its targeted nature and established use. As such, pegunigalsidase alfa (PRX-102) would only be considered in those patients eligible for migalastat if ERT was being considered as a treatment option instead because they are unsuitable for treatment with migalastat for any reason (such as tolerance or issues with compliance or patient choice or any other reason). This updated positioning means that migalastat is no longer considered a relevant comparator for this submission.	As discussed under the population subheading above and in Section 2.2.1, the EAG is concerned that the company's definition of the population does not align with their proposed positioning for pegunigalsidase alfa because there is a population of patients who have an amenable mutation and are suitable for migalastat but who may be treated with an ERT instead. The EAG therefore considers migalastat is still a relevant comparator for pegunigalsidase alfa. The EAG also notes that the only comparative data for pegunigalsidase alfa is derived from the BALANCE RCT and compares pegunigalsidase alfa with agalsidase beta. The company has made an assumption of equal efficacy between agalsidase alfa and agalsidase beta in the economic model and the EAG is concerned about the lack or robust clinical evidence to support this decision.

				See Section 2.3.3 below for further discussion.
Outcomes	The outcome measures to be considered include: • Symptoms of FD (including pain, and gastrointestinal issues such as diarrhoea, nausea and abdominal pain) • Gb3 levels in kidney • Plasma lyso-Gb3 levels • Kidney function • Cardiac function and disease measurements (such as left ventricular mass index) • Event-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events) • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	The outcome measures to be considered include: • Symptoms of FD (including pain, and gastrointestinal issues such as diarrhoea, nausea and abdominal pain) • Gb3 levels in kidney • Plasma lyso-Gb3 levels • Kidney function • Cardiac function and disease measurements (such as left ventricular mass index) • Event-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events) • Mortality • Adverse effects of treatment (including ADAs) • Health-related quality of life (for patients) • Use of infusion premedication	Carer utilities were not expected to be influential for the value case for pegunigalsidase alfa (PRX-102) or a key driver in the model – therefore, carer utilities have not been considered in the model. Use of infusion premedication is required with current ERTs, and in some cases can cause the patient to stop treatment. Therefore, use of infusion premedication has been included as an outcome of interest within the submission.	The EAG notes that none of the clinical efficacy data from the BALANCE RCT was used in the economic model, and that an assumption of equal efficacy has been made between the ERTs and pegunigalsidase alfa. However, based on clinical expert advice, the EAG considers that the company has presented comprehensive outcome data from the BALANCE RCT within the CS for all of the key outcomes specified in the NICE final scope. The company conducted a scenario analysis which included the costs of AE management. Additionally, during the clarification stage, the company provided a scenario where disutilities associated with AEs were explored in the cost-utility analysis. See Section 2.3.4 below for further discussion.
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for	Given the non-inferiority of PRX-102 E2W compared with agalsidase beta E2W, and the conclusion of clinical equivalence between the ERTs accepted in the NICE submission for migalastat (HST4), we assume that PRX-102	N/A	The EAG notes that the time horizon was appropriate and costs considered were from an NHS and Personal Social Services perspective. Cost effectiveness results were also expressed in terms of cost per quality adjusted life year; however due to the

	estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective	E2W demonstrates equivalent efficacy to both ERTs. As such, the base case analysis is a cost comparison of ERTs, which establishes the difference between drug cost and resource costs for all considered treatments. A cost–utility analysis is presented as a scenario analysis as per the NICE reference case.		assumption of non-inferiority the company considered that a cost minimisation analysis was more appropriate for their base case analysis with a cost utility analysis provided as a scenario.
Subgroups to be considered	Patients who have an amenable mutation and are on migalastat.	Please note that we will not address this subgroup in the appraisal due to a lack of available evidence. PRX-102 will be positioned as a treatment option for all adults with FD who would usually be treated with ERTs in line with clinical guidelines.	BALANCE was not designed to examine outcomes in patients with amenable mutations. BRIDGE and BRIGHT demonstrated efficacy in a broader patient population (not just patients that were renally impaired). Clinicians from the advisory board also indicated that there was no reason to assume that mutation status is a treatment modifier (see advisory board summary report in Appendix P). However, in an integrated analysis of [redacted] patients from the PRX-102 trials, of which [redacted] had amenable mutations and [redacted] did not, results demonstrated that the presence of an amenable mutation [redacted]	The EAG notes that mutation status was not a prespecified subgroup in the BALANCE RCT and that neither baseline mutation status nor outcome data by mutation status are available in the CS. In response to clarification questions, the company presented subgroup data by sex, other prespecified subgroups for the primary outcome were provided in the CS from BALANCE. See Section 2.3.5 below for further discussion.

			[redacted] [redacted] (Appendix M5).	
Special considerations, including issues related to equity or equality				None reported by the company or EAG's clinical experts.

Abbreviations: BIMDG, British Inherited Metabolic Disease Group; EAG, external assessment group; FD, Fabry disease; Gb3, globotriaosylceramide; Lyso-Gb3, globotriaosylsphingosine; NICE, National Institute for Health and Care Excellence; PRX-102, pegunigalsidase alfa; TBC, to be confirmed.

2.3.1 Population

BALANCE[18, 19] is a multi-centre 2-year Phase III, randomised, double-blind, active-controlled study in symptomatic adults with FD experiencing kidney function deterioration (eGFR by CKD-EPI equation 40 to 120 mL/min/1.73 m^2) while on ERT (agalsidase beta for ≥ 1 year and on a stable dose for ≥ 6 months). The EAG notes that patients were enrolled across 29 centres in 12 countries: USA, the UK, the Netherlands, Spain, France, Italy, Norway, Slovenia, Switzerland, Finland, Hungary and the Czech Republic. The EAG's clinical experts reported that inclusion and exclusion criteria for BALANCE appear reasonable but agreed with the EAG that it doesn't reflect the full FD population likely to be eligible for pegunigalsidase alfa in UK clinical practice.

The EAG is particularly concerned that the BALANCE trial only includes people with deteriorating renal function and that this may not be a feature that all patients with FD have (e.g., those with the cardiac variant). In response to clarification question A6, the company reported that they had conducted a naïve comparison to determine how similar the outcomes were for the population in BALANCE compared with the differing population of BRIDGE, but the analyses were very limited due to small patient populations and differing baseline characteristics between trials such as sex and age. The company considered that the results of the naïve comparisons suggested [redacted] in efficacy of pegunigalsidase alfa for key outcomes of interest between BALANCE (pegunigalsidase alfa E2W in renally impaired population) and the single-arm study BRIDGE (pegunigalsidase alfa E2W in non-renally impaired population) but the EAG does not consider this naïve comparison to be a robust source of evidence for drawing such conclusions.

The EAG also notes that BALANCE comprises of pre-treated patients and thus does not necessarily represent the outcomes of treatment naïve patients. In response to clarification question A7, the company reported that comparison between all of the trials demonstrated that treatment-naïve patients treated with pegunigalsidase alfa E2W for 12 months exhibited similar results in regards to the efficacy outcomes investigated. The EAG notes that this comparison is again a naïve comparison involving the use of data from single-arm study PB-102-F01 and therefore considers the conclusion of generalisability lack a robust evidence base.

Additionally, the company reported that UK clinical experts consulted at an advisory board were asked specifically about the demographics of the participants in BALANCE and whether they are representative of the FD population in the UK. The company's experts noted some variations in

terms of generalisability to UK clinical practice and these included that the age of patients was slightly lower than seen in practice and younger patients, especially younger female patients, maybe associated with better renal function. There was also considered to be a slightly higher proportion of classical patients in BALANCE compared to clinical practice. However, the company concluded that there is no biological rationale for a difference in the function of ERT in the full FD population versus the renally-impaired FD population and there was general agreement among the company's experts that the results from BALANCE would be generalisable to the full FD population.[16] The company stated that this generalisability is assumed to also apply to the treatment naïve population. The EAG is concerned that there is insufficient evidence to support the generalisability of the results from BALANCE and notes that renal impairment is not present in all patients with FD (it is less common in non-classical FD than in classic FD). Additionally, the EAG notes that the primary endpoint in BALANCE for assessing non-inferiority in based on renal function.

In terms of baseline characteristics in BALANCE, the EAG notes that there was an imbalance in males and females randomised to each study arm, with a greater proportion of males in the agalsidase beta E2W arm compared to the pegunigalsidase alfa arm (72% versus [vs] 56%, respectively). It was specified in the study protocol that enrolment of females could not exceed 50% and randomisation was not stratified by sex. However, it is unclear to the EAG how the restriction on female enrolment was carried out and if there is a methodological flaw that may have led to the imbalance in sex between the trial arms in BALANCE.[20]

In the company response to clarification questions, it is reported that all female patients in BALANCE were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic ([redacted] in the pegunigalsidase alfa arm and [redacted] in the agalsidase beta arm). The EAG also notes that there are other imbalances in baseline characteristics between treatment arms in BALANCE such as [redacted] and a lower proportion with UPCR ≤ 0.5 gr/gr in the pegunigalsidase alfa arm ([redacted] vs [redacted]).[20] The EAG and its clinical experts consider it impossible to predict the overall likely direction of any resulting bias from these imbalances in baseline characteristics in BALANCE, although the EAG considers that some of the imbalance suggest the

pegunigalsidase alfa arm may have had people with less severe FD at baseline. Full details of the baseline characteristics of patients in BALANCE are presented in the CS, table 8.

The EAG also considers it important to highlight that the BALANCE RCT comprises of just 77 randomised patients and only 25 of these are in the comparator treatment arm (due to 2:1 randomisation). The EAG is therefore concerned that BALANCE comprises of a relatively small sample size and the generalisability of the results to the full FD population is unknown, although as discussed in Section 2.2, the estimated diagnosed prevalent FD population in the UK is also relatively small (n=1,050).

In the economic model the company outline a population starting age of 40 years old, justifying this age with evidence that average symptom onset is thought to be after 37 years [21] and the pooled average age across the BALANCE, BRIDGE and BRIGHT studies was between 40.5 to 44.3, which the EAG agrees with.

Unlike the BALANCE trial, the majority of FD patients at baseline in the model were not considered to be renal impaired, with no patients distributed to the end stage renal disease (ESRD) health state at cycle 0. Despite this key difference between the trial and model, the company draw on the conclusions from the BALANCE subgroup analysis which showed no significant difference of primary outcome measures across all pre-specified study groups. The EAG notes, however, that as the population only consisted of those renally impaired, no healthy renal subgroup comparison would be possible based on BALANCE. This point is further evaluated in Section 4.2.2, which discusses the modelling approach and structure.

2.3.2 Intervention

Pegunigalsidase alfa (PRX-102; Elfabrio®) is a pegylated recombinant form of human α-galactosidase-A and acts as an ERT in FD patients.[17] Pegunigalsidase alfa received a positive opinion from the EMA CHMP on 23 Feb 2023 for the long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase) and European marketing authorisation application (MAA) approval is expected on [redacted].

The anticipated recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once E2W by intravenous infusion. The EAG notes that the CS also included an alternative E4W posology but the company reported in their response to clarification questions that the E4W treatment regimen is no longer under consideration in this appraisal.

The EAG notes that the pegunigalsidase alfa treatment regimen in the BALANCE RCT was consistent with the anticipated recommended dose in clinical practice (pegunigalsidase alfa 1 mg/kg E2W) and that treatment in BALANCE was continued for up to 24 months. The EAG also notes that there is an ongoing open-label extension study and this is discussed in Section 3.2.

The EAG notes that the first few pegunigalsidase alfa infusions were administered at the study site in BALANCE but patients could thereafter receive treatment at home if the investigator and the sponsor's Medical Monitor agreed that it was safe to do so.[20] The EAG's clinical experts agree that this is likely to happen for most patients in clinical practice but that the majority of patients who receive treatment at home will still require a nurse or health care professional to set-up and start the infusion, if not fully administer the treatment. The EAG notes that in the economic model the company's base case assumption is that 50% of patients are assumed to have treatment administered without a nurse. Contrary to this, opinion provided by the EAG's independent clinical experts is that most patients require nurse assistance, with this dependent proportion being approximately 90%. The EAG requested the company to conduct a scenario with this updated proportion which led to a slight increase in total costs across treatments. This assumption is incorporated into the EAG's base case.

2.3.3 Comparators

This section contains key issues 1, 2 and 5 as outlined in Table 1.

The comparators specified in the NICE final scope are agalsidase alfa, agalsidase beta and migalastat. The EAG notes that the BALANCE RCT provides comparative data for pegunigalsidase alfa versus agalsidase beta and that the dose of both treatments (1 mg/kg E2W) is consistent with the recommended treatment regimens.

The EAG considers that the company makes a strong assumption that pegunigalsidase alfa demonstrates equivalent efficacy to both agalsidase alfa and agalsidase beta in the CS and that the evidence underpinning this assumption is limited. In response to clarification question A2, the company explain that their rationale for this decision includes that:

- BALANCE provides head-to-head data vs agalsidase beta showing non-inferiority of pegunigalsidase alfa to agalsidase beta;

- BRIDGE provides supportive switch-over evidence that shows patients treated with pegunigalsidase alfa after switching from agalsidase alfa and agalsidase beta show stable renal function;
- two RCTs providing head-to-head comparisons of agalsidase alfa and agalsidase beta (Vedder 2007[22] and Sirrs 2014[23]) demonstrate no statistical difference;
- three SLRs and meta-analyses provide no evidence that one of the existing ERTs is superior to the other;[24-26]
- an independent international retrospective cohort study (Arends *et al.* 2018) of 387 patients (192 females) found no difference in Fabry clinical events (FCEs) or eGFR slope in patients treated with agalsidase alfa or beta with a median follow-up of 4.9 years (range, 0.8–14.4 years);[27]
- NICE HST4 appraisal[10] accepted the assumption of clinical equivalence of agalsidase beta and agalsidase alfa;
- a naïve comparison between BALANCE and BRIDGE suggested there were no significance differences in pegunigalsidase alfa efficacy for key outcomes of interest between the studies, adding further evidence that the efficacy demonstrated in BALANCE was reflective of the efficacy of pegunigalsidase alfa in other studies (CS, Appendix D.1.3.1), although the analyses are limited due to small patient populations and differing baseline characteristics such as sex and age; and
- in an advisory board, the 4 UK clinical experts consulted by the company considered that the non-inferiority conclusion from BALANCE and the precedent in HST4 would be supportive of clinical equivalence of PRX-102 to the existing comparator treatments.[16]

The EAG notes that the Sirrs *et al.* 2014 RCT[23] comprised of 92 ERT naïve patients who were randomised to either agalsidase alfa 0.2 mg/kg E2W or agalsidase beta 1.0 mg/kg E2W. The study observed no statistically significant difference in endpoints between the agalsidase alfa and agalsidase beta arms (HR alfa versus beta 1.29; p=0.67) but the power was noted to be limited as 294 subjects were required within each arm to detect a 10% difference in the rate of the composite clinical endpoint (renal event, cardiovascular event, cerebrovascular event or death). Additionally, the EAG notes that 62 patients were randomised to agalsidase alfa and only 26 of the 30 patients randomised to agalsidase beta remained on agalsidase beta throughout the study due to drug supply shortages.

The EAG considers the dose of agalsidase beta (0.2 mg/kg E2W) in the RCT by Vedder *et al*. 2007[22] not to be applicable to the decision problem as the dose used is substantially lower than the 1mg/kg E2W dose recommended in UK clinical practice. Additionally the EAG notes that the study was open-label and comprised of only 34 patients.

In terms of the three systematic reviews identified as relevant sources of evidence for the comparison of agalsidase alfa versus agalsidase beta, the EAG does not consider them to provide any new robust evidence to confirm a conclusion that agalsidase alfa and agalsidase beta can be considered to have equivalent efficacy. In summary, the EAG notes that:

- El Dib *et al.* 2016[24] is a Cochrane review that evaluates the effectiveness and safety of ERT compared to other interventions, placebo or no interventions for treating FD and for the comparison of agalsidase alfa versus agalsidase beta identified only the Sirrs *et al.*[23] and Vedder *et al.*[22] RCTs discussed above;
- Lidove *et al.* 2010[25] was a literature review with no quantitative synthesis and it did not report specifically on any studies comparing agalsidase alfa with agalsidase beta, although 3 studies were mentioned in the discussion (Vedder *et al.* discussed above, second study by Vedder *et al.* which is also not relevant as it combines 0.2mg agalsidase alfa and agalsidase beta data to compare with 1mg agalsidase beta data and a third unpublished study that is potentially the Sirrs RCT discussed above); and
- Pisani *et al.* 2017[26] which assessed the impact of switching from agalsidase beta to agalsidase alfa, given a shortage of agalsidase beta. The study concluded that switching to agalsidase alfa does not worsen renal and cardiac function or FD-related symptoms, at least in the short term but does not comprise of RCT data.

The EAG also notes that the focus of HST4 was not to assess the efficacy of agalsidase alfa versus agalsidase beta and therefore does not consider it a robust source of evidence for assuming equivalent efficacy for this technology appraisal. Additionally, as discussed in Section 2.3.1, the EAG is concerned that there is insufficient evidence to support the generalisability of the results from BALANCE to the full FD population. Nevertheless, the EAG considers the available evidence does not demonstrate a statistically significant difference between agalsidase alfa and agalsidase beta.

As discussed in Section 2.2.1, the EAG is concerned about the company's positioning of pegunigalsidase alfa in the current treatment pathway and that the company has omitted migalastat as a comparator. The company clearly states that they are positioning pegunigalsidase alfa as an

additional treatment option for adults with FD *who would be treated with an ERT* and that this includes patients who are treatment-naïve, and those previously treated with currently available therapies. However, as discussed in Section 2.2.1, the EAG considers that for patients with an amenable mutation, migalastat or ERTs would be relevant treatment options. The EAG therefore disagrees with the company's proposed positioning and exclusion of migalastat as a relevant comparator and considers clinical and economic evidence should be provided to enable a comparison of pegunigalsidase alfa with migalastat. The EAG has conducted an exploratory cost-utility analysis of pegunigalsidase alfa versus migalastat which is discussed further in Section 6.2.

The EAG's clinical experts also considered it likely that neither agalsidase alfa or agalsidase beta would be considered cost-effective. The Rombach *et al.*[28] study used to inform the model economic structure, transition probabilities and health care provider (HCP) follow up in this STA and HST4 concluded that even with a willingness to pay threshold of €1M/quality adjusted life years (QALYs), the probability of cost effectiveness would be less than 0.1. At the NICE preferred willingness to pay thresholds of £20,000 and £30,000 /QALY, the probability of ERTs being considered cost-effective is almost 0. As such, the EAG is concerned that pegunigalsidase alfa is being compared to treatments that are not cost-effective, with the inherent problems that causes for this appraisal and any subsequent appraisals (especially if pegunigalsidase alfa is approved). Treatments for FD such as migalastat, which was suggested as non-inferior to ERTs in HST4[10], have also been shown to be comparable to placebo in other studies[29] . While the EAG accepts that an independent evaluation of all treatments for FD is beyond the scope of the current appraisal, and would be more appropriately undertaken with a Multiple Technologies Appraisal (MTA), the EAG considers it important to highlight this issue and the likely impact that any decisions made on this appraisal are likely to have on any future evaluations. This consideration is also aligned with the EAGs concerns in the factual accuracy check (FAC) of HST4[10].

2.3.4 Outcomes

Outcome measures from BALANCE reported in the CS that are relevant to decision problem include:

- Symptoms of FD: change in pain severity (measured using the Brief Pain Inventory [BPI]), frequency of pain medication use, Mainz severity score index (MSSI), occurrence of Fabry clinical events (FCE);
- FD biomarkers: Plasma lyso-Gb3 concentration, Urine lyso-Gb3 concentration and Plasma Gb3 concentration;

- Kidney function: Annualised change (slope) in $eGFR_{CKD\text{-}EPI}$, change in urine protein/creatinine ratio (UPCR), achievement of kidney function therapeutic goals as per the European Expert Consensus Statement on Therapeutic Goals in FD;[39]
- Cardiac function and disease measurements: left ventricular mass index (LVMI [g/m^2]) based on cardiac MRI, normal exercise stress test and normal echocardiography measurements;
- Health-related quality of life (for patients): Change in EQ-5D-5L scores;
- Mortality; and
- Adverse effects of treatment.

The EAG notes that follow-up in BALANCE was up to 24 months and considers that both the small sample size and the duration of follow-up were not sufficient to adequately capture any differences in treatment effect on the outcome of mortality. The EAG also notes that event-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events) was specified in the NICE final scope and the only outcome for which Kaplan–Meier data were presented was time to first FCE. However, the company reports that the results for time to first FCE reflect pre-existing organ involvement in ERT-experienced patients and do not allow any conclusions to be drawn on the effect of changing to a new ERT. The EAG also notes that the occurrence of the individual FCE events in BALANCE were few and therefore does not consider it possible to draw conclusions on these time-to-event data.

The company did not include the impact of adverse events (AEs) in the model, although the company conducted a scenario analysis which included the costs of AE management. Additionally, during the clarification stage, the company provided a scenario where disutilities associated with AEs were explored in the cost-utility analysis and the AEs included in the model for this scenario were reported to be treatment emergent adverse events (TEAEs) reported in >10% of patients (any grade) from BALANCE. However, the EAG considers there to be some discrepancies in the AEs included in the model compared to those reported in CS Table 29, with some AEs missing from the model but included in CS Table 29 and vice versa. The EAG is unclear of the exact impact of these potential discrepancies but notes that AEs are not a primary driver of cost-effectiveness for pegunigalsidase alfa (approximately £225 cost savings and [redacted] additional quality adjusted life years (QALYs) for pegunigalsidase alfa compared to the other ERTs). As the AE profiles between treatments are broadly comparable, the EAG agrees with their omission from the model, as the company has done in their base case analysis.

2.3.5 Subgroups

Pre-planned subgroups for the primary efficacy outcome of change in eGFR slope at 2 years in BALANCE were as follows:

- Sex (male or female);
- ADA status at baseline (negative or positive);
- FD classification (classic/non-classic);
- Baseline eGFR category (≤ 60; 60 < and ≤ 90; > 90 mL/min/1.73m^2);
- Baseline eGFR slope category (≤ -5; > -5 mL/min/ 1.73m^2/year);
- Use of ACEi/ARB at baseline (Yes/No);
- UPCR category at baseline (≤ 0.5 gr/gr; 0.5 < and < 1 gr/gr; ≥1 gr/gr); and
- Region (USA/ex-USA).

In their response to clarification questions, the company provided additional subgroup data from BALANCE on sex but reported they were unable to provide a further breakdown for sex by FD type (classic or non-classic) due to a lack of data for some of the categories. Additionally, the EAG notes that subgroup analysis for patients who have an amenable mutation and are on migalastat was requested in the NICE final scope but the EAG notes that data for this subgroup were not available from BALANCE. However, the company provided a subgroup analysis of patients with/without amenable mutations through an integrated *post-hoc* analysis of patients receiving PRX-102 within the BALANCE, BRIGHT, BRIDGE and Phase I/II studies (CS, Appendix M5). The EAG notes that the integrated *post-hoc* analysis does not include comparative data for patients on migalastat. The EAG also agrees with the company that sample size for this analysis is small (N = [redacted] with amendable mutations) and there are some imbalances between baseline characteristics between the amenable and non-amenable groups; therefore, results should be interpreted with caution.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence for this submission, which covered randomised controlled trials (RCTs) and non-randomised/observational studies. Methods and search results for the SLR are provided in Section B.2.2 and Appendix D of the company submission (CS). Limited information is provided about the methods and processes involved in the SLR process; no details are provided about whether searches were conducted according to best practice guidance, for example that provided by Cochrane,[30] or about screening and data extraction processes, such as whether this was performed by two reviewers.

There are some concerns about the search strategies for MEDLINE and Embase, for example typographical errors, the use of 'NOT' operator and methods used to limit by study design, which are discussed in Table 9 below in the EAG's critique of the SLR methods; the EAG cannot be sure that relevant studies have not been missed. On review of the Cochrane review of comparator enzyme replacement therapies (ERTs) highlighted by the company in the CS,[24] the EAG is not concerned that any relevant RCTs have been missed for these two comparators but are unsure if the same is true for potentially relevant non-randomised/observational studies of these comparators. The EAG considers it unlikely that the company would have missed any evidence (RCTs or non-randomised /observational) involving pegunigalsidase alfa (PRX-102).

The searches for the SLR were broader than the positioning described by the company in the decision problem (see Section 2.3); it covered the Fabry disease (FD) population as a whole (not limiting to those usually eligible for ERT) and also included migalastat as a possible comparator (which the company excludes from the submission). The EAG considers the coverage of the SLR to be appropriate, particularly as at the clarification stage (clarification question A1) the EAG noted that (based on clinical expert feedback) migalastat may be a relevant comparator and requested this comparison be included in the appraisal (see Section 2.2.1).

The original searches were conducted in May 2021, which were updated in late September 2022 to capture any studies published since. A total of 165 studies were said to be included in the clinical SLR, with 16 of these being RCTs. Exclusion of studies deemed by the company to be investigating interventions that are not of relevance (lucerastat [n=1] or migalastat [n=2]) further narrowed this down to 13 RCTs that investigated pegunigalsidase alfa (1 study), agalsidase alfa (6 studies) or

agalsidase beta (6 studies), and 5 non-randomised/observational studies that investigated pegunigalsidase alfa.

In the submission, the company focuses on evidence for pegunigalsidase alfa (1 RCT and 5 observational studies), with particular attention to the Phase III studies: BALANCE RCT and the single-arm studies BRIGHT and BRIDGE.[20, 31-35] However, as discussed in Section 2.3.2, the company has withdrawn the 4 weekly (E4W) regimen of pegunigalsidase alfa from this evaluation and so the company deems BRIGHT to be no longer relevant. The EAG agrees and notes that BRIGHT is a single-arm study assessing E4W treatment with pegunigalsidase alfa. Further details and a critique of included pegunigalsidase alfa studies are provided in Section 3.2 of this report. RCTs involving agalsidase alfa or agalsidase beta are also mentioned in terms of the feasibility assessment for indirect comparisons (Section 3.4). The feasibility assessment included 8 of the 13 identified RCTs,[20, 22, 23, 36-40] as some were excluded because they were dose-ranging studies only.

Table 9. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1	**The EAG considers the sources and dates searched to be comprehensive, although limited details are provided for non-database searches.** Databases searched: • Embase; MEDLINE (including In-Process); the Cochrane Library (including CDSR and CENTRAL). Registries: • ClinicalTrials.gov Conference proceedings: • Manual hand-searching of key conference proceedings from the last 2 years (2021-2022; the Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium; and the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM)) Other Grey Literature: • Reference list searches of relevant studies and SLRs • HTA websites as part of the SLR updates The original database searches were conducted in May 2021, which were updated in September 2022. Although the Cochrane Collaboration also recommend that the WHO ICTRP registry is searched,[30] based on simple searches of both registries by the EAG (searching for the term 'Fabry') there is not a concern that any relevant studies have been missed due to this omission.

		The EAG also notes that while the searching of HTA websites increases the comprehensiveness of the search strategy, the HTA websites are not named by the company, meaning it is not possible to check whether those searched were relevant or exhaustive.
Search strategies	Appendix D.1.1	**The EAG cannot be sure that search strategies used to limit by study design have not led to relevant evidence being missed in the MEDLINE and Embase searches but are not concerned that relevant RCTs have been missed** The search strategies for the literature review used free-text keywords, MeSH and EMTREE terms for the population and interventions of interest. The EAG considers the methods used for limiting study design to be appropriate for the Cochrane Library search and the MEDLINE In-Process search but could not validate the method used for the MEDLINE and Embase searches (rows 20 and 21 of Tables 1 and 4 of the CS appendices). The use of the 'NOT' operator is usually avoided or limited to avoid inappropriate exclusions, particularly if not part of a validated search filter.[30] The EAG believes rows 20 and 21 attempt to exclude literature reviews (other than systematic reviews or meta-analyses), case reports, studies in animals only, letters and editorials. Combining this row with population and intervention terms led to the removal of 1047 records (from 3727 records) from the updated (September 2022) search results (Table 4 of CS appendices). Based on the Cochrane review of comparator ERTs highlighted by the company in the CS, the EAG are not concerned that any relevant RCTs have been missed for these two comparators but are unsure if the same is true for potentially relevant non-randomised/observational studies of these comparators. The EAG notes that non-randomised/observational studies have only been focused on in the CS for pegunigalsidase alfa (Sections B.2.6.2 to B.2.6.4 of the CS), with only RCTs used in the indirect comparison feasibility assessment (Section B.2.9 of the CS). The EAG considers it unlikely that the company would have missed any evidence (RCTs or non-randomised /observational) involving pegunigalsidase alfa. .
Inclusion criteria	Appendix D.1.2 (Table 7)	**The EAG considers that migalastat is a relevant comparator and studies involving migalastat should be included in the CS.** The eligibility criteria for the SLR were slightly broader than the NICE final scope for the target population (not limited to adults) and interventions (included additional interventions lucerastat and venglustat).[1] However, inclusion criteria eventually used in the CS meant that only pegunigalsidase alfa, agalsidase alfa and agalsidase beta were considered relevant interventions (migalastat was excluded, which the EAG does not consider appropriate; see Section2.3.3). Outcomes were in line with those defined by NICE in the final scope.[1] Records were limited to English language studies. Only studies with a sample size of at least 10 were eligible for inclusion, which the EAG considers to be reasonable given the difficulty associated with making conclusions in very small sample sizes. Compared to the Cochrane review for ERTs,[24] this criterion only led to the exclusion of one study relevant to the CS.[41] Conference abstracts published prior to 2018 were excluded; the rationale for this is unclear, but the EAG does not consider it to have impacted RCTs

		included in the CS based on review of the Cochrane review for ERTs in Fabry disease.[24] It is unclear whether screening by outcomes was performed only at the full-text stage or at the abstract and title stage as well; if the latter, this could have led to relevant studies being excluded. The EAG requested that reasons for exclusion of studies from the CS were provided at the clarification stage (clarification question A10) and the company provided an Excel file with full details in their response to clarification.
Screening	Appendix D.1.2	**Limited details on the screening methods or processes are provided** It is unclear whether screening was done independently by multiple reviewers at the title and abstract screening or full text screening stages. Although dual screening was mentioned for health economic searches described in Appendix G.1.2.1, the EAG cannot be sure this was also the case for the clinical SLR.
Data extraction	Appendix D.1.2 and Section B.2.6 of the CS	**Limited details on data extraction methods or processes are provided** Data extraction appears to have been performed for the 6 relevant pegunigalsidase alfa studies included in the CS. Table 7 of the CS appendices suggests that extractions were done for comparator studies as well. No further details are provided about methods for data extraction and it is unclear if similar approaches to those described in Section G.1.2.2 for health economic searches were used.
Tool for quality assessment of included study or studies	Appendix D.3 and Section B.2.5 of the CS	**The EAG considers the company's choice of quality assessment tool for RCTs and non-randomised studies to be reasonable** Quality assessments are only provided for studies involving pegunigalsidase alfa (including 1 RCT and 5 non-randomised studies). Different checklists were used for the RCT and non-randomised studies. The EAG considers that in both cases, the minimum requirements for the respective study type set out by NICE in Section 2.5 of the user guide appendices have been provided.[42] The EAG critique of the key features of BALANCE is presented in Section 3.2.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; EAG, External Assessment Group; EMTREE, Embase subject headings; ERTs, enzyme replacement therapies; HTA, health technology assessment; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; RCTs, randomised controlled trials; SLR, systematic literature review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

3.2 Critique of trials of the technology of interest

The five studies relating to pegunigalsidase alfa that were identified in the company's SLR (Section 3.1) and included in the CS were:

- BALANCE (NCT02795676): a 2-year Phase III randomised, double-blind, active controlled study comparing the safety and efficacy of pegunigalsidase alfa 1 mg/kg E2W with agalsidase beta 1 mg/kg E2W in patients with FD with impaired renal function who were previously treated with agalsidase beta;[20]
- BRIGHT (NCT03180840): a Phase III open-label study assessing the safety, efficacy, and pharmacokinetics (PK) of pegunigalsidase alfa 2 mg/kg administered every 4 weeks (E4W) in patients with FD who were switched from either agalsidase alfa or agalsidase beta E2W after receiving either treatment for at least 3 years, and on a stable dose for at least 6 months;[32]
- BRIDGE (NCT03018730): a Phase III open-label switch study assessing the safety and efficacy of pegunigalsidase alfa 1 mg/kg E2W in patients with FD who were switched from agalsidase alfa E2W after receiving this treatment for at least 2 years;[31]
- PB-102-F01 (NCT01678898): a Phase I/II open-label, dose-ranging study of pegunigalsidase alfa in treatment-naïve adults with FD to assess the safety, tolerability, PK, immunogenicity and exploratory efficacy of pegunigalsidase alfa administered E2W at 0.2 mg/kg, 1.0 mg/kg or 2.0 mg/kg for 12 weeks;[17]
- PB-102-F02 (NCT01678898): an extension of PB-102-F01 to evaluate the safety, tolerability, PK and exploratory efficacy parameters of pegunigalsidase alfa administered E2W for 38 weeks (9 months, at the same dose that patients received in study PB-102-F01) in adults with FD;[17]
- PB-102-F03 (NCT01981720): a multi-centre extension study (for patients who completed PB-102-F02) of pegunigalsidase alfa administered E2W (gradually adjusted to receive 1 mg/kg) for up to 60 months in adults with FD.[17]

The company reported that the Phase I/II single arm study and its two extension studies were provided as supporting evidence but the key evidence of relevance to the NICE final scope was from the Phase III studies. The EAG notes that the only RCT of pegunigalsidase alfa presented in the CS is BALANCE and the EAG considers it to provide the most relevant and robust clinical data to address the decision problem. Additionally, the EAG notes that the BRIGHT single-arm study is no longer of relevance as the company has withdrawn the E4W regimen from this evaluation.

BRIDGE is also a single-arm study (efficacy population n=20), albeit in a different population (patients with stable renal function and with prior treatment with agalsidase alfa), to the population in BALANCE (patients with impaired renal function and prior treatment with agalsidase beta). The EAG notes that the Phase I/II study (PB-102-F01) and it's two extension studies (PB-102-F02 and PB-102-F03) provide the only evidence for pegunigalsidase alfa in treatment naïve patients.

The EAG focuses its critique below on BALANCE but notes that results for the included single-arm studies are presented in the CS and its appendices. Additionally the EAG notes that BALANCE has an open-label extension which is ongoing (NCT03566017 [PB-102-F60]) and involves patients continuing to receive pegunigalsidase alfa E2W for up to 4 years and the estimated primary completion date is October 2026.[43]

The EAG's assessment of the design, conduct and internal validity of the BALANCE trial is summarised in Table 10. The EAG broadly agrees with the company's assessment of BALANCE as generally being at low risk of bias for analysis of the primary outcome, although as discussed in Section 2.3.1, the EAG is concerned about the impact of the imbalance in sex between the pegunigalsidase alfa and agalsidase beta arms. The EAG is also concerned that the sample size in BALANCE is relatively small (ITT population n=77) particularly for the comparator arm (agalsidase beta n=25) and so it is difficult to draw any robust conclusions on the comparative efficacy of the treatments albeit the EAG also notes that FD is a relatively rare disease.

Table 10. EAG's summary of the design, conduct and analysis of BALANCE

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.2.3.1.1	**Appropriate** Eligible patients were randomised in a 2:1 ratio to either switch to pegunigalsidase alfa (n=53) or continue treatment with agalsidase beta (n=25). Randomisation was stratified according to whether the UPCR was equal to or greater than 1 or below 1 gr/gr protein/creatinine.
Concealment of treatment allocation	[redacted]	**Likely to be appropriate** No details of the method of allocation concealment were provided in the CS but the EAG notes from the [redacted] was used in the allocation of patients to study treatment.
Eligibility criteria	B.2.3.1.2	**Not representative of the whole population eligible for pegunigalsidase alfa in UK clinical practice** Key inclusion criteria for BALANCE: • Symptomatic adult FD patients aged 18–60 years; • eGFR at screening of ≥ 40 – ≤ 120 ml/min/1.73 m^2 by CKD-EPI equation; • Linear negative slope of eGFR of ≥ 2 mL/min/1.73 m^2/year based on at least 3 serum creatinine values over approximately 1 year; and • Treatment with a dose of 1 mg/kg agalsidase beta per infusion E2W for at least 1 year. Full details of the eligibility criteria for BALANCE are available in the CS Table 8. The EAG notes that FD patients in BALANCE were all required to be stable on agalsidase beta ERT therapy and to have renal impairment which as discussed in Section 2.3.1 is not representative of the whole spectrum of FD patients likely to be eligible for pegunigalsidase alfa in clinical practice.
Blinding	B.2.3.1.1	**Appropriate**

		BALANCE was a double-blind RCT with patients and the study staff administering the treatment blinded. The EAG notes from the CSR that [redacted] The EAG considers the blinding in BALANCE to be reasonable and appropriate. Additionally the EAG notes that the primary outcome was an objective measure: annualised change in eGFR (slope) and so blinding is less important compared to the subjective outcome measures such as symptoms of FD and HRQL.
Baseline characteristics	B.2.3.1.3	**Imbalance in sex with higher proportion of females in the pegunigalsidase alfa study arm** The EAG notes that [redacted] restricted enrolment of females to not more than 50% in BALANCE, although the methods used to restrict enrolment are not described in the CS. The EAG considers there to be a large imbalance in the proportions of males and females between the study arms with a higher proportion of males enrolled in the agalsidase beta arm (72.0%) compared to the pegunigalsidase alfa arm (55.8%). The EAG also notes that randomisation was not stratified by sex. With the exception of sex, the EAG considers the baseline characteristics to be reasonably well balanced between the treatment arms, although there are further smaller differences discussed in Section 2.3.1. Additionally, the applicability of the baseline characteristics in BALANCE to the decision problem and UK practice is discussed in Section 2.3.1.
Dropouts	Appendix D.2.1	Imbalanced but reasonably small number of discontinuations The EAG notes that there was a slightly higher rate of discontinuations in the pegunigalsidase alfa study arm (5 [9.4%]) compared to the agalsidase beta study arm (1 [4%]). However, only 2 [3.8%] of those in the pegunigalsidase alfa arm were due to AEs and the remaining discontinuations were due to withdrawal of consent.
Statistical analysis		
Sample size and power	B.2.3.1.1 and B.2.4	**Small sample size in BALANCE may limit the robustness of any conclusions** The study sample size was planned to demonstrate non-inferiority after 1 year of treatment (interim analysis) and superiority after 2 years of treatment (final analysis) but this was updated to a non-inferiority analysis of the 24-month data following a trial amendment agreed with the FDA. The pre-planned non-inferiority (NI) margin from the interim analysis was used for the final analysis. [redacted]

		The initial sample size of approximately 66 patients in a 2:1 randomisation ratio was kept, which results in at least 90% power to demonstrate the non-inferiority of pegunigalsidase alfa vs agalsidase beta in terms of the primary efficacy outcome: annualised change (slope) in eGFR. The power was computed assuming a one-sided two-sample t-test with a one-sided alpha level of 0.025 and a non-inferiority margin of -3.0 mL/min/1.73 m^2/year. The true difference in slopes was assumed to be 1.1 mL/min/1.73 m^2/year in favour of pegunigalsidase alfa, and the standard deviation of the slopes was assumed to be 1.5 mL/min/1.73 m^2/year in each arm. To allow for a drop-out rate of 15%, 78 patients were planned to be randomised. The EAG notes that the final ITT analysis for the primary outcome included 77 patients and that despite being only 1 patient less than planned it still represents a small study sample size, especially for the comparator arm given the 2:1 randomisation.
Handling of missing data	Appendix M.1.3.1	**Unclear but appropriate for the primary outcome in BALANCE** The EAG notes from the CSR that: [redacted] The sensitivity analyses included an analysis investigating the influence of missing data by using multiple imputation under the assumption that data are missing at random (MAR) for the primary outcome in BALANCE. The company reported that the results of this sensitivity analysis suggest that missing data did not influence the primary efficacy analysis in a meaningful way (CS Appendix, Table 69).
Outcome assessment	B.2.4	**Appropriate** The ITT population in BALANCE (n=77) consisted of all randomised patients who received ≥ 1 dose of study medication, based on the assigned treatment arm in the randomisation and was the main data set for the efficacy analyses. The EAG notes that 1 randomised patient in the pegunigalsidase alfa arm was omitted from this analysis set due to withdrawal of consent prior to receiving their first dose of study treatment. The PP population (n=72) included all ITT patients who completed ≥ 24 months of treatment, with study drug compliance of ≥ 80%, and with no major protocol deviations that could have impacted the primary endpoint and those were pre-specified in the SAP. The PP analysis set was used for sensitivity analyses for the primary endpoint. All safety analyses were performed on the safety population (n=77) which consisted of all patients who were randomised and who received ≥ 1 partial dose of study medication with assignment by actual treatment received. Unless otherwise specified, baseline values were defined as the last assessment before the first treatment infusion.

Abbreviations: CS, company submission; EAG, External Assessment Group; MAR, missing at random; N/A, not applicable.

3.3 Critique of the clinical effectiveness analysis and interpretation

Results presented here from BALANCE reflect the relevant outcomes specified in the NICE final scope although the EAG notes that none of the efficacy data are utilised in the company's base case in the economic model for the analysis of cost-effectiveness.

3.3.1 Primary outcome: eGFR slope

The primary endpoint in BALANCE was the annualised change in eGFR (slope), derived from the eGFR assessments over time[20] and the primary objective of BALANCE was to assess whether pegunigalsidase alfa was non-inferior to agalsidase beta for this endpoint. The EAG notes that the study sample size was previously planned to demonstrate non-inferiority after 1 year of treatment (interim analysis) and superiority after 2 years of treatment (final analysis), although the EAG is unclear what was in the original protocol as the above analyses were reported as part of the amendments made in version 2 of the protocol. Subsequent to the FDA granting full approval of agalsidase beta, the company reported that it was no longer necessary to demonstrate treatment superiority of pegunigalsidase alfa over agalsidase beta and instead, a non-inferiority analysis of the 24-month data was performed, as agreed with the FDA. The EAG notes that

[redacted]

The EAG notes that in the revised draft Summary of Product Characteristics[17] (SmPC) provided with the company response to clarification questions it states,

"[redacted]." The EAG considers that [redacted], "*PRX-102 [pegunigalsidase alfa] E2W is not inferior to agalsidase beta E2W, meaning that the primary endpoint [of BALANCE] was met*[19, 20]" .

The EAG notes that to meet non-inferiority the lower bound of the 95% CI was required to be above -3 mL/min/1.73 m²/year. The company reported results using the ITT population (n = 77) in the CS

but the EAG notes that results for the per protocol (PP) population (n = 72) are also available in the CSR for BALANCE for the primary analysis. In the ITT population, the mean slopes for eGFR at month 12 in BALANCE were -[redacted] mL/min/1.73 m²/year for the pegunigalsidase alfa arm and [redacted] for the agalsidase beta arm with a difference of [redacted] and 95% confidence interval (95%CI) of [redacted].(Figure 2). At month 24, the median slopes for eGFR were -2.51 mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -2.16 for the agalsidase beta arm with a difference of -0.36 and 95% CI of -2.44 to 1.73. The difference in estimated median annual eGFR slopes at month 24 in the PP population for pegunigalsidase alfa compared to agalsidase beta [redacted] The EAG notes that the 12 month data comprise mean values, whereas the 24 month data are medians and so it is not possible to directly compare the results. However, the EAG consider that at month 12 [redacted] at month 24 the criterion for non-inferiority was met based on the median slopes. The EAG also notes that at 24 months the difference in median slopes for eGFR favour treatment with agalsidase beta, although the 95% CIs included 0, indicating no significant difference between treatment groups. The EAG thus considers there to be uncertainty in the conclusion of non-inferiority given it has been met following a protocol amendment resulting in a longer data collection period and [redacted]

The company reported that the robustness of the finding that pegunigalsidase alfa was non-inferior to agalsidase beta was confirmed in a wide variety of sensitivity and supportive analyses and the 95% CI for the difference in all models included 0 suggesting no significant difference between treatments. The point estimate for the difference is close to 0 in all models apart from the Mixed Model Repeated Measure (MMRM), and in some cases it was positive. For the primary analysis, analysis of quantile regression for the median of eGFR slopes was used as the outcome measure. The company reported that using mean instead of median slope data (random intercept [RI] and random intercept random slope [RIRS] analyses), confirmed non-inferiority of pegunigalsidase alfa to agalsidase beta. For RIRS and RI, the difference in mean annualised eGFR slopes (95% CI) for the ITT population, were [redacted] and [redacted], respectively. However, the EAG notes that for 2 of the supportive analyses, the non-inferiority criterion was not met:[20]

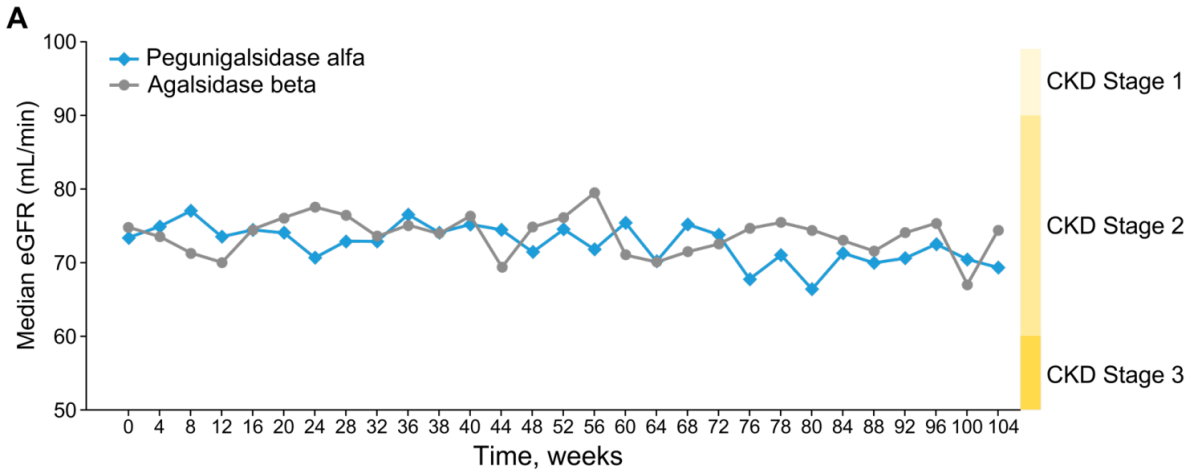
- For the analysis of the group difference in eGFR change from baseline using an MMRM model, the lower limit of the 95% CI for the difference between the groups at week 104 was [redacted], and so did not meet the criterion for non-inferiority (criterion was -6 as it was looking at

change over 2 years). The company stated that this model does not estimate the slope but assessed change in baseline for eGFR and unlike the other models, it does not assume a linear relationship between eGFR and time. The EAG's clinical experts agreed that in clinical trials it is generally assumed to be a linear relationship, although they noted it could become non-linear in advanced kidney disease.

- For the 2-stage analysis with the second stage using ANCOVA, the lower limit of the 95% CI was [redacted]. The company stated that patient(s) who terminated early, whose slope was based on a small number of eGFR assessments over a short period in time, had considerable impact on the variability and hence on the width of the CI in this analysis.[20] The EAG notes that in the PP population [redacted]

The EAG is concerned about the robustness of the company's claim of non-inferiority for pegunigalsidase alfa and consider it to be associated with uncertainty. The EAG also notes that full results for the interim analysis at 12 months were not provided in the CS.

Figure 2. Median eGFR values over time in the BALANCE trial: ITT population (Reproduced from CS, Figure 7)



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eGFRCKD-EPI, chronic kidney disease-epidemiology collaboration equation; ITT, intention-to-treat.

Source: Wallace et al. 2022[19]

3.3.2 *Secondary efficacy endpoints: Kidney function*

3.3.2.1 *Urine protein/creatinine ratio*

In the pegunigalsidase alfa arm, the proportion of patients categorised as having severe proteinuria (UPCR ≥ 1 g/g) [redacted] with [redacted] at baseline and [redacted] at Week 104, while in the agalsidase

beta arm, the proportion [redacted] from [redacted] to [redacted] (CS, Table 14).[20] In both trial arms, a deterioration in category was seen in [redacted] patients between baseline and Week 104.

3.3.2.2 Achievement of kidney function therapeutic goals

The EAG notes that [redacted]% of patients achieved kidney function therapeutic goals by week 104 in BALANCE with [redacted] (pegunigalsidase alfa vs agalsidase beta mean difference [redacted].

3.3.3 Secondary efficacy endpoints: Cardiac function

3.3.3.1 Left ventricular mass index (g/m^2) by magnetic resonance imaging

Cardiac complications of FD may include a thickening of the left ventricular wall, or hypertrophy.[20] Hypertrophy, as defined by cardiac magnetic resonance imaging (MRI), is an left ventricular mass index (LVMI) greater than 91 g/m^2 for males or greater than 77 g/m^2 for females.[20] The company reported that data for cardiac outcomes were missing for a large number of patients and one of the reasons for this was cardiac MRI could not be performed because of COVID-19 restrictions at the hospital. The EAG notes that in addition to not all patients having baseline assessments, [redacted]

For patients who had hypertrophy at baseline (n = [redacted]), the results for mean change from baseline in LVMI at week 104 (n = [redacted]) [redacted]: difference in means [redacted]

For patients without hypertrophy at baseline (n = [redacted]), the difference in mean change from baseline for LVMI at week 104 (n = [redacted]) [redacted]: difference in means for pegunigalsidase alfa vs agalsidase beta: [redacted]

Data presented by sex were broadly in keeping with overall results but showed high levels of uncertainty with wide CIs.[20] All CIs contained 0, suggesting no statistically significant differences between treatments.

3.3.3.2 Echocardiography

Statistical measures for differences between treatment arms were not reported for the echocardiography results presented in the CS. The EAG notes that

[redacted] (CS, Table 13).

3.3.3.3 Exercise tolerance (stress test)

The EAG notes that results for 'normal' exercise stress test at week 104 [redacted] but there was no statistical measure reported for the difference between arms in the CS.

3.3.4 Secondary efficacy endpoints: FD biomarkers

FD results in the accumulation of Gb3 due to the absence or insufficiency of the GAL-A enzyme.[20] Accordingly, the change from baseline in levels of Gb3 and its metabolite, lyso-Gb3, are important biomarkers of the extent and progression of FD. . The EAG's clinical experts reported that large percentage changes from baseline in these measures are more clinically relevant than the absolute values, although the EAG notes that absolute values were provided in the CS. The EAG has extracted percentage change data from the CSRs where available.

3.3.4.1 Plasma lyso-Gb3

At Week 104, the mean concentration of plasma lyso-Gb3 had i[redacted] slightly ([redacted] nM) in the pegunigalsidase alfa arm and had [redacted] slightly ([redacted] nM) in the agalsidase beta arm. The median change from baseline was [redacted] for both arms compared to the mean changes (median change [redacted] nM in the pegunigalsidase alfa arm and [redacted] nM in the agalsidase beta arm). The EAG notes that the results of an analysis of the changes in plasma lyso-Gb3 using a Mixed Model Repeated Measure (MMRM) model to control for a number of variables was presented in the CS. The results of the MMRM analysis of mean log difference [redacted]). In terms of percentage change, the EAG notes that the difference in means for mean percentage change from baseline at week 104 for pegunigalsidase alfa compared to agalsidase beta was [redacted]

3.3.4.2 Urine lyso-Gb3 concentrations

At Week 104, mean urine lyso-Gb3 concentration had increased slightly (by [redacted] creatinine) in the pegunigalsidase alfa arm and decreased ([redacted] creatinine) in the agalsidase beta arm. The EAG notes that the difference in mean

[redacted] (pegunigalsidase alfa vs agalsidase beta difference in means [redacted]; 95% CI: [redacted]). Additionally, the EAG notes there was a [redacted])

3.3.4.3 Plasma Gb3 concentrations

At baseline, the mean Gb3 plasma concentration was higher in the pegunigalsidase alfa arm than in the agalsidase beta arm (5087.7 nM vs. 4695.4 nM, respectively). In the pegunigalsidase alfa arm, there was a mean increase from baseline of 138.0 nM, while in the agalsidase beta arm, there was a mean decrease of -81.8 nM. Since the CIs contained 0, this suggests no statistically significant difference between the two arms, and the company reported that changes in both treatment arms for were not considered clinically significant. The EAG notes that the SEs were [redacted] and the mean percentage change from baseline was [redacted] with an overall difference in means for percentage change in plasma Gb3 concentrations from baseline at week 104 of [redacted] for pegunigalsidase alfa compared to agalsidase beta.

3.3.5 Secondary efficacy endpoints: Symptoms of FD

3.3.5.1 Change in pain severity

The Short Form Brief Pain Inventory (BPI) is designed to rapidly assess the severity of pain and its impact on functioning. It yields scores for “Pain at Its Worst in Last 24 Hours”, “Pain at Its Least in Last 24 Hours”, “Pain Right Now”, and “Pain on Average”. The scales are scored from 1 to 10, with a score of 1–4 points indicating mild pain, 5–6 indicating moderate, and 7–10 indicating severe. Change in scores from baseline in the BPI at Week 104 for ‘Pain at Its Worst in Last 24 Hours’ and ‘Pain on Average’ suggest no statistically significant difference between the arms and ‘Pain at Its Least in Last 24 Hours’ and ‘Pain Right Now’ were reported to have similar results (not all data were shown in the CS or CSR). Improvement or no change in pain severity was [redacted] reported in the pegunigalsidase alfa arm ([redacted]%) than the agalsidase beta arm ([redacted]%). Worsening in pain severity was

reported by a [redacted] proportion of patients in the pegunigalsidase alfa compared with the agalsidase beta arm ([redacted]% vs [redacted]%, respectively).

3.3.5.2 Frequency of pain medication use

The company reported that for most patients, there was no change in the frequency of pain medication use over the study period although detailed results were not presented in the CS but the EAG notes they were available in the CSR.

3.3.5.3 Mainz Severity Score Index (MSSI)

The MSSI[44] yields scores for general, neurological, cardiovascular, renal, and overall assessments. An overall score of less than 20 points is considered mild, 20–40 is considered moderate, and greater than 40 is considered to reflect severe signs and symptoms of FD.[20] At baseline, the overall mean score in both groups was at the [redacted] ([redacted] for pegunigalsidase alfa and [redacted] for agalsidase beta; CS, Table 17). Difference in means for mean change from baseline to week 104 showed [redacted] pegunigalsidase alfa (pegunigalsidase alfa vs agalsidase beta difference in means [redacted]). However, the EAG's clinical experts reported that MSSI was not typically used in clinical practice and the EAG is unclear whether this is a clinically significant change.

3.3.5.4 Incidence of Fabry clinical events (FCEs)

The company stated that all patients reporting FCEs had either experienced a similar event when untreated or receiving treatment with agalsidase beta before the study, or had signs/symptoms of organ damage when the study started. The company therefore considers these results reflect pre-existing organ involvement in ERT-experienced patients and do not allow any conclusions to be drawn on the effect of changing to a new ERT. The EAG considers the definitions of 'events' to reflect the occurrence of events during the study and notes that the overall FCE (as defined by Hopkin *et al.*[45]) event rate in BALANCE and FCE rates for [redacted] pegunigalsidase alfa arm compared with the agalsidase beta arm (Table 11).

Table 11. Number of patients with Fabry clinical events – ITT population (Reproduced from CS, Table 18)

	Pegunigalsidase alfa		Agalsidase beta	
FCE categories	Number (%) of patients (n = 52)	Number of events (rate)[a]	Number (%) of patients (n = 25)	Number of events (rate)a
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac events	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular events	[redacted]	[redacted]	[redacted]	[redacted]
Renal events	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac related death	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; E2W, every 2 weeks; FCE, Fabry clinical events; ITT, intention-to-treat.

Notes: [a] Rate is calculated as the adjusted number of events per 100 years of exposure.
Source: Chiesi, BALANCE CSR.[20]

3.3.6 *Quality of life: change in EQ-5D-5L scores*

A QoL questionnaire (EQ-5D-5L) was conducted for each domain (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the mean overall health scores at baseline were similar. The mean changes in overall health score between baseline and Week 104 were [redacted] ([redacted]points in the pegunigalsidase alfa arm and [redacted]points in the agalsidase beta arm; CS, Table 19).[20] However, when considering the individual domains, the rate of worsening was [redacted] in the pegunigalsidase alfa arm for 'usual activities' ([redacted]% pegunigalsidase alfa vs [redacted]% agalsidase beta) and anxiety/depression ([redacted]% pegunigalsidase alfa vs [redacted]% agalsidase beta). For the 'pain/discomfort' domain, the rate of worsening was [redacted] in the agalsidase beta arm ([redacted]% agalsidase beta vs [redacted]% pegunigalsidase alfa). Results were [redacted] between treatment arms for the mobility and self-care domains.

3.3.7 *Subgroup analyses*

The company conducted a number of subgroup analyses for the primary endpoint in BALANCE (change in eGFR slope)[20] and the EAG notes that there was wide variation in the point estimates for the adjusted median difference in change in eGFR slop between pegunigalsidase alfa and agalsidase beta (Figure 3). All 95% CIs crossed zero, but the CIs are generally wide. Additionally, the EAG notes that for several subgroups [redacted]. In the company's response to clarification questions, subgroup results by sex were presented for additional outcomes. However, the EAG notes subgroups were [redacted] and for some outcomes, such as cardiac outcomes, there was a large amount

of missing data at baseline making it difficult to interpret the results. The company also reported that all female patients in BALANCE were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic [redacted] in the pegunigalsidase alfa arm and [redacted] in the agalsidase beta arm). The EAG thus considers this difference in FD subtype is likely to be confounding the results for the sex subgroup making it difficult to draw any conclusions. The EAG also notes that there were similar proportions of classic FD between the two trial arms at baseline despite the imbalance in sex (higher proportion of males in the agalsidase beta arm) and other characteristics at baseline (see Section 2.3.1 for further details).

Figure 3. Forest plot for subgroup analysis on the primary endpoint, change in eGFR slope in the BALANCE trial – ITT population (Reproduced from CS, Figure 19)

Key: ACEi, angiotensin-converting enzyme inhibitor; ADA, anti-drug antibody; ARB, angiotensin II receptor blocker; CI, confidence interval; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FD, Fabry disease; ITT, intention-to-treat; UPCR, urine protein to creatinine ratio.

Source: Chiesi, BALANCE CSR.[20]

3.3.8 *Safety*

The EAG notes that a slightly higher proportion of patients in the agalsidase beta arm of BALANCE ([redacted]%) received 24 months of treatment compared with the pegunigalsidase alfa arm ([redacted]%).

The EAG notes that the company did not include the impact of adverse events (AEs) in the model, although the company conducted a scenario analysis which included the costs of AE management. Additionally, during the clarification stage, the company provided a scenario where disutilities associated with AEs were explored in the cost-utility analysis and the AEs included in the model for this scenario were reported to be treatment emergent adverse events (TEAEs) reported in >10% of patients (any grade) from BALANCE. However, the EAG considers there to be some discrepancies in the AEs included in the model compared to those reported in CS Table 29, with some AEs missing from the model but included in CS Table 29 and vice versa. The EAG is unclear of the exact impact of these potential discrepancies but notes that AEs are not a primary driver of cost-effectiveness for pegunigalsidase alfa.

The EAG notes that most patients in BALANCE experienced ≥ 1 TEAE (90.4% with pegunigalsidase alfa and 96.0% with agalsidase beta) and the rate of treatment-related TEAEs (events per 100 patient-years) was higher in the agalsidase beta arm (153 events per 100 patient-years) compared with the pegunigalsidase alfa arm (43 events per 100 patient-years). However, the proportions of patients experiencing treatment related TEAEs were similar (44% vs 40% [Table 12]). Additionally, the EAG notes from the subgroup results that there was a [redacted] reporting any drug related adverse effect.

In general, the EAG considers the safety profile of pegunigalsidase alfa and agalsidase beta in BALANCE to be comparable although the EAG notes that there were differences in the frequencies of some AEs between the trial arms (CS, Table 29). For pegunigalsidase alfa, only [redacted] were reported at a rate of at least [redacted] than for agalsidase beta.[20] The most common TEAEs with pegunigalsidase alfa were [redacted]. Among patients who received agalsidase beta, the most common TEAEs were [redacted], all of which were reported in [redacted]% of patients. The EAG notes that there were no deaths reported in either trial arm.

Table 12. Summary of treatment-emergent adverse events – Safety population (Reproduced from CS, Table 28)

	Pegunigalsidase alfa E2W (N = 52)		Agalsidase beta E2W (N = 25)	
	Patients with ≥1 event n (%)	Number of events (rate)[a]	Patients with ≥ 1 event n (%)	Number of events (rate)[a]
All TEAEs				
Any TEAE	47 (90.4)	561 (572.36)	24 (96.0)	406 (816.85)
Mild or moderate TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs only				
Any related TEAE	21 (40.4)	42 (42.85)	11 (44.0)	76 (152.91)
Related mild or moderate TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Related severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Related serious TEAE	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to withdrawal	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]

Key: CSR, clinical study report; E2W, every 2 weeks; TEAE, treatment-emergent adverse event.

Notes: [a]per 100 exposure years.
Source: Chiesi, BALANCE CSR.[20]; Wallace *et al.* 2022.[33]

The treatment-emergent antidrug antibody (ADA)-positive rate in BALANCE was lower for patients who switched to pegunigalsidase alfa (6 [11.5%]) than for patients who remained on agalsidase beta (4 [16.0%]).[19] Additionally, the EAG notes that the proportion of ADA-positive patients with neutralising antibodies was lower for pegunigalsidase alfa (64%) than for agalsidase beta (100%) at 24 months (CS, Section B.2.10.1.6).[19]

Similar proportions of patients in both trial arms experienced infusion-related reactions (IRRs) but the number of IRR events and the normalised rate of IRR events was higher for agalsidase beta compared to with pegunigalsidase alfa (approximately 4-fold and 8-fold, respectively [CS, Table 31]).[19] The EAG notes that there was only 1 serious IRR reported in BALANCE and it was in the pegunigalsidase alfa arm.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company conducted a feasibility assessment exploring the possibility of an indirect treatment comparison of pegunigalsidase alfa, agalsidase alfa and agalsidase beta as the only head-to-head data for pegunigalsidase alfa are compared with agalsidase beta from the BALANCE RCT. The company concluded that any statistical analysis would lead to substantial uncertainty because of the limited clinical evidence and the heterogenous nature of the identified evidence. The EAG notes that 8 studies (1 pegunigalsidase alfa study, 3 agalsidase alfa studies and 4 agalsidase beta studies) were included in the feasibility assessment (as identified in the SLR discussed in Section 3.1 [Table 13]).

Table 13. Randomised studies considered in the company's ITC feasibility assessment (Reproduced from CS, Table 24).

Study name	ITT N	Intervention	Intervention dose
BALANCE[20]	52	Pegunigalsidase alfa	1.0 mg/kg E2W
	25	Agalsidase beta	**1.0 mg/kg E2W**
Vedder 2007[22]	18	Agalsidase alfa	**0.2 mg/kg E2W**
	16	Agalsidase beta	0.2 mg/kg E2W
Hughes 2008[39]	7	Agalsidase alfa	**0.2 mg/kg E2W**
	8	Placebo	NA
Banikazemi 2007[36]	51	Agalsidase beta	**1.0 mg/kg E2W**
	31	Placebo	0.25 mg/min
Schiffmann 2001[40]	14	Agalsidase alfa	**0.2 mg/kg E2W**
	12	Placebo	0.2 mg/kg E2W
Sirrs 2014[23]	62	Agalsidase alfa	**0.2 mg/kg E2W**
	30	Agalsidase beta	**1.0 mg/kg E2W**
Eng 2001[37]	29	Agalsidase beta	**1.0 mg/kg E2W**
	29	Placebo	0.25 mg/min
Hajioff 2003[38]	8	Agalsidase alfa	**0.2 mg/kg E2W**
	7	Placebo	NR

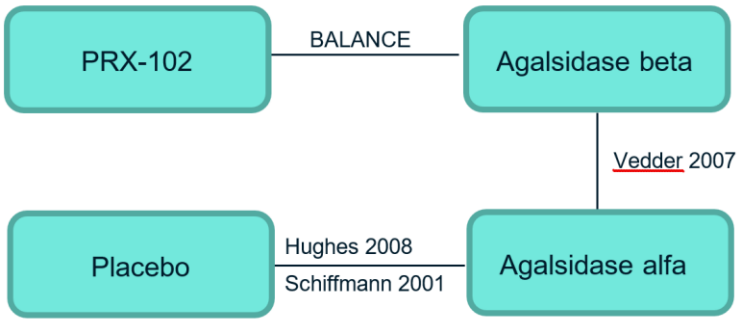
Key: E2W, every 2 weeks; ERT, enzyme replacement therapy; ITT, intention-to-treat; IV, intravenously; N, number of patients; NA, not applicable; NR, not reported; SLR, systematic literature review; SmPC, summary of product characteristics.

Notes: Bolded doses are the indicated dose in the SmPC.

The company reported that there were no suitable outcome data available for Sirrs 2014[23] and Hajioff 2003[38] for the endpoints explored in the ITC feasibility assessment. For eGFR, the company concluded that 4 of the 8 studies reported data that could potentially be used in an analysis. However, the EAG notes that the network would rely on Vedder 2007[22] to provide the link to agalsidase beta in the network and the EAG notes that the dose of agalsidase beta used in Vedder

2007 is lower than the SmPC recommended dose (Figure 4). The EAG thus considers this network to be flawed and agrees with the company that ITC analyses for pegunigalsidase alfa with agalsidase beta using only the agalsidase alfa and agalsidase beta evidence base are not feasible. The EAG notes that the company has not explored the potential of including migalastat in ITCs, due to its exclusion of migalastat as a relevant comparator, and the EAG considers migalastat should be included as a comparator. However, the EAG also notes that the RCTs used to provide the evidence base for migalastat in HST4 were a placebo-controlled RCT and a two-arm RCT comparing migalastat with ERT, and ERT comprised a mixture of agalsidase alfa (65%) and agalsidase beta (33%) with no stratification.

Figure 4. Network diagram for analysis of eGFR (Reproduced from CS, Figure 20)



Key: eGFR, estimated glomerular filtration rate.

Note: Vedder 2007 includes a lower dose (0.2 mg/kg E2W) of agalsidase beta than is recommended in the SmPC (1.0 mg/kg E2W)

The company also presented a naïve comparison between the BALANCE RCT and the Phase III single-arm pegunigalsidase alfa BRIDGE study (CS Appendix D.1.3.1), but acknowledged that the analyses are very limited due to small patient populations and differing baseline characteristics between trials such as sex and age. However, despite the limitations the company considered that the results of the naïve comparisons suggest that there are [redacted] in efficacy of pegunigalsidase alfa for key outcomes of interest between BALANCE (pegunigalsidase alfa in a renally impaired population) and BRIDGE (pegunigalsidase alfa in non-renally impaired population). The EAG considers the data to be too heterogenous to draw any robust conclusions.

3.5 Conclusions of the clinical effectiveness section

The EAG considers the key evidence submitted by the company in support of the clinical efficacy and safety of pegunigalsidase alfa for treating Fabry disease (FD) to be the double-blind RCT BALANCE.

BALANCE compared pegunigalsidase alfa with agalsidase beta in patients who had already received prior enzyme replacement therapy (ERT) and who had renal impairment at baseline. The EAG notes the company has also submitted supportive evidence from single-arm studies with the key single-arm trial being the BRIDGE study which was comprised of patients without renal impairment (Section 3.2). The EAG considers the BALANCE trial to align well with the NICE final scope in terms of intervention and outcomes but considers there to be limitations in relation to its generalisability to the UK FD population (Section 2.3.1).

The EAG's clinical experts raised concerns relating to the generalisability of BALANCE to the UK Fabry disease population as it restricted trial entry to patients treated with an ERT and additionally required patients to have renal impairment as part of its trial inclusion criteria (Section 2.3.1). The EAG notes that renal impairment is not present in all patients with FD (it is less common in non-classical FD than in classic FD) and that the primary endpoint in BALANCE for assessing non-inferiority in based on renal function. The EAG acknowledges that the company provided supportive data from BRIDGE and other single-arm studies but nevertheless remains concerned that there is insufficient evidence to support the generalisability of the results from BALANCE to the full FD population. In addition, the EAG notes that there were imbalances between the treatment arms in BALANCE in some characteristics and that some of these imbalances may potentially favour the patients in the pegunigalsidase alfa arm by having less severe FD at baseline. However, the EAG considers it difficult to predict the overall resulting direction of bias that the imbalances at baseline may have on the results of BALANCE.

BALANCE was powered as a non-inferiority trial, but the EAG notes that the timepoint for assessment of non-inferiority was moved from 12 months to 24 months, with the study previously designed to show superiority at 24-months. The EAG notes that the 12 month data are not reported in the CS and the assessment of non-inferiority at 24-months is based on the use of annualised data from week 104. The EAG is thus concerned about the robustness of the company conclusion that pegunigalsidase alfa is non-inferior to agalsidase beta and notes that the draft [redacted] (Section 3.3.1).

The EAG considers the safety profile of pegunigalsidase alfa and agalsidase beta was generally comparable in BALANCE in terms of numbers of treatment-emergent AEs and that the rates of IRRs, and treatment-emergent antidrug antibody (ADA)-positive rates favoured pegunigalsidase alfa (Section 3.3.8).

The EAG notes that there is a lack of head-to-head data comparing pegunigalsidase alfa with agalsidase alfa and that the company explored the feasibility of conducting indirect treatment analyses to enable this comparison but it was deemed to be unfeasible. The EAG notes that the company assumes clinical equivalence between pegunigalsidase alfa, agalsidase alfa and agalsidase beta in the cost-effectiveness analyses but the EAG considers there to be a lack of robust clinical evidence to draw conclusions of clinical equivalence between pegunigalsidase alfa and any of the comparators in this appraisal. However, the EAG notes that in HST 4[10] the committee did not reject the assumption of equivalence for the comparison of migalastat with agalsidase alfa and agalsidase beta: "The committee concluded that, despite some important uncertainties in the clinical evidence, migalastat may provide similar outcomes to ERT".

Finally, the EAG notes that migalastat was deemed not to be a relevant comparator by the company but based on clinical expert advice, the EAG considers it to be a relevant comparator for patients with an amenable mutation. The EAG's clinical experts reported that for patients with an amenable mutation, migalastat or ERTs would be treatment options and thus pegunigalsidase alfa would represent an additional treatment option for patients with an amenable mutation. The EAG, therefore, disagrees with the company's proposed exclusion of migalastat as a relevant comparator and considers clinical and economic evidence should be provided to enable a comparison of pegunigalsidase alfa with migalastat.

4 Cost effectiveness

Table 14 and Table 15 presents the results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses cost minimisation analysis (CMA). A patient access scheme discount (PAS) of [redacted] for pegunigalsidase alfa is applied in the company's base case and is therefore reflected in the results presented in this report.

Table 14. Company's post clarification deterministic base case results – CMA

Interventions	Total costs	Incremental costs vs pegunigalsidase
Pegunigalsidase alfa	[redacted]	-
Agalsidase alfa	[redacted]	-£476,243
Agalsidase beta	[redacted]	-£470,950

Abbreviations: CMA, cost-minimisation analysis

Table 15. Company's post clarification probabilistic base case results – CMA

Interventions	Total costs	Incremental costs vs pegunigalsidase	Range of maximum and minimum probabilistic costs
Pegunigalsidase alfa	[redacted]	-	-£495,493
Agalsidase alfa	[redacted]	-£482,962	-£612,874
Agalsidase beta	[redacted]	-£477,529	-£612,985

Abbreviations: CMA, cost-minimisation analysis

4.1 EAG comment on the company's review of cost effectiveness evidence

The company carried out three systematic literature reviews (SLRs) to identify published cost-effectiveness studies for treatments for Fabry disease (FD) and to identify resource use data and utilities related to FD. Searches were run in May 2021 but were not updated. In their clarification response, the company explained that update searches were not run as the initial searches were robust and identified the key evidence for the topic, verified by clinical experts at an advisory board meeting.

A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 16. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 16. EAG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G 1.2	Appendix H 1.2	Appendix I 1.2	Appropriate
Inclusion/ exclusion criteria	Appendix G 1.3	Appendix H 1.3	Appendix I	The EAG considered that the exclusion criterion of a blended comparator was not appropriate. However, the company confirmed that only one study (Rombach *et al.*)[28] met the criterion, but was still identified for use in the model based on HST4.[10]
Screening	Appendix G 1.2.1	Appendix G 1.2.1	Appendix G 1.2.1	Appropriate
Data extraction	Appendix G 1.2.2	Appendix G 1.2.2	Appendix G 1.2.2	Appropriate
Quality assessment of included studies	Appendix G 1.4.3	Appendix H 1.4.2	Appendix G 1.4.3	Appropriate

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

The company's search for cost-effectiveness studies identified 630 publications, of which five studies were selected for inclusion. The health-related quality of life (HRQoL) search identified 331 publications, of which 14 unique studies from 22 publications were selected for inclusion. For the costs and resource use search, the company's search found 720 studies and 22 unique studies from 24 publications were selected for inclusion.

Of the studies identified in the company's review of the economic literature, HST4[10] was used as the primary source to inform the model structure and main assumptions of the economic model, including resource use and costs. For utilities, a study by Arends *et al.*[27] informed the base case and scenarios were explored using utility values from Rombach *et al.* and BALANCE. Each of the studies and how the data were used in the model is discussed in Section 4.2.4.

The EAG was concerned that a blended comparator was an exclusion criterion and as such, the Rombach *et al.*[28] study was excluded, yet it informs the key transition probabilities in the model. During the clarification stage, the company explained that Rombach *et al.*[28] was the only study that met the blended comparator exclusion criterion. As such, the EAG is satisfied that no key studies were missed based on the blended comparator exclusion criterion.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 17 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 17. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All relevant health effects for adult patients with FD have been included
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost utility analysis has been included as a scenario, however the company's base analysis to evaluate cost effectiveness is a cost comparison. If the assumption of non-inferiority between pegunigalsidase alfa and ERTs is considered valid then the EAG considers a cost comparison is sufficient to inform a cost effectiveness decision.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (60 years)
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review. The EAG had initial concerns around the blended comparator exclusion criteria, however this had no impact on the articles considered.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs, based on EQ-5D study data.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Health related quality of life values were used from multiple sources

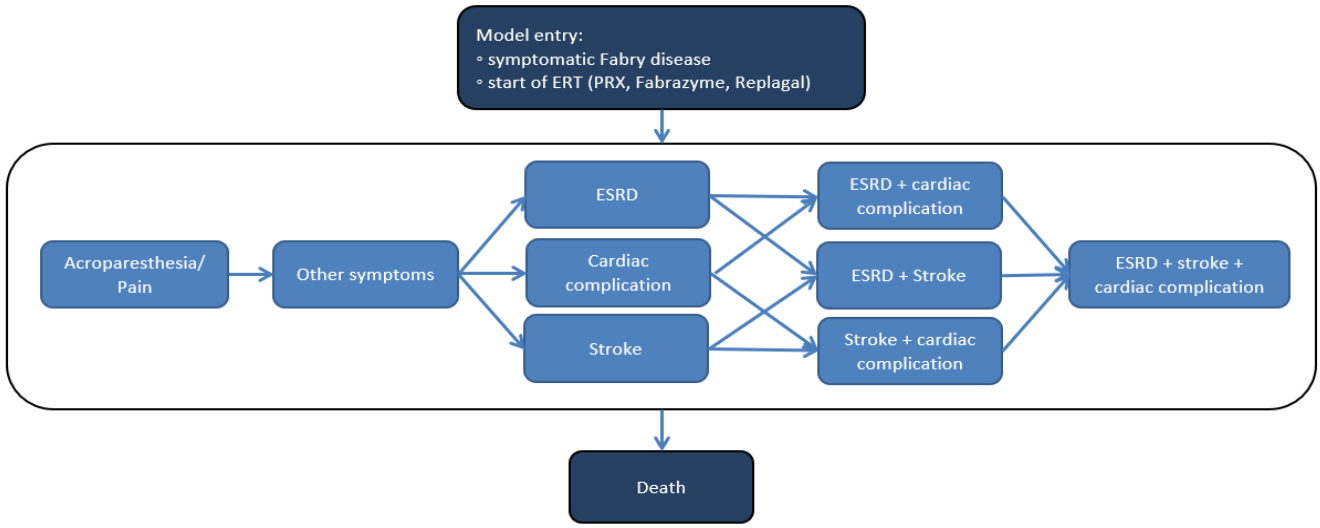
		with those from Arends *et al.*[46] adjusted to the baseline values of BALANCE used in the company base case. Scenarios using other sources were also explored due to the uncertainty around these values.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The HRQoL values from Arends *et al.*[46] adjusted to baseline values of BALANCE were preferred as these included UK patient populations.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Drug administration and acquisition were relevant to the NHS. One omission to this was the health care practitioner resources use which was based on the Dutch healthcare system from a study by *Rombach et al.*[28]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	A discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: EAG, External Assessment Group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 *Modelling approach and model structure*

The company developed a *de novo* Markov model in Microsoft Excel to assess the cost-effectiveness of pegunigalsidase alfa compared to agalsidase alfa and agalsidase beta for the treatment of patients with FD. The structure of the model was based on the model developed for HST4[10] which in turn was informed by a study by Rombach *et al*.[28] The company's model consisted of 10 distinct health states with independent health state utility values (HSUVs), mortality rates and costs which aimed to reflect the progression of FD (Figure 5). In contrast to the *Rombach et al.*[28] and HST4[10] model, the company's model lacked a health state for "no symptoms" as the data used to populate the model was taken from trials with only symptomatic patients. The company also did not allow for patients to regress from the end-stage renal disease (ESRD) health state following renal transplant to simplify the model, mirroring the HST4 model.

Figure 5. Model schematic (Reproduced from CS, Figure 27)



Abbreviations: ERT, enzyme replacement therapy; ESRD, end-stage renal disease.

A description of the 10 health states included in the model are as follows:

- Pain: neuropathic pain in the extremities;
- Other symptoms: clinical signs and/or symptoms of left ventricular hypertrophy, CKD Stages 1–4 or white matter lesions;
- ESRD: chronic kidney disease (CKD) Stage 5 or kidney transplant;
- Cardiac complications: atrial fibrillation, any other rhythm disturbance needing hospitalisation, a pacemaker or an implantable cardiac defibrillator (ICD) implantation, cardiac congestion for which hospital admittance was needed, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft;
- Stroke: as diagnosed by a neurologist;
- ESRD and cardiac complications;
- Cardiac complications and stroke;
- ESRD and stroke;
- ESRD, cardiac complications and stroke;
- Death.

Patients enter the model at age 40 years old and immediately commence treatment. This starting age is in line with the pooled average age of the BALANCE, BRIDGE and BRIGHT trials (40.5 to 44.3 years old) and was supported by a UK cohort study by Malottki *et al.*[47], which observed a mean age at diagnosis of 37 years old. Patients were also disaggregated by sex, with the model assuming a 50:50 split. FD patients were distributed across the health states using the Fabry registry given the

committee stated preferences for this in HST4. The Fabry Registry data was reweighted to exclude patients with ESRD, as these patients were not considered appropriate to start a new therapy. To reflect the progressive nature of FD, patients could only remain in their current health state or progress to more severe health states with backwards transitioning not permitted by the model.

The model cycle length was one year (with a half cycle applied) and the timeline was set to 60 years at which time the patient cohort age would be 100. The perspective of the analysis was based on the UK NHS, with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case[48].

4.2.2.1 EAG critique

The EAG considers the model accurately reflects the natural epidemiology of FD and built on the model submitted in HST4. While the justifications of using the Fabry registry to inform patient distribution at baseline was outlined by the company, the EAG notes that patients were constrained to single symptom health state. As the EAG's independent clinical experts consider that by 40 years old patients may have already developed multiple complications, this restriction was not considered to be clinically accurate. When asked by the EAG to further justify their approach, company stated that the only possible health state with multiple complications a patient could be allocated to, given the exclusion of patients from the ESRD health state at the beginning of the model, would be for CV and stroke and that there was no evidence available to determine the percentage of patients with CV and stroke from the literature.

As the EAG considers that the distribution of patients across these health states would also be available from BALANCE, the EAG requested the company to provide a scenario where the baseline distribution of patients across the health states was reflective of BALANCE. The company was unable to provide this scenario as patient starting health states were not formally gathered in BALANCE, adding that and it would be difficult to allocate patients to a specific health state based on the data that was in the trial.

In contrast to HST4, the functionality of transitioning from a ESRD to a non-ESRD related health state following a kidney transplant had been removed in efforts to simply the model. As the EAG considered this functionality to be more generalisable to the disease pathway the company was asked to further validate this simplification given that the company also assumed 27% of patients entering the ESRD health state at each cycle would receive a kidney transplant. The company

justified their approach by stating that there is no known data for the outcomes of FD patients following renal transplant, therefore any amendments would be based on assumed inputs. The company suggested that the uncertainty of the current input is partially mitigated by the assumption of equal efficacy between treatments and the consideration that the health-related quality of life for these patients is unlike to differ from their pre-transplant state due to exposure to immunosuppressants.

4.2.3 Treatment effectiveness

This section contains key issues 3 and 4 as outlined in Table 1

Given the results of the BALANCE trial, the company concluded that pegunigalsidase alfa was non-inferior to agalsidase beta for the treatment of FD patients as described in Section 3. Given the additional assumption of non-inferiority between agalsidase alfa and agalsidase beta in HST4, the company modelled pegunigalsidase alfa with the same treatment effectiveness as the agalsidase alfa and agalsidase beta. Applying the same transition probabilities, probability of FD mortality and treatment discontinuation rates. As in HST4, distinct sets of transition probabilities were used for males and females, and those on and discontinuing treatment (Tables Table 18,Table 19,Table 20 and Table 21).

To address the concern raised in HST4 by the EAG that the model reflected an unrealistically high life expectancy for FD patients, the company adjusted the probabilities of FD mortality to reflect the average male and female life expectancy as identified by Waldek[21] (58.2 years and 74.7 years, respectively). Background probability of all cause mortality by age and sex was also calculated using up to date ONS life tables with the maximum of this value and the probability of FD related mortality being applied for each health state.

Table 18. Transition probabilities for PRX-102 and ERTs (male patients), reproduced from Table 40 in the CS

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.9289	0.0711	0	0	0	0	0	0	0	0
Other symptoms	-	0.9869	0.0017	0.0085	0.0029	0	0	0	0	0.0006
ESRD	-	-	0.9851	0	0	0.0086	0	0.0063	0	0.0109
Cardiac complications	-	-	-	0.9873	0	0.005	0.0077	0	0	0.0134
Stroke	-	-	-	-	0.9861	0	0.0094	0.0045	0	0.012
ESRD and cardiac	-	-	-	-	-	0.8621	0	0	0.1379	0.4068
Cardiac and stroke	-	-	-	-	-	-	0.8621	0	0.1379	0.4068
ESRD and stroke	-	-	-	-	-	-	-	0.8621	0.1379	0.4068
ESRD, cardiac and stroke	-	-	-	-	-	-	-	-	1	0.4068

Table 19. Transition probabilities for patients who discontinue treatment (male patients), reproduced from Table 41 in the CS

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.9289	0.0711	0	0	0	0	0	0	0	0
Other symptoms	-	0.9849	0.002	0.0097	0.0034	0	0	0	0	0.006
ESRD	-	-	0.9769	0	0	0.0133	0	0.0098	0	0.0169
Cardiac complications	-	-	-	0.9805	0	0.0077	0.0118	0	0	0.0206
Stroke	-	-	-	-	0.9784	0	0.0146	0.007	0	0.0186
ESRD and cardiac	-	-	-	-	-	0.8621	0	0	0.1379	0.4068
Cardiac and stroke	-	-	-	-	-	-	0.8621	0	0.1379	0.4068
ESRD and stroke	-	-	-	-	-	-	-	0.8621	0.1379	0.4068
ESRD, cardiac and stroke	-	-	-	-	-	-	-	-	1	0.4068

Table 20. Transition probabilities for PRX-102 and ERTs (female patients), reproduced from Table 42 in the CS

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.898	0.102	0	0	0	0	0	0	0	0
Other symptoms	-	0.9898	0.0016	0.0062	0.0024	0	0	0	0	0
ESRD	-	-	0.9851	0	0	0.0086	0	0.0063	0	0.011
Cardiac complications	-	-	-	0.9873	0	0.005	0.0077	0	0	0.0134
Stroke	-	-	-	-	0.9861	0	0.0094	0.0045	0	0.012
ESRD and cardiac	-	-	-	-	-	0.8621	0	0	0.1379	0.4068
Cardiac and stroke	-	-	-	-	-	-	0.8621	0	0.1379	0.4068
ESRD and stroke	-	-	-	-	-	-	-	0.8621	0.1379	0.4068
ESRD, cardiac and stroke	-	-	-	-	-	-	-	-	1	0.4068

Table 21. Transition probabilities for patients who discontinue treatment (female patients), reproduced from Table 43 in the CS

	Pain	Other symptoms	ESRD	Cardiac complications	Stroke	ESRD and cardiac	Cardiac and stroke	ESRD and stroke	ESRD, cardiac and stroke	Death
Pain	0.898	0.102	0	0	0	0	0	0	0	0
Other symptoms	-	0.988	0.0018	0.0071	0.0027	0	0	0	0	0
ESRD	-	-	0.977	0	0	0.0133	0	0.0098	0	0.0169
Cardiac complications	-	-	-	0.981	0	0.0077	0.0118	0	0	0.0206
Stroke	-	-	-	-	0.978	0	0.0146	0.007	0	0.0186
ESRD and cardiac	-	-	-	-	-	0.862	0	0	0.1379	0.4068
Cardiac and stroke	-	-	-	-	-	-	0.862	0	0.1379	0.4068
ESRD and stroke	-	-	-	-	-	-	-	0.862	0.1379	0.4068
ESRD, cardiac and stroke	-	-	-	-	-	-	-	-	1	0.4068

Abbreviations: ERT, enzyme replacement therapy; ESRD, end-stage renal disease.

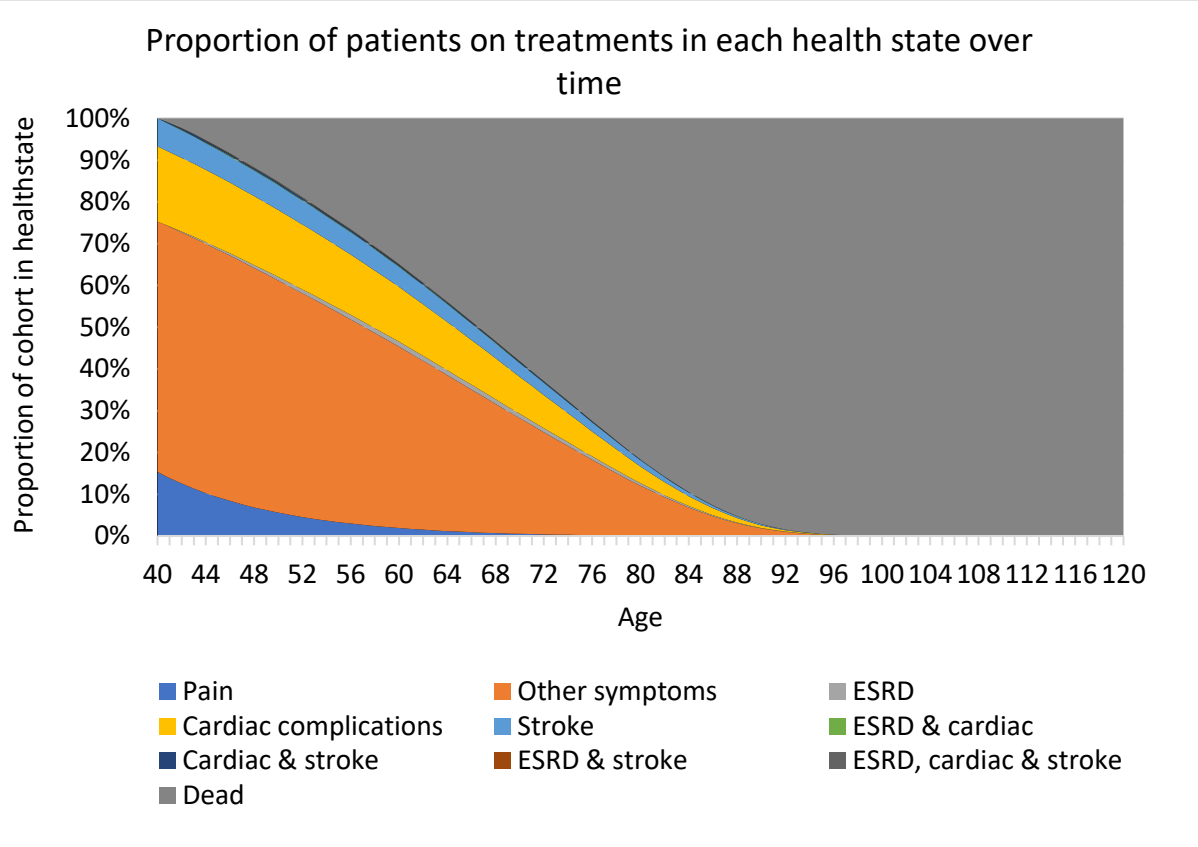
4.2.3.1 EAG critique

The EAG highlights that as non-inferiority between pegunigalsidase alfa and ERT treatments has been assumed by the company and adverse events have not been included in the company's base, no clinical data from BALANCE has been inputted into the model. Likewise, as the company's base case approach is a CMA based on the assumption of non-inferiority, treatment effectiveness is not a key driver of the model as parameters such as transition probabilities are the same between treatments. As the QALYs generated via health state occupancy in the model are therefore the same, cost-effectiveness is driven exclusively by the incremental difference in costs. While the assumption of clinical equivalence has been discussed in Section 2.3.2 , the EAG raises similar concerns regarding the generalisability of the treatment effect within FD patient populations and their cost-effectiveness.

With respect to transition probabilities, those used in the model were the same as those applied in HST4[10]. These originate from the 2013 Dutch Fabry cohort, which consisted of 142 patients (of whom 20% were children). The EAG for HST4[10] was concerned about their generalisability to UK populations and whether or not the children were excluded from transition probability calculations. The current EAG shares these concerns and also questions their replication of FD disease progression.

The CS clearly defines FD as a progressive disease, with symptoms getting worse over time before death, which was supported by the EAG's clinical experts. Indeed, a core component of the model is the flow from single symptom health states to those of progressive complications. In the economic model, however, almost half of patients die in their baseline health states aside from those starting in the pain health state. In the cycle with the highest proportion of patients transitioning between health states, 97.7% of patients remain in their current health state. In only five cycles does the percentage of patients progressing to other health states exceed 2%, of which more than half are patients transition from the pain health state to other symptoms (Figure 6)(as the values for pegunigalsidase alfa are the same for other ERTs only results for pegunigalsidase alfa have been provided).

Figure 6. Markov trace plot of pegunigalsidase alfa (Reproduced from the CE Results tab of the economic model)



These transition probabilities do not describe a progressive condition of the magnitude outlined by the EAG's clinical experts and the company and therefore questions the validity of the transition probabilities.. For example, based on an on-treatment UK population of 885 as calculated in HST4[10] and reiterated by the company in this appraisal, and at any cycle in the model the highest proportion of patients in a health state with more than one symptom is 0.79%, the model suggests that there are only 7 FD patients in the UK who would be categorised into a health state with more than one symptom. The EAG understands that there is a lack of available data to inform health-state transition probabilities but would like to draw attention to how the utilised transition probabilities in HST4 and this submission lack external validity given the opinion of the EAGs clinical experts.

In the CS the company outlined that newer Fabry registry studies exist, which could be used to inform the transition probabilities, but stated these can be prone to selection bias in terms of patient inclusion in the registry. No further explanation or description around the selection bias was provided by the company and as such the EAG requested a scenario which utilised the newer Fabry

registry studies to inform the transition probabilities of the model. The company was unable to conduct the scenario as requested, stating that the transition probabilities identified and used in the model were deemed the most appropriate source by the company's clinical experts at an advisory board meeting.

The company stated that to address the concerns of unrealistic life expectancies for FD patients as described in HST4[10], the FD mortality probability had been adjusted so that average life expectancy in the model matched the life expectancy of FD patients as identified by Waldeck[21]. The EAG was unable to validate the company's estimates of life expectancy in the model and noted that the transition probabilities to death were the same in the company's model and the HST4 model. On clarification by the EAG, the company outlined that the mortality adjusting functionality had been accidently excluded from the model and so was supplied in an updated version of the model. This mortality adjustment, via the application of a standard mortality ratio, was included in a scenario by the company and is used in the EAG's base case.

The company was also asked to validate their approach of excluding transition probabilities from the probabilistic sensitivity analysis (PSA). The EAG is concerned that the model failed to incorporate any of the uncertainty captured in BALANCE given the uncertainty around non-inferiority as outlined in Section 2.3.2 . The EAG suggested a scenario where transition probabilities could be adapted to include the treatment effect observed in BALANCE. In response, the company stated that there was no explicit uncertainty around the treatment effect identified in BALANCE which could be varied within the PSA. The company also stated that the transition probabilities were previously omitted from probabilistic analysis as uncertainty parameters had not been identified. However, as a scenario the company included these transition probabilities and created random variation in their values using 95% confidence intervals and a beta distribution. As the same probabilistic values were applied to pegunigalsidase alfa and ERT treatments alike, the EAG considers that the PSA fails to control for the uncertainty around treatment effectiveness between treatments and therefore is flawed in its use for decision making. While the company suggests the assumption of non-inferiority between pegunigalsidase alfa and agalsidase beta has been substantiated, the company has chosen to equate this with clinical equivalence which is how pegunigalsidase alfa has been modelled.

While there is inherent uncertainty in BALANCE around the treatment effectiveness, the EAG's independent clinical experts did consider pegunigalsidase alfa to have a similar treatment

effectiveness to ERTs. As such, the use of a CMA to infer cost-effectiveness as conducted by the company may be seen as appropriate if non-inferiority can be substantiated.

The EAG agrees with the discontinuation rate of 0.5% used for both pegunigalsidase alfa and ERTs in the company's base. This rate was used in HST4[10], accepted by committee, and supported by the EAG's clinical experts. While the discontinuation rates of pegunigalsidase alfa and agalsidase beta in BALANCE were 9.4% and 4% respectively, these percentages were based on small numbers of patients (i.e. 5 vs 1 patients discontinuing from the trial, of which 3 vs 1 were due to the withdrawal of consent, pegunigalsidase alfa vs agalsidase beta, respectively).

4.2.4 Health-related quality of life

The company's base case was a CMA and as such utilities did not inform the analysis. However, the company conducted a cost-utility scenario to demonstrate that there would be no difference in QALYs between pegunigalsidase alfa and ERTs under the assumption of equivalence of clinical efficacy and safety of treatments. In HST4, the main difference in utilities was due to the inclusion of a disutility associated with IV infusions, as well as disutilities for AEs, in the base case. However, for the current appraisal all treatments are IV infusions and the impacts of AEs have been excluded from the model in the company's base case. As transition probabilities between health states are the same for all treatments, overall QALYs for each treatment are identical. Thus, the utility value used for each health state is only meaningful to estimate the total QALYs expected for a Fabry disease patient on treatment as incremental QALYs will always be zero.

Nonetheless, the EAG presents a brief overview of the utilities used for the cost-utility scenario for reference. In the company's scenario, utility values were obtained from a study by Arends *et al.*,[27] which were identified in the company's HRQoL SLR. As a scenario, the company explored utility values from Rombach *et al.*,[28] also identified in the SLR and used in HST4. The company preferred the use of Arends *et al.*[27] for the primary scenario as the data were more recent, from a bigger sample size and more aligned to the health states in the model. Table 48 in the company submission (CS) presents the utility data from the two studies.

The company stated that EQ-5D-5L data were collected in BALANCE and that a regression analysis, based on mapped EQ-5D-3L data, was explored but ultimately health-state utility values (HSUVs) from the trial were not included in the model. The company explained that a limited number of Fabry clinical events were observed in BALANCE, such that deriving HSUVs from the data was

challenging. However, the company did use the baseline utility value from BALANCE (0.762) to adjust the utility values from Arends *et al.*[27] and Rombach *et al.*,[28] using the multiplicative approach as recommended in the NICE Decision Support Unit Technical Support Document (DSU TSD) 12.[49]

Table 22 presents an overview of the adjusted utility values used for the cost-utility scenario.

Table 22. Adjusted health state utility values used for the cost-utility scenario

Health state	Utility value (Arends *et al.*)[27]	BALANCE adjusted utility value*
Pain	0.73	[redacted]
Other symptoms	0.78	[redacted]
ESRD	0.83	[redacted]
Cardiac complications	0.71	[redacted]
Stroke	0.73	[redacted]
ESRD & cardiac	0.53	[redacted]
Cardiac & stroke	0.53	[redacted]
ESRD & stroke	0.53	[redacted]
ESRD, cardiac & stroke	0.53	[redacted]

Abbreviations: ESRD, end-stage renal disease.
*Values corrected in the company's clarification response.

The company adjusted utility values for age and sex during the clarification stage, and updated the adjustment methods to be derived from the HSE 2014 dataset, as recommended by the NICE DSU TSD.[50]

4.2.4.1 EAG critique

As mentioned previously, the cost-utility analysis was only provided as a scenario to demonstrate that there were no QALY differences between pegunigalsidase alfa and ERTs. As such, the EAG's key issues are only briefly described but alternative utility assumptions do not feature in the EAG's base case, as that is also a CMA.

The EAG considers the key issues with utilities included in the cost-utility scenario to be as follows:

- EQ-5D data were collected in BALANCE directly from patients, but only the baseline utility value was used to adjust the published utility data used in the model. During the clarification stage, the EAG requested the company to explore the use of HSUVs from BALANCE in the model. The company were only able to estimate HSUVs for pain ([redacted]) and other symptoms ([redacted]) as they advised that there were a limited number of clinical events during

the trial to inform the other health states. Nonetheless, the company provided a scenario using BALANCE utility data for the pain and other symptoms health states, with base case utility values used for the remaining health states (Table 22). The BALANCE scenario reduced total QALYs from [redacted] to [redacted]. The EAG considers that as utility data to inform the health states from BALANCE is limited, the company's base case approach to use a single published source, adjusted to BALANCE, to inform all health states is appropriate.

- In the company's cost-utility scenario, utility values for the two and three complication health states were the same but the EAG's clinical experts considered that the HRQoL of patients with three complications would be lower than patients with two complications. As such, during the clarification stage the EAG requested, and the company provided, a scenario where the utility value for the three-complication health state was lower than the two-complication health state. Due to lack of data to inform the three-complication health state, the company estimated a multiplier based on the percentage decrement in HRQoL from a patient moving from a single to double complication health state (29% reduction), informed by Arends *et al*.[27] The company applied the multiplier to the three-complication health state utility, reducing the value from 0.53 to 0.37. Use of the multiplier to adjust the three-state utility value had minimal impact on total QALYs due to the limited number of patients occupying the health state.
- The company's cost-utility scenario should have included the impact of AEs on HRQoL. During the clarification stage, the EAG requested, and the company provided, a scenario including disutilities associated with AEs (see the company's response to clarification question B13 for further detail). As incidence of AEs differed between treatments (see Section 2.3.4), this scenario resulted in a QALY difference of [redacted] and pegunigalsidase alfa dominating ERTs (lower costs, increase in QALYs). However, as the company's base case assumption is that there is no clinically meaningful difference in safety between pegunigalsidase alfa and ERTs, which the EAG agrees is appropriate, the inclusion of disutilities associated with AEs based on numerical differences should be considered as illustrative.

4.2.5 Resource use and costs

The costs included in the economic model consist of drug acquisition and administration costs, health state costs, and terminal care costs. The details of each are given in the following subsections. Unit costs used in the model were based on 2021/22 price years. Unit costs used in the model were

based on the British National Formulary (BNF) 2022,[33] Drugs and pharmaceutical electronic market information tool (eMIT),[51] NHS reference cost schedule for 2020/21[52] and published costs.

4.2.5.1 Drug acquisition costs

As mentioned in Section 2.3.22.3.3, the dosing schedule of pegunigalsidase alfa used in the company base case is 1 mg/kg E2W, which is reflective of the dosing regimen used in BALANCE. The dosing regimen assumed in the model for agalsidase alfa and agalsidase beta is 0.2 mg/kg and 1 mg/kg E2W, respectively.

Drug acquisitions costs are presented in Table 23. A patient access scheme discount (PAS) of [redacted] for pegunigalsidase alfa is applied in the company's base case. It should be noted that upon request from NICE, the company updated the source of the price for agalsidase beta from the BNF (list price) to eMIT, which is a less expensive price.

The company used the Method of Moments (MoM) approach to account for variation in patient weight when estimating the weight-based dose for each treatment. Mean weight and standard deviation to inform the MoM calculations were obtained from Malottki *et al*.[47]

Table 23. Drug acquisition costs

Drug	Pack size and formulation	Unit cost per pack	Cost per mg	Cost per dose*	Cost per annual cycle	Source
Pegunigalsidase alfa	1 vial x 20 mg	£1,255.19 ([redacted])**	£67.76 ([redacted])**	£4,530.10 ([redacted])**	£118,187 ([redacted])**	List price with [redacted] PAS applied
Agalsidase alfa	1 vial x 3.5 mg	£1,049.94	£299.98	£4,326.95	£112,887	BNF[53]
Agalsidase beta	1 vial x 5 mg	£293.78	£58.76	£4,277.99	£111,610	eMIT[51]
	1 vial x 35 mg	£2,081.36	£59.47			

Abbreviations: PAS, patient access scheme,

*Based on a mean weight of 72.2 kg and standard deviation of 20.4 kg from Malottki *et al*.[47]

** PAS discounted cost

The company accounted for drug wastage in the model by taking a pragmatic approach to dosing, informed by clinical experts. Pragmatic dosing was defined as where drug dosage based on patient weight is rounded up or down to the nearest vial to minimise vial wastage. The EAG's clinical experts confirmed that in UK clinical practice, the pragmatic dosing approach is typically used when delivering ERT to Fabry disease patients and it is likely the same approach would be used when

patients are treated with pegunigalsidase alfa. The company explored alternative scenarios using full drug wastage and no drug wastage assumptions and these are presented in Section 5.2.

4.2.5.2 Drug administration costs

Pegunigalsidase alfa and ERTs are chronic IV infusion-based treatments. When patients initiate agalsidase beta and pegunigalsidase alfa, initial infusions are of a longer duration, with the duration of the maintenance infusion reduced based on SmPC guidance. Table 24 presents an overview of the initial and maintenance treatment infusion times.

Table 24. Initial and maintenance infusion duration times and frequency of administration (Table 51 of the company submission)

Treatment	Dose per administration	Duration of infusion (hours)		No. of infusions at initial duration	Dosing frequency/ month	Total number of infusions per year
		Initial	Maintenance			
Pegunigalsidase alfa	1 mg/kg	3	1.5	6	2	26.09
Agalsidase alfa	0.2 mg/kg	0.67	0.67	6	2	26.09
Agalsidase beta	1 mg/kg	3	2	6	2	26.09

Abbreviations: mg, milligram; kg, kilogram.

The company assumed the following for delivery of infusions for all treatments:

- First two infusions at the initial duration take place in a hospital setting and subsequent administrations are delivered at home.
- For the remaining four infusions at the initial duration that take place at home, a nurse administers the infusion.
- For home-based infusions at the maintenance duration, 50% of patients require a nurse to administer the infusion and remaining 50% of patients self-administer (or use an informal caregiver to deliver) their infusion.
- All home-based infusions incur a cost of homecare, which includes home delivery, cost of pre-infusion medication and disposal of medical waste.
- For all nurse-led administrations at home, the cost of an additional 45 minutes for pre-infusion prep and post-infusion monitoring is assumed.
- For the patients that self-administer (or use an informal caregiver to deliver) their infusion, one nurse visit is assumed per year.

Tables 52 and 53 of the CS outlines the company's estimate of the administration costs for the initial and maintenance phases of treatment. However, the EAG identified several errors with the company's calculation of administration costs based on the assumptions outlined in the CS (described above). As such, the EAG presents corrected administration costs and company base case results in Section 6.1.

4.2.5.3 Health state costs

In the model the following categories of costs were estimated to calculate overall health state costs:

- Costs of acute complications applied to new incident patients entering the health state per cycle.
- Ongoing costs of complications applied to prevalent patients in a health state, including:
    - Acute complication follow-up costs.
    - Other healthcare provider (HCP) visits.
    - Costs associated with the general management of Fabry disease.
- Terminal care costs.

The company stated that an SLR was performed to inform cost and resource use assumptions used in the model and that HST4[10] was deemed to be the most relevant source of data as assumptions had been previously validated and accepted by NICE.

An overview of the health state costs is provided in Table 25 and descriptions of each category are given below.

Table 25. Overview of health state costs

Health state	Acute complication costs	Ongoing complication costs			
		General FD management costs	Other HCP costs	Acute complication follow-up costs	Total ongoing complication costs
Pain	-	£827	£572	£0	£1,399
Other symptoms	£2,463	£827	£495	£0	£1,322
ESRD	£9,450	£827	£960	£26,364	£28,151
Cardiac complications	£3,612	£827	£960	£729	£2,516
Stroke	£8,910	£827	£960	£483	£2,270
ESRD & cardiac complications	£13,062	£827	£582	£27,093	£28,502

Stroke & cardiac complications	£12,521	£827	£582	£1,212	£2,622
ESRD & stroke	£18,360	£827	£582	£26,847	£28,257
ESRD & stroke & cardiac complications	£21,972	£827	£582	£27,576	£28,986
Death	£8,524	-	-	-	-

Abbreviations: ESRD, End-stage renal disease; FD, Fabry disease; HCP, health care provider.

Costs of acute complications for each health state (Table 26) were estimated based on NHS references costs for a range of different healthcare resource group (HRG) codes representing different levels of severity for each health state (Table 54 of the CS). The company used a simple average of the HRG codes (i.e. the total cost of several HRG codes, divided by the number of HRG codes included), rather than a weighted average of the HRG codes (e.g. the total cost of several HRG codes divided by the total activity for the included HRG codes), which was used in HST4.[10]

The weighting of acute complications within a health state was taken from HST4 and revalidated by the company's clinical experts. However, in their clarification response, the company confirmed that the weighting of 0% of chronic kidney disease (CKD) stage 1-4 in the other symptoms health state was an error and should have been 0.3%. However, rather than correct the model, the company provided a scenario exploring the impact of changing the weighting of CKD stage 1-4. The EAG considers the model should be corrected as the company acknowledged the error and thus presents corrected results, using the weightings for other symptoms from HST4, in Section 6.1.

Table 26. List of acute complications for costs included in each health state

Health state	Acute complications assumed within health state	Cost weighting within health state
Other symptoms	White matter lesions	51%
	Left ventricular hypertrophy	49%
	Chronic kidney disease (stage 1-4)	0%
End-stage renal disease	Chronic kidney disease (stage 5)	100%
	Renal transplant	27%
Cardiac complications	Atrial fibrillation/ Rhythm disturbance requiring hospitalization	23%
	Pacemaker	1%
	Cardiac congestion requiring hospitalization	39%
	Myocardial infarction	34%
	Percutaneous coronary intervention	0%
	Implantable cardiac defibrillator	1%

	Coronary artery bypass graft	2%
Stroke	Stroke	100%

Follow up costs for ESRD, cardiac and stroke complications have been included in the economic model and in their clarification response, the company explained that the assumptions were obtained from HST4.[10] The EAG presents the HST4 follow up costs for each complication in Table 27.

Table 27. Follow-up costs by complication from HST4[10]

Health state	Cost details	Annual frequency	Unit cost	Inflated total cost (2022)
ESRD	Cost per patient with coronary heart disease in the UK 2015	1	£627	£729
Cardiac complications	Dialysis at a frequency of 156 sessions per year	156	£169	£26,364
Stroke	Annual cost of post-acute care for stroke survivors	1	£415	£483

Abbreviations: ESRD, end-stage renal disease

As per HST4, the company included other healthcare provider (HCP) follow-up costs for patients with Fabry disease. Other HCPs included GP visits, physiotherapist, and psychologist/psychiatrist appointments as well as visits with a social worker. The resource use for each HCP type was split by health state. However, resource use assumptions were assumed to be the same for single complications irrespective of type and for multiple complications, irrespective of the combination of complications. The HCP resource use and unit costs are presented in Table 55 and 56 of the company submission and are aligned with assumptions presented in HST4.[10] The company assumed that each GP visit is 9.22 minutes, based on data from PSSRU,[54] and the duration of visit for the other HCPs was assumed to be one hour.

For the general management of Fabry disease, the company included costs associated with ambulatory care, diagnostics, imaging and laboratory tests, aligned with HST4.[10] However, the annual frequency for each of the resources included for the general management of Fabry disease was based on a clinical expert survey conducted by the company (presented in Table 57 of the company submission). As a scenario, the company explored annual frequency of resource use for the general management of Fabry disease from HST4, but this only affected total costs and did not change incremental costs, due to the assumption of clinical equivalence for pegunigalsidase alfa and ERTs.

The company assumed that all patients incurred a one-off terminal care cost (£8,524) prior to death, consisting of the costs of three months of palliative care, based on inflated costs obtained from Georghiou and Bardsley 2014.[55]

4.2.5.4 EAG critique

The company's approach to resource use and costs are generally aligned with the approach adopted in HST4, but the ERG considers there are several areas where assumptions in HST4 may not be appropriate or have not been implemented correctly. However, the EAG caveats that these issues can be considered minor if the assumption of non-inferiority between pegunigalsidase alfa and ERTs is considered valid. The main costs that differ between treatments are drug acquisition and administrations costs and thus are the primary drivers of incremental costs in the economic model.

The EAG considers that drug acquisition costs have been estimated appropriately. However, as mentioned previously, the EAG considers the company made several errors when estimating drug administration costs and thus corrected these costs to produce a corrected company base case presented in Section 6.1.

The EAG consulted with its clinical experts regarding the assumptions around setting of delivery of IV infusions (hospital or at home) as well as the independence of patients to self-administer treatment. The EAG's clinical experts mostly agreed with the drug administration assumptions but highlighted that most patients are not fully independent to deliver their own IV treatment and instead estimated that 90% of patients would require a nurse to administer their treatment, with the remaining 10% assumed to self-administer treatment. The company provided a scenario exploring alternative drug administration assumptions in their clarification response. An EAG scenario exploring the assumption of 90% nurse led IV infusions and 10% of IV infusions self-administered by patients is presented in Section 6.3 based on corrected company results and is also included in the EAG base case, presented in Section 6.4.

The remaining issues discussed below apply equally to pegunigalsidase alfa and ERTs and thus do not affect incremental costs. Nonetheless, the issues are relevant to provide a more accurate estimate of total costs for each treatment.

For the calculation of the acute complication costs, the company based their assumptions, in particular the weighting of sub-complications and HRG codes, on those used in HST4. Additionally, the company used a simple average of the unit costs of the HRG codes for a category (with different

codes representing different severity for each event) rather than a weighted average of the HRG codes (e.g. the total cost of the HRG codes for a category divided by the total activity for the HRG codes in a category), which was used in HST4.[10] When verifying the calculation of unit costs presented in Table 54 of the company submission against the assumptions made in HST4, the EAG identified a number of discrepancies with HRG codes and the setting used (such as elective inpatient vs non-elective long/short stay). Furthermore, there was an error in the calculation of the stroke cost (average of non-elective long stay costs added to the average of both non-elective long and short stay costs) and the EAG could not replicate the company's costs for white matter lesions and left ventricular hypertrophy. As such, the EAG recalculated acute complication costs based on assumptions presented in HST4[10] and costs weighted by activity (presented in Table 28) and results of a scenario using these costs are presented in Section 6.3. The EAG's version of acute complication costs are also included in the EAG base case presented in Section 6.4.

Table 28. Comparison of acute complication costs – company vs. EAG approach

Health state/ acute complication	Company assumptions (simple average)		HST4 assumptions + EAG weighted average approach	
	Unit cost	HRG codes[52]	Unit cost	HRG codes[52]
Other symptoms				
White matter lesions	£2,554.00	Cerebral Degenerations or Miscellaneous Disorders of Nervous System - AA25C-G non-elective long and short stay	£5,285.28	Cerebral Degenerations or Miscellaneous Disorders of Nervous System - AA25C-G non-elective long and short stay
Left ventricular hypertrophy*	£2,368.30	Other Acquired Cardiac Conditions – EB14A-E non-elective long and short stay	£5,018.18	Other Acquired Cardiac Conditions – EB14A-E non-elective long and short stay
Chronic kidney disease (stage 1-4)	£2,301.04	Chronic Kidney Disease without Interventions – LA08N-P elective inpatient	£2,239.89	Chronic Kidney Disease without Interventions – LA08N-P elective inpatient
End-stage renal disease				
Chronic kidney disease (stage 5)	£3,615.35	Chronic Kidney Disease without Interventions – LA08K-M elective inpatient	£3,337.36	Chronic Kidney Disease without Interventions – LA08K-M elective inpatient
Renal transplant	£21,610.32	Kidney transplant – LA01A, LA02A, LA03A elective inpatient	£21,552.74	Kidney transplant – LA01A, LA02A, LA03A elective inpatient
Cardiac complications				
Atrial fibrillation/ Rhythm disturbance requiring hospitalization	£2,529.23	Arrhythmia or Conduction Disorders – EB07A-E elective inpatient	£3,526.69	Arrhythmia or Conduction Disorders – EB07A-E non-elective long and short stay
Pacemaker	£5,473.78	Implantation of Single-Chamber Pacemaker – EY08A-E – elective inpatient	£4,474.37	Implantation of Single-Chamber Pacemaker – EY08A-E – elective inpatient
Cardiac congestion requiring hospitalization	£3,591.77	Heart Failure or Shock – EB03A-E non-elective inpatient long stay	£4,870.62	Heart Failure or Shock – EB03A-E non-elective inpatient long and short stay

Myocardial infarction	£3,362.92	Cardiac Arrest – EB05A-C non-elective long stay	£3,998.75	Actual or Suspected Myocardial Infarction – EB10A-E non-elective long and short stay
Percutaneous coronary intervention	£7,452.59	Standard Other Percutaneous Transluminal Repair of Acquired Defect of Heart – EY23A-C non-elective long stay	£7,773.02	Standard Other Percutaneous Transluminal Repair of Acquired Defect of Heart – EY23A-C elective inpatient
Implantable cardiac defibrillator	£10,004.79	Implantation of Cardioverter Defibrillator – EY02A-B non-elective long stay	£5,399.13	Implantation of Cardioverter Defibrillator – EY02A-B elective inpatient
Coronary artery bypass graft	£16,548.50	Standard Coronary Artery Bypass Graft – ED28A-C non-elective long stay	£17,133.73	Standard Coronary Artery Bypass Graft – ED28A-C elective inpatient
Stroke				
Stroke	£8,909.83	Stroke – AA35A-F non-elective long and short stay	£7,461.83	Stroke – AA35A-F non-elective long and short stay

Abbreviations: EAG, External Assessment Group; HRG, healthcare resource group.

*In the CS, the HRG code was listed as AA25C-G, which the EAG considers and error. In HST4, the HRG code of BB14A-E, which was also and error, thus the EAG considers the correct code to be EB14A-E.

One cost area where the company deviated from HST4 was around the resource use assumptions for the annual general management for patients with Fabry disease. The company conducted a survey among its clinical experts to estimate the annual frequency of diagnostics, imaging, and laboratory testing. Additionally, the company provided a scenario exploring the resource use assumptions from HST4. The EAG considers that the resource assumed for the general management of Fabry disease patients is aligned with the British Inherited Metabolic Disease Group (BIMDG) guidelines for the treatment of Fabry disease.[56] Generally, the EAG's clinical experts agreed with the company's base case assumptions for the general management of Fabry disease but considered there were some tests that were assumed to be provided by the NHS but in clinical practice pharmaceutical companies cover the costs. The tests included plasma Lyso-Gb3, assay for alpha-galactosidase A Ab, GL-3G and Lyso-GL-3G and antibody test & neutralizing assays. Table 29 provides a comparison of the company's base case assumptions and the EAG's clinical expert assumptions for the general management of Fabry disease. In their clarification response, the company provided a scenario exploring the EAG's clinical expert assumptions and these have been included in the EAG base case, presented in Section 6.4.

Table 29. Annual frequency of resource for the general management of Fabry disease

Resource	Company base case assumptions	EAG clinical expert assumptions
Full blood count	2.38	2.38
Urine test	2.75	2.75
ECG	1.00	1.00
Liver function test	**1.50**	**2.00**
Fasting lipid profile	**1.00**	**2.00**
2D echocardiography with Doppler	0.63	0.63
Glomerular filtration rate	2.13	2.13
24-hour urine protein / creatinine	0.08	0.08
Exercise testing	0.21	0.21
Renal USS	0.06	0.06
MRI	**0.23**	**0.50**
Audiogram	0.63	0.63
Plasma Lyso-Gb3	**0.18**	**0.00**
Assay for alpha-galactosidase A Ab	**1.33**	**0.00**
GL-3G and Lyso-GL-3G	**1.25**	**0.00**
Holter	1.17	1.17
Antibody test & neutralizing assay	**1.50**	**0.00**

Abbreviations: EAG, External Assessment Group; ECG, electrocardiogram; MRI, Magnetic resonance imaging; USS, ultrasound.

With regards to the company's assumptions of other HCP follow-up costs, although assumptions were based on HST4, the EAG's clinical experts considered that social worker visits would not be funded by the NHS but instead the Department of Health and therefore should be excluded from the analysis. As such, the EAG ran a scenario which removed resource use associated with social workers and this is presented in Section 6.3 and carried forward to the EAG base case, presented in Section 6.4.

The EAG notes some secondary issues with resource use and costs but as these apply to all treatments equally and have minimal impact on total costs, they are not amended for the EAG base case. The secondary issues are as follows:

- The estimates of other HCP resource use are based on Rombach *et al.*[28] (also used in HST4)[10], which represents resource use for patients utilising the Dutch healthcare system and does not provide estimates separately for stroke, ESRD and cardiac complication, which likely require differing amounts of resource use. For instance, the EAG's clinical experts commented that the physiotherapist appointments for single complications likely reflect acute stroke. However, because of varying practice across the country for Fabry disease patients, the EAG's clinical experts could not advise on alternative HCP estimates. The EAG notes that changes to other HCP resource use had minimal impact on total costs.
- The EAG's clinical experts considered the proportions of acute complications within the cardiac complication health state may not be reflective of what is seen in UK clinical practice. In particular, use of pacemakers, percutaneous coronary intervention and implantable cardiac defibrillators may be higher. However, the EAG's clinical experts noted there were no robust data available to inform the estimates. During the clarification stage, the EAG requested, and the company provided, a scenario exploring alternative estimates of acute cardiac complications, but this had minimal impact on total costs.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 30 and Table 31 present the results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. For the probabilistic sensitivity analysis (PSA), the company ran 1,000 simulations to assess the joint parameter uncertainty of all inputs in the model.

The company asserts that pegunigalsidase alfa is non-inferior to agalsidase alfa and agalsidase beta and therefore have compared the treatments using a cost-minimisation analysis. As a scenario, the company performed a cost-utility analysis (presented in Table 32) but as the assumption of non-inferiority has been interpreted and modelled as equivalence, there is no difference in QALYs in the deterministic or probabilistic sensitivity analyses (PSA), thus the results are the same as the cost-minimisation results presented in Table 30. A patient access scheme discount (PAS) of [redacted] for pegunigalsidase alfa is applied in the company's base case and is therefore reflected in the results presented in this report.

The EAG was unable to validate the company results included in the clarification question response against the updated model shared by the company. However the company confirmed that the results presented in the updated model accompanying the clarification response contained the correct results and are presented below.

Table 30. Company's post clarification deterministic base case results – CMA

Interventions	Total costs (£)	Incremental costs (£) – pegunigalsidase vs
Pegunigalsidase alfa	[redacted]	-
Agalsidase alfa	[redacted]	-£476,243
Agalsidase beta	[redacted]	-£470,950
Abbreviations: CMA, cost-minimisation analysis		

Table 31. Company's post clarification probabilistic base case results – CMA

Interventions	Total costs (£)	Incremental costs (£) – pegunigalsidase vs.	Range of maximum and minimum probabilistic costs (£)
Pegunigalsidase alfa	[redacted]	-	£495,493
Agalsidase alfa	[redacted]	£482,962	£612,874
Agalsidase beta	[redacted]	£477,529	£612,985
Abbreviations: CMA, cost-minimisation analysis			

Table 32. Company's base case results - CUA

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pegunigalsidase alfa	[redacted]	19.82	[redacted]	-	-	-	-
Agalsidase alfa	[redacted]	19.82	[redacted]	£470,951	0.00	0.00	Cost saving
Agalsidase beta	[redacted]	19.82	[redacted]	£476,243	0.00	0.00	Cost saving
Abbreviations: CUA, cost-utility analysis; ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year.							

5.2 Company's scenario analyses

As the company's base case was a cost-minimisation analysis, the company did not perform a one-way-sensitivity analysis. Instead, the company explored several deterministic scenarios to assess the impact on costs arising from varying key assumptions in the model. The company also conducted several additional scenarios requested by the EAG during the clarification stage. Results of all the scenario analyses conducted by the company are presented in Table 33.

Table 33. Company scenario analyses - deterministic

#	Results per patient	Pegunigalsidase alfa (1)	Agalsidase alfa (2)	Agalsidase beta (3)	Inc. costs (1-2)	Inc. costs (1-3)
0	**Company updated base case - post clarification**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950

1	**Time horizon – 40 years**					
	Total costs	[redacted]	[redacted]	[redacted]	-£457,630	-£452,561
2	**Time horizon – 20 years**					
	Total costs	[redacted]	[redacted]	[redacted]	-£341,092	-£337,422
3	**Time horizon – 10 years**					
	Total costs	[redacted]	[redacted]	[redacted]	-£217,441	-£215,258
4	**No discounting**					
	Total costs	[redacted]	[redacted]	[redacted]	-£872,224	-£862,175
5	**5% discount rate**					
	Total costs	[redacted]	[redacted]	[redacted]	-£390,529	-£386,266
6	**Healthcare resource use – Hughes *et al.*[39]**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
7	**FD complication distribution – KOL survey**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
8	**Utility source – Rombach *et al.* [28]**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
9	**Utility source – Arrends *et al.* [46] (no adjustment for BALANCE)**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
10	**Utility source – Rombach *et al.* [28] (no adjustment for BALANCE)**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
11	**No drug wastage**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
12	**Full drug wastage**					
	Total costs	[redacted]	[redacted]	[redacted]	-£478,269	-£452,131
13	**Include AE management costs**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,468	-£471,175
	EAG requested scenarios					
B4	**Use mean weight pooled from BALANCE, BRIDGE and BRIGHT**					
	Total costs	[redacted]	[redacted]	[redacted]	-£523,582	-£516,495
B11	**Use HSUVs estimated from BALANCE**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B12	**Allow for the utility associated with the 3 complications health state to be lower than the 2 complications health state**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B14	**Adjust mortality rates to reflect life expectancy outlined in Waldeck[21]**					
	Total costs	[redacted]	[redacted]	[redacted]	-£395,598	-£391,274
B15	**0.3% weighting of patients with chronic kidney disease stages 1-4**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B17	**Increase the proportion of patients requiring nurse assisted infusions to 90%**					

	Total costs	[redacted]	[redacted]	[redacted]	-£466,382	-£476,532
B18	**Change the HCRU rates for healthcare professionals to align with data from Malottki[47]**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B19	**Change the weighting of cardiac events experienced by patients to values preferred by the EAG**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B20	**Change the annual frequency of FD management resource use to better reflect services offered by the NHS (scenario 1)**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B20	**Change the annual frequency of FD management resource use to better reflect services offered by the NHS (scenario 2)**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
B13	**Including AE associated disutility into the cost utility analysis**					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,468	-£471,175

Abbreviations: AE, adverse event; EAG, External Assessment Group; FD, Fabry disease; Inc., incremental.

5.3 Model validation and face validity check

The company stated that the model was validated by internal and external modellers. An independent programmer not involved with the model development reviewed all formulae and labelling in the model. After this, black box testing (extreme values) was performed to ensure that the predicted direction of impact on the results was observed.

The company also checked the clinical validity of the model by reviewing key aspects of the model methods and inputs in a virtual advisory board with health economic and clinical experts.

The EAG's review of the model identified errors with the calculation of drug administration costs and has corrected this with results presented in Section 6.1.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

As mentioned in Section 4.2.5.2, the External Assessment Group (EAG) identified several errors with the company's calculation of drug administration costs. For each treatment in the model, setting, delivery and duration of infusions vary based on the initial and maintenance phases of treatment and these assumptions affect the costs incurred for administration. The company attempted to calculate drug administration costs per treatment by combining several assumptions in one long, single formula, resulting in several errors. Examples of the errors include accounting for the costs of homecare to patients receiving care in hospital and applying nurse homecare costs to all initial duration infusions (not accounting for all initial infusions taking place in hospital).

As such, based on the description of the company's drug administration assumptions (outlined in Section 4.2.5.2), the EAG estimated the drug administration costs associated with hospital based initial duration infusions, home-based initial duration infusions delivered by a nurse, home-based maintenance infusions delivered by a nurse for a proportion of patients unable to self-administer treatment and home-based maintenance infusions for those able to self-administer treatment (or using an informal caregiver). Table 34 presents the EAG's estimation of drug administration costs, based on the unit costs provided in Table 52 of the company submission.

Table 34. EAG estimation of drug administration costs

	Pegunigalsidase-alfa	Agalsidase alfa	Agalsidase beta
Drug administration costs for the first year			
Cost of two hospital infusions	£786.00	£786.00	£786.00
Cost of four home-based initial infusions – nurse led	£1,780.62	£1,251.47	£1,780.62
Maintenance home-based infusions - nurse led (50%)	£3,617.21	£3,142.65	£3,901.94
Maintenance home-based infusions - self-administration (50%)	£2,335.90	£2,335.90	£2,335.90
Total	**£8,519.72**	**£7,516.02**	**£8,804.46**
Average cost per administration	**£326.56**	**£288.09**	**£337.47**
Drug administration costs for subsequent years			

Maintenance home-based infusions - nurse led	£4,697.55	£4,081.25	£5,067.32
Maintenance home-based infusions - self-administration	£3,161.11	£3,113.87	£3,189.46
Total	**£7,858.66**	**£7,195.12**	**£8,256.78**
Average cost per administration	**£301.22**	**£275.79**	**£316.48**

Abbreviations: EAG, Evidence Assessment Group.

The EAG considers that another correction (albeit minor) was required for acute complications within the other symptoms health state. In their clarification response, the company acknowledged that the weighting for patients with chronic kidney disease (CKD) stages 1-4 should be 0.3% and not 0%, but did not correct this in their base case. As such, for the corrected company base case the EAG has included the correct weighting for CKD stage 1-4 and reweighted white matter lesions (50.9%) and left ventricular hypertrophy (48.7%), as per HST4. The results of the corrections incorporated into the company's base case are highlighted in Table 35 below.

Table 35. Company's corrected base case post-clarification

#	Results per patient	Pegunigalsidase-alfa (1)	Agalsidase alfa (2)	Agalsidase beta (3)	Inc. costs (1-2)	Inc. costs (1-3)
0	Post clarification company base case					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
1	Corrected administration costs					
	Total costs	[redacted]	[redacted]	[redacted]	-£475,181	-£471,243
2	Corrected CKD weighting					
	Total costs	[redacted]	[redacted]	[redacted]	-£476,243	-£470,950
1+2	Corrected administration costs and CKD weighting					
	Total costs	[redacted]	[redacted]	[redacted]	-£475,181	-£471,243

Abbreviations: CKD, chronic kidney disease; inc., incremental.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

In Section 4 of this report, the EAG has described several scenarios that warranted further exploration in addition to the company's own sensitivity and scenario analyses to measure the impact of these changes on incremental costs. At clarification the company conducted many of the

scenarios as requested by the EAG. The EAG deterministic scenarios around the corrected company base case are as follows and results are presented in Table 36 in Section 6.3.

- For IV infusions delivered at home, 90% of patients require a nurse to deliver the infusion and 10% of patients are able self-administer treatment (or use an informal caregiver) - 4.2.5.4.
- Removal of resource associated with social workers - 4.2.5.4.
- EAG estimation of acute complication costs - 4.2.5.4.
- Comparison to migalastat – 2.3.3

The EAG additionally conducted a cost utility analysis (CUA) between pegunigalsidase alfa and migalastat based on a dosing regimen for migalastat of one tablet taken every other day at a list price of £16,153.85 per a 14-tablet pack (Table 37). As migalastat is an oral treatment, no administration cost has been assumed. The cost and dosing regimen were both sourced from the BNF.[53] In the confidential appendix a scenario with a patient access scheme (PAS) discount has been applied. The comparison assumes non-inferiority between treatments as non-inferiority was accepted by committee in HST4[10] between migalastat and enzyme replacement therapies (ERTs), and BALANCE equally suggests non-inferiority between pegunigalsidase alfa and ERTs. In line with the consideration that no meaningful difference in clinical adverse events were seen between pegunigalsidase alfa and ERTs, costs and utilities relating to adverse events have not been included in the analysis. The only event associated with disutility included was a disutility of 0.025 applied annually to those receiving treatments intravenous infusions. This value was preferred by the EAG for HST4 who considered a value of -0.05 for nurse administered infusion, calculated through a discrete choice experiment, to be too high in comparison to adverse events of worse severity. The EAG notes that the incremental difference in QALYs in the model is comparable to that of HST4[10] when EAG assumptions are applied, this being 0.41 and 0.44, respectively.

Ideally, the EAG considers the company should present a formal indirect treatment comparison of pegunigalsidase alfa and migalastat to inform the economic model and notes that the EAG's scenario should be considered as illustrative.

6.3 EAG scenario analysis

Table 36. Results of the EAG's scenario analyses

Results per patient	Pegunigalsidase-alfa (1)	Agalsidase alfa (2)	Agalsidase beta (3)	Inc. costs (1-2)	Inc. costs (1-3)
Company corrected base case					
Total costs	[redacted]	[redacted]	[redacted]	-£475,181	- £471,243
Removal of costs associated with social care					
Total costs	[redacted]	[redacted]	[redacted]	-£475,181	-£471,243
EAG estimation of acute complication costs					
Total costs	[redacted]	[redacted]	[redacted]	-£475,181	-£471,243

Abbreviations: EAG, external assessment group; Inc., incremental.

Table 37. Migalastat cost utility analysis.

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pegunigalsidase alfa	[redacted]	[redacted]	[redacted]	-	-	-	**£4,591,047[a]**
Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year.

[a]Please note, this ICER sits in the south-west quadrant as pegunigalsidase alfa is less expensive but also less effective than migalastat.

6.4 EAG preferred assumptions

Listed below are the EAG's preferred base case assumptions. Table 38 outlines the cumulative impact of each assumption on the incremental cost of pegunigalsidase alfa compared to agalsidase alfa and agalsidase beta. The independent effect of each assumption can be found in either Table 33 and Table 36. Table 39, Table 40 and Table 41 presents the EAG's deterministic, probabilistic base case results and CUA scenario analysis given the assumptions below.

- Increasing the proportion of FD patients requiring nurse assistance for infusions to 90% - this was in line with the opinion of the EAG's clinical experts;
- EAG estimation of acute complication costs – the EAG considers that a weighted approach to calculating acute complication costs is more clinically accurate than taking the average of the relevant cost codes;

- Removal of costs associated with social works – the EAG considers that these costs lie outside the STA perspective;
- Mortality adjusted to FD patient average life expectancy – the EAG considers the mortality adjustment more closely aligns model patient life expectancy to that of FD patient populations making it more generalisable;
- EAG clinical expert assumptions for general management of FD – the EAG considers that the resource use for FD patients outlined by the EAG's independent clinical experts is more generalisable to clinical practice compared to the company's assumptions which include resources not paid for by the NHS.

Table 38. EAG's preferred model assumptions, cumulative difference in incremental costs

Preferred assumption	Section in EAG report	Pegunigalsidase-alfa (1)	Agalsidase alfa (2)	Agalsidase beta (3)	Inc. costs (1-2)	Inc. costs (1-3)
Post clarification corrected company base case						
Total costs	-	[redacted]	[redacted]	[redacted]	-£475,181	-£471,243
Increase the proportion of patients requiring nurse assisted infusions to 90%						
Total costs	4.2.5.2	[redacted]	[redacted]	[redacted]	-£465,595	-£476,995
EAG estimation of acute complication costs						
Total costs	4.2.5.3	[redacted]	[redacted]	[redacted]	-£465,595	-£476,995
Removal of costs associated with social workers						
Total costs	4.2.5.2	[redacted]	[redacted]	[redacted]	-£465,595	-£476,995
Mortality adjusted to FD patient average life expectancy						
Total costs	4.2.3	[redacted]	[redacted]	[redacted]	-£386,796	-£396,288
EAG clinical expert assumptions for general management of FD						
Total costs	4.2.5.2	[redacted]	[redacted]	[redacted]	-£386,796	-£396,288

Abbreviations: EAG, External Assessment Group; FD, Fabry disease; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 39. EAG's base case post clarification deterministic base case results – CMA

Interventions	Total costs	Incremental costs – pegunigalsidase vs
Pegunigalsidase alfa	[redacted]	-
Agalsidase alfa	[redacted]	-£386,796
Agalsidase beta	[redacted]	-£396,288

Abbreviations: CMA, cost-minimisation analysis

Table 40. EAG's base case post clarification probabilistic base case results – CMA

Interventions	Total costs	Incremental costs – pegunigalsidase vs	Range probabilistic maximum and minimum costs
Pegunigalsidase alfa	[redacted]	-	-£490,214
Agalsidase alfa	[redacted]	-£389,803	-£586,786
Agalsidase beta	[redacted]	-£399,620	-£601,116

Abbreviations: CMA, cost-minimisation analysis

Table 41. Cost utility analysis with EAG assumptions

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pegunigalsidase alfa	[redacted]	[redacted]	[redacted]	-	-	-	**£4,538,221**[a]

Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year.

[a]Please note, this ICER sits in the south-west quadrant as pegunigalsidase alfa is less expensive but also less effective than migalastat.

6.5 Conclusions of the cost effectiveness sections

Overall, the primary concerns highlighted by the EAG regarding cost effectiveness are similar to that of the clinical effectiveness section. Specifically around the uncertainty of the assumption of non-inferiority and the appropriate comparators considered.

In the model, pegunigalsidase alfa is assumed to have the same treatment effectiveness as agalsidase alfa and agalsidase beta. The company justify this approach using BALANCE, which they assert demonstrated non-inferiority between pegunigalsidase alfa and agalsidase beta. While the company claims they have assumed non-inferiority in the model, the EAG considers they have instead applied assumptions associated with clinical equivalence. With the same transition probability values being applied across all treatments in the PSA. As such the model fails to capture the uncertainty associated with the difference in treatment effects. The EAG also considers these transition probabilities to lack face validity given the CS and the EAG's independent clinical experts description of FD epidemiology.

The EAG's independent clinical experts also highlighted the uncertainty in cost effectiveness for FD treatments generally, drawing on studies whose results reflected no significant difference between placebo and treatments considered non-inferior to ERTs for treating FD.[29] While the EAG accepts that an independent evaluation of all treatments for FD is beyond the scope of the current appraisal, and would be more appropriately undertaken with a Multiple Technologies Appraisal (MTA), the EAG considers it important to highlight this issue and the likely impact that any decisions made on this appraisal are likely to have on any future evaluations. This consideration is also aligned with the previous EAG's concerns in the factual accuracy check (FAC) for HST4.[10]

Given the treatment pathway, the EAG also considers that migalastat would have been an appropriate comparator given the NICE final scope. The EAG notes the inconsistency between the initial scope for the STA, which outlined that pegunigalsidase alfa would only be considered for patients without an amenable mutation or those unable to be prescribed migalastat, and the company's response to the EAG's clarification questions which described the scope to include those

with adherence issues, patient choice and any other reasons. Patient choice was highlighted as a key driver of treatment options available to patients by the EAG's clinical experts and as such the EAG was concerned this was not considered in the initial scope of this appraisal. The EAG therefore considers the company should provide a formal comparison with migalastat.

These concerns aside, in both the company's and EAG's base case cost minimisation analysis, pegunigalsidase alfa was found to be cost saving when compared to ERTs.

7 References

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Single Technology Appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 26 April 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Availability of mean/median eGFR slope data for 12-month and 24-month analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15: Text states: "The EAG only had access to limited data from the 12-month analysis, which were provided in the draft SmPC, and comprised mean values whereas the primary analysis of the 24-month data in BALANCE was based on median values." And "The EAG considers this issue likely to be unresolvable based on the clinical evidence available at this time but the EAG considers results for mean and median eGFR and change from baseline should be consistently provided for both the 12 and 24 month time-points in BALANCE to enable comparison and support the	Please revise the text to clarify that both mean and median eGFR slope data were available within the CSR for the final analysis at 24 months, and mean data were available for the interim analysis at 12 months. Median values for the 12-month interim analysis are available in the CSR appendices, which can be supplied upon request.	To ensure the reader is aware of the full body of available evidence	Not a factual inaccuracy, no change required.

company's conclusion of non-inferiority." However, the full CSR was supplied, which contained details of the eGFR slope data for the interim 12-month analysis including mean values, and included both mean and median eGFR slope values for the 24-month analysis. Median values for the 12-month interim analysis are available in the CSR appendices, which can be supplied upon request.			
Page 49: Text states "The EAG also notes that full results for the interim analysis at 12 months were not provided in the CS." This is not fully accurate because the key results for the 12-month interim analysis from the ITT population were presented	Please update text to read: "The EAG also notes that although full results for the interim analysis at 12 months were not provided in the CS, results for the ITT population for the interim analysis were presented (Appendix M.1.3.1), and the full interim analysis (ITT and PP populations) was presented in the CSR (section 11.4.1.3 on page 95)."	To ensure the reader is aware of the full body of available evidence	Not a factual inaccuracy, no change required. The EAG has re-reviewed Appendix M.1.3.1 and Table 69 (Selected sensitivity and supportive analyses for eGFR slope from BALANCE: ITT population) and is unable to identify any results

in the CS Appendices (Table 69 in Appendix M.1.3.1) and the full 12-month analysis (ITT and PP populations) was presented in the CSR (section 11.4.1.3 on page 95). We request that the text is updated to reflect this.			from the12 month interim analysis of BALANCE. Additionally, the EAG has reviewed the CSR Section 11.4.1.3, page 95 and can find no results reported as explicitly originating from the 12 month interim analysis.
Page 61: Text states “The EAG notes that the 12 month data are not reported in the CS and the assessment of non-inferiority at 24-months is based on the use of annualised data from week 104.” This is not fully accurate because the key results for the 12-month interim analysis from the ITT population were presented in the CS Appendices (Table 69 in Appendix M.1.3.1). The full 12-month analysis (ITT and PP	Please update the text to clarify that the 12-month interim analysis from the ITT population were presented in the CS Appendices (Table 69 in Appendix M.1.3.1).		Not a factual inaccuracy, no change required. Please see response above for further details.

populations) was presented in the CSR (section 11.4.1.3 on page 95). We request that the text is updated to reflect this.			

Issue 2 Clarity of prevalent FD population in England

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21: "..estimated that the prevalent FD population in England is approximately 2,100 patients, with approximately 90 incident patients per year." Page 31: "…, although as discussed in Section 2.2, the estimated prevalent population in the UK is also relatively small (n=2,100)." The population size of 2,100 patients represents both diagnosed and undiagnosed patients; as detailed in	Please update the wording to reflect the size of the diagnosed population in England, as follows: "..estimated that the prevalent FD population in England is approximately 2,100 patients, with approximately 90 incident patients per year. Of the prevalent FD population, only 50% are estimated to be diagnosed, resulting in an estimated 1,050 diagnosed FD patients in England." And: "…, although as discussed in Section 2.2, the estimated diagnosed prevalent population in England is also relatively small (n=1,050)."	The diagnosed FD population is a better reflection of the prevalent FD population of England.	Thank you for highlighting this; the EAG has updated the EAG report to include details of the diagnosed and undiagnosed FD populations as requested by the company.

Document of the CS, is it anticipated that only 50% of all FD patients are diagnosed, which equates to an estimated ~1,050 patients diagnosed with Fabry disease in England.			

Issue 3 Positioning of PRX-102

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22: Text states "The EAG notes that the company are defining eligibility for pegunigalsidase alfa for patients with an amenable mutation as being restricted to only those patients in whom migalastat is deemed to be unsuitable. The EAG therefore considers there is potentially a population of patients who have an amenable mutation and are suitable for migalastat or ERT but won't be eligible for	Please could the first sentence be expanded to state: "The EAG notes that the company are defining eligibility for pegunigalsidase alfa for patients with an amenable mutation as being restricted to only those patients in whom migalastat is deemed to be unsuitable, due to issues with adherence, tolerance, patient or clinician choice, or any other reason." Please consider removing the second sentence as this does not accurately reflect the positioning of PRX-102.	To provide clarity around the positioning of PRX-102.	Not a factual inaccuracy, no change required. Please note the EAG describes the company's definition of 'unsuitable' for migalastat earlier on Page 22.

pegunigalsidase alfa due to the restricted positioning proposed by the company." The first sentence misses the context of what is meant by "unsuitable" here so we would like to request that this is expanded upon. The second sentence misinterprets the proposed positioning of PRX-102, because the company propose that patients who have an amenable mutation but who are unsuitable for migalastat (due to issues with adherence, tolerance, patient or clinician choice, or any other reason) would indeed be eligible for PRX-102 as PRX-102 would be considered as another ERT option.			

Issue 4 Context of Fabry disease as a rare disease

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31: "…The EAG is therefore concerned that BALANCE comprises of a relatively small sample size…" Page 36: Text states: "The EAG notes that follow-up in BALANCE was up to 24 months and considers that both the small sample size " Page 44: "The EAG is also concerned that the sample size in BALANCE is relatively small (ITT population n=77) particularly for the comparator arm (agalsidase beta n=25) and so it is difficult to draw any robust conclusions on the comparative efficacy of the treatments albeit the EAG	Please remove mention of BALANCE being a relatively small sample size	To provide context for the sample size within the BALANCE trial, when considered within the rare Fabry disease population.	Not a factual inaccuracy, no change required.

also notes that FD is a relatively rare disease." Page 46: In Table 10, the text states "The EAG notes that the final ITT analysis for the primary outcome included 77 patients and that despite being only 1 patient less than planned it still represents a small study sample size, especially for the comparator arm given the 2:1 randomisation." The notion of BALANCE having a relatively small sample size does not seem to be factually correct when we are discussing such a rare condition such as Fabry disease, and in particular given than, BALANCE is the largest Phase III RCT ever conducted in Fabry disease. Furthermore, BALANCE is also the only active-controlled RCT conducted in Fabry disease			

Issue 5 Evidence for assumption of equivalent efficacy between pegunigalsidase alfa and both agalsidase alfa and agalsidase beta

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32: Text states “In response to clarification question A3, the company explain that their rationale for this decision includes that:” and then a series of bullets are presented representing evidence for the assumption of equivalent efficacy between pegunigalsidase alfa and both agalsidase alfa and agalsidase beta. However, two bullets that are considered to be part of this supporting evidence have not been included in the EASG report and we suggest they are included for additional support for this assumption.	Please add to the list of bullets the following two bullets: • “In addition, a naïve comparison between BALANCE and BRIDGE suggested there were no significance differences in PRX-102 efficacy for key outcomes of interest between the studies, adding further evidence that the efficacy demonstrated in BALANCE was reflective of the efficacy of PRX-102 in other studies (see Appendix D.1.3.1), although the analyses are limited due to small patient populations and differing baseline characteristics such as sex and age • In an advisory board, the 4 UK clinical experts consulted considered that the non-inferiority conclusion from BALANCE and the precedent in HST4 would be supportive of clinical equivalence of	To provide the full extent of evidence for the assumption of equivalent efficacy between pegunigalsidase alfa and both agalsidase alfa and agalsidase beta	Thank you for highlighting this; the EAG has updated the EAG report to include details relating to the two bullets highlighted by the company and the EAG’s critique.

	PRX-102 to the existing comparator treatments."		
Page 33: One bullet states: "two RCTs providing head-to-head comparisons of agalsidase alfa and agalsidase beta (Vedder 2007[22] and Sirrs 2014[23]) demonstrate no statistical difference;" This does not accurately reflect the company's interpretation of this published evidence and is somewhat oversimplifying. The company provide further detail on the two published studies mentioned in terms of which outcomes showed differences between the treatments investigated. As such, we suggest expanding to present this detail and reducing the chance of misinterpretation	Please update this bullet to read: • "two RCTs providing head-to-head comparisons of agalsidase alfa and agalsidase beta (Vedder 2007[22] and Sirrs 2014[23]) demonstrated the following: ○ Sirrs et al, 2014: A total of 92 patients who were ERT naïve were randomised to either agalsidase alfa 0.2 mg/kg E2W or agalsidase beta 1.0 mg/kg E2W. The study observed no statistical difference in endpoints between the agalsidase alfa and agalsidase beta arms (HR alfa versus beta 1.29; p=0.67) but the power was noted to be limited. There was no significant difference in the proportion of patients receiving agalsidase alfa or agalsidase beta (19.4% vs 13.3%; p=0.57) that met the composite clinical endpoint (renal events [development	To accurately reflect the published information comparing agalsidase alfa ad agalsidase beta and provide additional detail on the results of these comparisons	Not a factual inaccuracy, no change required.

		of end-stage renal disease OR decline in GFR of 50% or greater, sustained for 30 days and excluding other causes], cardiovascular events [pacemaker or other intracardiac device, coronary artery bypass grafting, valve replacement surgery, coronary angioplasty or stent, cardioversion, hospitalization or emergency room visit for unstable angina/acute coronary syndrome, myocardial infarction, congestive heart failure, tachy- or brady-arrhythmia, heart block, cardiac arrest], cerebrovascular event [TIA or stroke documented by a physician or acute hearing loss], or death) ○ Vedder et al, 2007: A total of 34 patients with FD were randomised to either agalsidase alfa 0.2 mg/kg E2W or agalsidase beta 0.2 mg/kg E2W within an open-		

	label trial. The authors concluded that the study revealed no difference in reduction of LVM or other disease parameters after 12 and 24 months of treatment with either agalsidase alfa or beta at a dose of 0.2 mg/kg E2W. Treatment failure occurred frequently in both groups and seemed to be related to age and severe pre-treatment disease.		
Page 34: No additional explanation as to whether the retrospective cohort study (Arends et al 2018) is robust enough to support the clinical equivalence of agalsidase alfa and beta	Please can an explanation be provided as to whether the EAG considers the Arends et al, 2018 study as supportive of the assumption of clinical equivalence of agalsidase alfa and beta	To provide a full assessment of the evidence provided for the assumption of clinical equivalence of agalsidase alfa and beta	Not a factual inaccuracy, no change required.

Issue 6 Extent of subgroup data provided

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 37: Text states “Additionally, the EAG notes that subgroup analysis for patients who have an amenable mutation and are on migalastat was requested in the NICE final scope but the EAG notes that data for this subgroup were not available from BALANCE” Whilst we did not provide these specific data for BALANCE, we did provide a subgroup analysis of patients with/without amenable mutations from an integrated analysis of BALANCE, the other two Phase III trials (BRIDGE and BRIGHT) and the Phase I/II studies, which we feel should be mentioned here to be fully accurate.	Please could the text be updated to read: “Additionally, the EAG notes that subgroup analysis for patients who have an amenable mutation and are on migalastat was requested in the NICE final scope but the EAG notes that data for this subgroup were not available from BALANCE. However, the company did provide a subgroup analysis of patients with/without amenable mutations through an integrated post-hoc analysis of patients receiving PRX-102 within the clinical trial programme (BALANCE, BRIGHT, BRIDGE and Phase I/II studies; Appendix M5). The results demonstrated that the presence of an amenable mutation [redacted] when treated with PRX-102.[81]	To ensure the reader is aware of the full body of available subgroup analyses	Thank you for highlighting this; the EAG report has been amended to include information about the integrated *post-hoc* analysis.

Issue 7 Additional details on clinical systematic review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39: Table 9 states: "Conference proceedings: • Manual hand-searching of key conference proceedings from the last 2 years (further details not provided)" And: "The EAG also notes that while the searching of conference proceedings and HTA websites increases the comprehensiveness of the search strategy, these proceedings and websites are not named by the company, meaning it is not possible to check whether those searched were relevant or exhaustive."	Please add details of the conference proceedings that were searched, as follows: "Conference proceedings were searched for the last 2 years (2021–2022) in both the original and update to identify any abstracts of interest, as follows: • Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium • Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM)"	To provide full details of the websites searched within the systematic review	Thank you for highlighting this; the EAG report has been updated to include details of the conference proceeding searches.

However, on page 9 of the CS Appendices, details of the conference proceedings searched are provided and we would ask that this is reflected in EAG report			

Issue 8 Conclusions around non-inferiority of PRX-102 to agalsidase beta from BALANCE trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 47 Text states "The EAG considers that this conflicts with the conclusions reported in the CS, "PRX-102 [pegunigalsidase alfa] E2W is not inferior to agalsidase beta E2W, meaning that the primary endpoint [of BALANCE] was met" However, it should be highlighted that the conclusion in the draft EMA SmPC not only conflicts with the conclusion in the CS but it also conflicts with the conclusions presented in the	Please update the wording to: "The EAG considers that this conflicts with the conclusions reported in the CS: 'PRX-102 [pegunigalsidase alfa] E2W is not inferior to agalsidase beta E2W, meaning that the primary endpoint [of BALANCE] was met'; in the CSR: 'The study met its pre-specified primary endpoint and demonstrated that PRX-102 was statistically non-inferior to agalsidase beta'; and in the publication: 'Pegunigalsidase alfa showed non-inferiority to agalsidase beta based on	To present the supportive evidence for the conclusion of non-inferiority of PRX-102 to agalsidase beta from BALANCE	Not a factual inaccuracy, no change required.

CSR and in the Wallace 2022 publication. The CSR states “Considering a non-inferiority margin of -3 mL/min/1.73 m^2 /year, these results indicate non-inferiority of PRX-102 compared to agalsidase beta.” and “The study met its pre-specified primary endpoint and demonstrated that PRX-102 was statistically non-inferior to agalsidase beta” The Wallace publication states: “Pegunigalsidase alfa showed non-inferiority to agalsidase beta based on the median eGFR annualized slope, a key measure of FD progression” As such, we would request that these additional sources are referenced here.	the median eGFR annualized slope, a key measure of FD progression’”		
Page 49 When presenting the following information “The EAG notes that in the PP	Please include the time point for this analyses within the document for completeness	To improve clarity and accuracy of the document	Not a factual inaccuracy, no change required. Additionally, the EAG is unclear what the company means by,

population [redacted] please can the time points for this analysis be included			"the timepoint for this analysis."

Issue 9 Conclusions around feasibility of migalastat ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 59 The EAG have considered the appropriateness of migalastat trials within an ITC with pegunigalsidase alfa. However, there is no conclusion presented within the report We would request that then EAG also include their assessment of the feasibility of ITC for completeness.	Please update the wording to: "However, the EAG also notes that the RCTs used to provide the evidence base for migalastat in HST4 were a placebo-controlled RCT and a two-arm RCT comparing migalastat with ERT, and ERT comprised a mixture of agalsidase alfa (65%) and agalsidase beta (33%) with no stratification. Therefore, with the current evidence base for pegunigalsidase alfa and migalastat, a robust ITC would not be feasible" Please also acknowledge this conclusion in Page 62; Page 95 and Page 99 of the report for consistency	To provide the reader with complete assessment of feasibility of a potential ITC comparing pegunigalsidase alfa to migalastat	Not a factual inaccuracy, no change required. The text referred to by the company provides a summary of the data informing HST4 and the EAG has not conducted a feasibility assessment of a potential ITC with migalastat.

Issue 10 Transitions from ESRD health state following renal transplant

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 66 and 68 The EAG refer to the company approach differing from the approach used in HST4, noting that HST4 included backward transitions from the ESRD health states following a transplant. This is inaccurate, this functionality was included in the original analysis by Rombach, but was not included in the HST4 model for simplicity.	Please correct the statement to say that "In contrast to the original study by Rombach, but in line with the accepted approach employed in HST4, the functionality of transitioning from a ESRD to a non-ESRD related health state following a kidney transplant had been removed in efforts to simply the model."	To improve the clarity and accuracy of the document.	The EAG thanks the company for identifying the inaccuracy and has adjusted the wording accordingly.

Issue 11 Tracking patients in a cohort level model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 72: Description of "In the economic model, however, the vast majority of patients die in their baseline health states."	The company proposes that the wording is deleted as the statement cannot be evidenced, or reflect that the specifics of where patients started and finished cannot be interpreted from a cohort model.	It is not possible to identify this within a cohort level model as patients are not tracked as they move through the model.	While this is not a factual inaccuracy the EAG agrees to amend the wording to reflect that aside from patients distributed to the pain

	The table in issue 12 presents the distributions of deaths and the movement between health states, this can be used to provide an alternative, evidenced, description.		health state, almost half of patients will die in the health state they are distributed to.

Issue 12 Model's reflection of FD

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 72 – 73, when critiquing the modelling of the transition probabilities in their report, the EAG significantly misrepresent how the model reflects Fabry disease	Remove interpretations that refer to transitions or occupancy within a single cycle. They constitute an inappropriate way of reviewing the models reflection of Fabry disease. The removal of the sentence "*These transition probabilities do not describe a progressive condition of the magnitude outlined by the EAG's clinical experts and the company but of static symptom development and then death.*", which is inaccurate.	The EAG frames the economic model as reflecting "static symptom development and then death" The table below presents the starting distribution of patients between health states in the model, it also shows the number of patients who exited that health state over the time horizon and the proportion of patients who died in that health state. Contrary to the EAG's statement, the table demonstrates the progression of patients over time. Approximately 13% of patients died having been in a health state reflecting two or more comorbidities.	The EAG agrees to amend the static description of the model. The EAG has therefore replaced this sentence with *"These transition probabilities do not describe a progressive condition of the magnitude outlined by the EAG's clinical experts and the company and therefore the EAG questions the validity of the transition probabilities."*

The greatest proportion of patients died in the clinical events of FD health state, which is to be expected given 75.3% of patients either started or could enter this state after one progression. The clinical events of FD is a broad description and therefore encompasses a lot of patients, it should be expected that many patients would remain in this health state long-term, especially if they are well managed with an ERT. However, 27.4% of the model population progressing from this state to a state associated with a comorbidity demonstrates the model is not static.

Health state	Starting distribution	Exited to another Health state	Died in health state
Pain	15.3%	14.4%	0.9%
Clinical events of FD	60.0%	27.4%	47.1%
Cardiac complications	18.1%	9.3%	25.9%
ESRD	0.0%	1.0%	2.9%
Stroke	6.7%	3.8%	9.2%
ESRD & Cardiac	0.0%	1.0%	3.2%

		Cardiac & Stroke	0.0%	2.0%	6.2%	
		ESRD & Stroke	0.0%	0.4%	1.2%	
		ESRD, Cardiac & Stroke	0.0%	0.0%	3.4%	

Issue 13 Varying transition probabilities in PSA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 74 states: "*as a scenario the company included these transition probabilities and created random variation in their values using 95% confidence intervals and a beta distribution.*"	Please could you amend this to: "The company varied the transition probabilities used in the model in their updated probabilistic base case. The transition probabilities were varied using a beta distribution back-calculated from the 95% confidence intervals reported for the transition probabilities in the supplementary materials of Rombach et al. 2013."	To improve the clarity and accuracy of the document.	Not a factual inaccuracy, no change required.

Issue 14 Assuming equivalence from the results of BALANCE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 74 states: "*While the company suggests the assumption of non-inferiority between pegunigalsidase alfa and agalsidase beta has been substantiated, they have confused this with clinical equivalence which is how pegunigalsidase alfa has been modelled.*" This is a misleading statement, the company assumed clinical equivalence based on the non-inferiority result observed in BALANCE. This assumption was then presented and validated by clinical experts at an advisory board.	Please amend the statement to reflect that clinical equivalence was the intended modelling assumption and this was rigorously validated.	The company appreciates that this is a modelling assumption, although one well supported by clinical opinion. Suggesting it was adopted through confusion undermines the consideration and clinical support given to the modelling approach.	While this is not a factual inaccuracy, the EAG was unsure if the company had indeed confused non-inferiority with equivalence but as the company has outlined this was an active decision the EAG will amend the statement accordingly.

Issue 15 Misinterpretation of the NICE reference case perspective for costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 95 and 97: In the third bullet of section 6.4 the EAG notes the removal of costs associated with social work as “these costs lie outside the STA perspective”	Primarily reinstate the costs associated with social work required by FD patients, in line with the company submitted sources. Otherwise, amend the justification for removing the cost, as social work should be considered within the NICE reference case scope.	The NICE reference case perspective for costs in “NHS and personal social services” The Unit Cost of Health and Social care 2022 Manual describes its unit costs as including face-to-face-appointment time with a social worker.	It is the understanding of the EAG that social work costs are covered by the Department of Health and Social Care and therefore lie outside the NICE reference case. The EAG will amend the justification to reflect this.

Issue 16 Table 32 ICER results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ICER for pegunigalsidase alfa compared to agalsidase alfa or agalsidase beta is described as inferior	Amend to dominant	Pegunigalsidase alfa has equal health outcomes versus the two ERTs and therefore cannot be considered inferior. It is then dominant by nature of its cost savings.	The EAG thanks the company for identifying the inaccuracy and has amended the wording accordingly. The EAG believes that dominant may be seen as inaccurate as there is no difference in QALY and

			so will mend to cost saving.

Issue 17 Text inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15: Text states “The EAG considers there to be differences in the population of the BALANCE RCT compared to the UK population limiting its generalisability;…”	Rather than the UK population, we understand this should read UK Fabry disease population. As such, please could we request this is updated to read: “The EAG considers there to be differences in the population of the BALANCE RCT compared to the UK Fabry disease population limiting its generalisability;…”	To improve clarity and accuracy of the document	The EAG thanks the company for highlighting this; the EAG report has been amended to include ‘UK Fabry disease population’ on pages 15, 24 and 60.
Page 15: Text states “The EAG is also concerned about the robustness of the company’s claims of non-inferiority for pegunigalsidase alfa compared with agalsidase beta and notes that there was a change to the time point for the assessment of non-inferiority in BALANCE,	Please update to read: “The EAG is also concerned about the robustness of the company’s claims of non-inferiority for pegunigalsidase alfa compared with agalsidase beta and notes that there was a change in the primary assessment endpoint of BALANCE as a result of a protocol amendment, from assessment of non-inferiority at 12-months	To provide context around the change in the primary assessment endpoint	While not a factual inaccuracy, the EAG has amended the EAG report in line with the company’s request.

from 12-months to 24-months." We request that some additional context is provided here to allow the reader understand the history to this decision, given that this was a protocol amendment, which determined that a non-inferiority analysis of the 24-month data was performed, as per agreement with the FDA. As such, the pre-planned non-inferiority margin from the interim analysis (after 1 year) was used for the final analysis (after 2 years of treatment).	to assessment of non-inferiority at 24-months."		
Page 31: "…and marketing authorisation application (MAA) approval is expected…" This seems unclear that we are referring here to	Please update text to read: "…and European marketing authorisation application (MAA) approval is expected…"	To improve clarity and accuracy of the document	The EAG thanks the company for highlighting this; the EAG report has been amended to add the word 'European'.

European marketing authorisation.			
Page 32: Text states “In response to clarification question A3,…” The question being referred to is question A2	Please update text to read: “In response to clarification question A2,..”	To improve clarity and accuracy of the document	The EAG thanks the company for highlighting this inaccuracy; the EAG report has been amended to refer to A2.
Page 35: “The EAG’s clinical exerts…”	Please update to read: “The EAG’s clinical experts…”	To improve clarity and accuracy of the document	The EAG thanks the company for highlighting this inaccuracy; the spelling has been corrected in the EAG report
Page 43: Text states: “The EAG notes that the Phase I/II study provides the only evidence for pegunigalsidase alfa in treatment naïve patients.” However, there are three Phase I/II studies (PB-102-F01) and its extension	Please update text to read: “The EAG notes that the three Phase I/II studies provide the only evidence for pegunigalsidase alfa in treatment naïve patients.”	To improve clarity and accuracy of the document	The EAG thanks the company for highlighting this inaccuracy; the EAG report has been amended to refer to the three Phase I/II studies.

<table>
<tr><td>studies PB-102-F02 and PB-102-F03, so we propose that the wording is updated to reflect this more clearly.</td><td></td><td></td><td></td></tr>
<tr><td>Page 44: Table 10 is incomplete and is missing information in the column entitled “Section of CS in which information is reported”

We request that these section numbers are provided for ease of reference</td><td>Please update the column entitled “Section of CS in which information is reported” within Table 10 as follows:
<table><tr><th>Aspect of trial design or conduct</th><th>Section of CS in which information is reported</th></tr><tr><td>Randomisation</td><td>B.2.3.1.1.</td></tr><tr><td>Concealment of treatment allocation</td><td>N/A</td></tr><tr><td>Eligibility criteria</td><td>B.2.3.1.2</td></tr><tr><td>Blinding</td><td>B.2.3.1.1.</td></tr><tr><td>Baseline characteristics</td><td>B.2.3.1.3</td></tr><tr><td>Dropouts</td><td>Appendix D.2.1</td></tr><tr><td>Sample size and power</td><td>B.2.3.1.1 and B.2.4</td></tr></table></td><td>To improve clarity and usability for the user</td><td>The EAG thanks the company for highlighting this; the EAG report has been amended to include the appropriate references to the CS.</td></tr>
</table>

	Handling of missing data: M1.3.1 Outcome assessment: B.2.4		
Page 51: Text states "The EAG notes that the difference between treatment arms in mean changes was not reported in the CS and in the CSR [redacted] This is not factually accurate as these data presenting mean log difference are presented in the CS within Table 13 of the main CS doc, albeit not presented within the text. As such, we request that the text is updated to reflect this.	Please update text to read: "The EAG notes that the difference between treatment arms in mean changes was reported in the CS by means of an analysis of the changes in plasma lyso-Gb3 using a Mixed Model Repeated Measure (MMRM) model to control for a number of variables. The results of the MMRM analysis of mean log difference suggest [redacted]"	To improve clarity and accuracy of the document	The EAG thanks the company for highlighting this inaccuracy; the EAG report has been amended to remove the text referring to the CSR and correct the text relating to the CS. The confidential marking has also been updated.
Page 58: Text states: "Additionally, the EAG notes that the proportion of ADA-positive patients with neutralising antibodies was lower for	Please update text to red: "Additionally, the EAG notes that the proportion of ADA-positive patients with neutralising antibodies was lower for pegunigalsidase alfa (64%) than for		The EAG thanks the company for highlighting this; the EAG report has been amended to include

pegunigalsidase alfa (64%) than for agalsidase beta (100%) at 24 months (CS,).” The cross reference to the CS is incomplete and this should be completed with the relevant section number which is Section B.2.10.1.6 on page 96.	agalsidase beta (100%) at 24 months (CS, Section B.2.10.1.6 on page 96).”		the section reference to the CS.
Page 60: Text states “The company also presented a naïve comparison between the BALANCE RCT and the Phase III single-arm pegunigalsidase alfa BRIDGE study (CS Appendix D.1.3.1), but acknowledged that the analyses are very limited due to small patient populations and differing baseline characteristics between trials such as sex and age.” We would request to clarify that this analysis, although	Please update text to read: “At the request of the EAG at the decision problem meeting and checkpoint meeting, the company also presented a naïve comparison between the BALANCE RCT and the Phase III single-arm pegunigalsidase alfa BRIDGE study (CS Appendix D.1.3.1), but acknowledged that the analyses are very limited due to small patient populations and differing baseline characteristics between trials such as sex and age.”	To add context and improve clarity of the document	Not a factual inaccuracy; no change required.

limited, was conducted in response to a request by the EAG at the decision problem meeting and checkpoint meeting.			
Page 60: Text states: “The EAG notes the company has also submitted supportive evidence from single-arm studies with the key single-arm trial being the BRIDGE study which was comprised of treatment naïve patients without renal impairment (Section 3.2).” This is factually inaccurate because the patients in BRIDGE were not treatment-naïve but had been previously treated with agalsidase alfa.	Please update text to read: “The EAG notes the company has also submitted supportive evidence from single-arm studies with the key single-arm trial being the BRIDGE study which was comprised of patients without renal impairment who had been previously treated with agalsidase alfa (Section 3.2).”		The EAG thanks the company for highlighting this inaccuracy; the EAG report has been amended to remove reference to treatment naïve patients.
Page 69: Mortality incorrectly spelt as “*morality*” on page 69	Correct spelling	To aid in both the accuracy and clarity of the document.	The EAG thanks the company for identifying the incorrect spelling.

Page 74: Waldek incorrectly spelt as "*Waldeck*"	Correct spelling	To aid in both the accuracy and clarity of the document.	The EAG thanks the company for identifying the incorrect spelling.
Page 75: Respectively spelt incorrectly "*Respaectively*"	Correct spelling	To aid in both the accuracy and clarity of the document.	The EAG was unable to locate this incorrect spelling.
Pages 77 and 91: Arends incorrectly spelt as "*Arrends*"	Correct spelling	To aid in both the accuracy and clarity of the document.	The EAG thanks the company for identifying the incorrect spelling.
Page 96: pegunigalsidase alfa incorrectly spelt "*pegunigalsidase alpha*"	Correct spelling	To aid in both the accuracy and clarity of the document.	The EAG thanks the company for identifying the incorrect spelling.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Pegunigalsidase alfa for treating Fabry disease [ID3904] EAG report – page number 27	However, in an integrated analysis of 112 patients from the PRX-102 trials, of which 17 had amenable mutations and 64 did not, results demonstrated that the presence of an amenable mutation [redacted]	However, in an integrated analysis of [redacted] patients from the PRX-102 trials, of which [redacted] had amenable mutations and [redacted] did not, results demonstrated that the presence of an amenable mutation [redacted]	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
EAG report – page 29	The company considered that the results of the naïve comparisons suggested no significant differences in efficacy of pegunigalsidase alfa for key outcomes of interest between BALANCE (pegunigalsidase alfa E2W in renally impaired population) and the single-arm study BRIDGE (pegunigalsidase alfa E2W in non-renally impaired population) but the EAG does not consider this naïve comparison to be a robust source of evidence for drawing such conclusions.	The company considered that the results of the naïve comparisons suggested [redacted] in efficacy of pegunigalsidase alfa for key outcomes of interest between BALANCE (pegunigalsidase alfa E2W in renally impaired population) and the single-arm study BRIDGE (pegunigalsidase alfa E2W in non-renally impaired population) but the EAG does not consider this naïve comparison to be a robust source of evidence for drawing such conclusions.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

Page 30	In the company response to clarification questions, it is reported that all female patients in BALANCE were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic (27/29 [93.1%] in the pegunigalsidase alfa arm and 14/18 [77.8%] in the agalsidase beta arm). The EAG also notes that there are other imbalances in baseline characteristics between treatment arms in BALANCE such as [redacted] and a lower proportion with UPCR ≤ 0.5 gr/gr in the pegunigalsidase alfa arm (69.2% vs 80.0%).	In the company response to clarification questions, it is reported that all female patients in BALANCE were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic [redacted] in the pegunigalsidase alfa arm and [redacted] in the agalsidase beta arm). The EAG also notes that there are other imbalances in baseline characteristics between treatment arms in BALANCE such as [redacted] and a lower proportion with UPCR ≤ 0.5 gr/gr in the pegunigalsidase alfa arm ([redacted] vs [redacted]).	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 44, Table 10	No details of the method of allocation concealment were provided in the CS but the EAG notes from the CSR that [redacted] was used in the allocation of patients to study treatment.	No details of the method of allocation concealment were provided in the CS but the EAG notes from the CSR that [redacted] was used in the allocation of patients to study treatment.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 45, Table 10	The EAG notes from the CSR that [redacted].	The EAG notes from the CSR that [redacted].	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

Page 45 – Table 10	[redacted] **reasonably small number of discontinuations** The EAG notes that there was a slightly [redacted] rate of discontinuations in the pegunigalsidase alfa study arm ([redacted] compared to the agalsidase beta study arm ([redacted]. However, [redacted]	**Imbalanced but reasonably small number of discontinuations** The EAG notes that there was a slightly higher rate of discontinuations in the pegunigalsidase alfa study arm (5 [9.4%]) compared to the agalsidase beta study arm (1 [4%]). However, only 2 [3.8%] of those in the pegunigalsidase alfa arm were due to AEs and the remaining discontinuations were due to withdrawal of consent.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 45 – Table 10	[redacted]	[redacted]	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 46 – Table 10	The EAG notes from the CSR that: [redacted]	The EAG notes from the CSR that: [redacted]	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

Page 47	The primary endpoint in BALANCE was the annualised change in eGFR (slope), derived from the eGFR assessments over time[20] and the primary objective of BALANCE was to assess whether pegunigalsidase alfa was non-inferior to agalsidase beta for this endpoint. The EAG notes that the study sample size was previously planned to demonstrate [redacted], although the EAG is unclear what was in the original protocol as the above analyses were reported [redacted]. Subsequent to the FDA granting full approval of agalsidase beta, the company reported that it was no longer necessary to demonstrate treatment superiority of pegunigalsidase alfa over agalsidase beta and instead, a non-inferiority analysis of the 24-month data was performed, as agreed with the FDA. The EAG notes that [redacted]	The primary endpoint in BALANCE was the annualised change in eGFR (slope), derived from the eGFR assessments over time[20] and the primary objective of BALANCE was to assess whether pegunigalsidase alfa was non-inferior to agalsidase beta for this endpoint. The EAG notes that the study sample size was previously planned to demonstrate non-inferiority after 1 year of treatment (interim analysis) and superiority after 2 years of treatment (final analysis), although the EAG is unclear what was in the original protocol as the above analyses were reported as part of the amendments made in version 2 of the protocol. Subsequent to the FDA granting full approval of agalsidase beta, the company reported that it was no longer necessary to demonstrate treatment superiority of pegunigalsidase alfa over agalsidase beta and instead, a non-inferiority analysis of the 24-month data was performed, as agreed with	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

		the FDA. The EAG notes that [redacted]	

Page 47	The company reported results using the ITT population (n = [redacted]) in the CS but the EAG notes that results for the per protocol (PP) population (n = [redacted]) are also available in the CSR for BALANCE for the primary analysis.	The company reported results using the ITT population (n = 77) in the CS but the EAG notes that results for the per protocol (PP) population (n = 72) are also available in the CSR for BALANCE for the primary analysis.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 48	At month 24, the median slopes for eGFR were -[redacted]mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -[redacted]for the agalsidase beta arm with a difference of [redacted] and 95% CI of -[redacted].	At month 24, the median slopes for eGFR were -2.51 mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -2.16 for the agalsidase beta arm with a difference of -0.36 and 95% CI of -2.44 to 1.73.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 48	The difference in estimated median annual eGFR slopes at month 24 in the PP population for pegunigalsidase alfa compared to agalsidase beta was [redacted]	The difference in estimated median annual eGFR slopes at month 24 in the PP population for pegunigalsidase alfa compared to agalsidase beta was [redacted]	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 48	The EAG also notes that [redacted], although the 95% CIs included 0, indicating no significant difference between treatment groups.	The EAG also notes that at 24 months the difference in median slopes for eGFR favour treatment with agalsidase beta, although the 95% CIs included 0, indicating no significant difference between treatment groups.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

Page 49	The EAG notes that in the PP population [redacted]	The EAG notes that in the PP population [redacted]	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 51	The EAG notes that the difference between treatment arms in mean changes was not reported in the CS and in the CSR [redacted] In terms of percentage change, the EAG notes that the difference in means for mean percentage change from baseline at week 104 for pegunigalsidase alfa compared to agalsidase beta was [redacted]%.	The EAG notes that the difference between treatment arms in mean changes was not reported in the CS and in the CSR the results of an analysis of the changes in plasma lyso-Gb3 using a Mixed Model Repeated Measure (MMRM) model to control for a number of variables was presented. The results of the MMRM analysis of mean log difference suggest [redacted] In terms of percentage change, the EAG notes that the difference in means for mean percentage change from baseline at week 104 for pegunigalsidase alfa compared to agalsidase beta was [redacted]%.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

Page 51	At Week 104, mean urine lyso-Gb3 concentration had increased slightly (by 7.0 pM/mM creatinine) in the pegunigalsidase alfa arm and decreased (-11.2 pM/mM creatinine) in the agalsidase beta arm. The EAG notes that the difference in mean change [redacted] (pegunigalsidase alfa vs agalsidase beta difference in means [redacted]; 95% CI: [redacted] to [redacted]). Additionally, the EAG notes there was a [redacted]	At Week 104, mean urine lyso-Gb3 concentration had increased slightly (by [redacted] creatinine) in the pegunigalsidase alfa arm and decreased [redacted] /mM creatinine) in the agalsidase beta arm. The EAG notes that the difference in mean change [redacted] (pegunigalsidase alfa vs agalsidase beta difference in means [redacted]; 95% CI: [redacted] to [redacted]). Additionally, the EAG notes there was a [redacted]	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 52	The EAG notes that the SEs were [redacted] and the mean percentage change from baseline was [redacted] %) with an overall difference in means for percentage change in plasma Gb3 concentrations from baseline at week 104 of [redacted] % for pegunigalsidase alfa compared to agalsidase beta.	The EAG notes that the SEs were [redacted] and the mean percentage change from baseline was [redacted] %) with an overall difference in means for percentage change in plasma Gb3 concentrations from baseline at week 104 of [redacted] % for pegunigalsidase alfa compared to agalsidase beta.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

Page 54	The company also reported that all female patients in BALANCE were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic (27/29 [93.1%] in the pegunigalsidase alfa arm and 14/18 [77.8%] in the agalsidase beta arm).	The company also reported that all female patients in BALANCE were categorised as non-classic (based on the criterion of low enzymatic activity) and most males were categorised as classic[redacted] in the pegunigalsidase alfa arm and [redacted] in the agalsidase beta arm).	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.
Page 57	The EAG notes that there were [redacted] reported in either trial arm.	The EAG notes that there were no deaths reported in either trial arm.	The EAG thanks the company for highlighting this and has amended the confidential marking in the EAG report.

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **03 June 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Company
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**I am an employee of Chiesi Limited who is the manufacturer of pegunigalsidase alfa (PRX-102, Elfabrio®)**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Exclusion of migalastat as a comparator.	No	The Company's optimised positioning of pegunigalsidase alfa (PRX-102) in the UK treatment pathway has not changed in that PRX-102 is anticipated to be used as a treatment option *for patients with symptomatic Fabry disease (FD) who would be treated with an enzyme replacement therapy (ERT).* This eligible patient population is smaller than the full licensed indication and would include patients without an amenable mutation for migalastat, but also patients with an amenable mutation who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). This proposed positioning was supported by 4 UK clinical experts whose opinion was consulted during an advisory board during the submission development and is in agreement with the positioning of PRX-102 as described by NHS England in its budget impact submission (page 5, section 3.3). In this optimised population, the only relevant comparators for this appraisal are the other ERTs, agalsidase alfa and agalsidase beta. The EAG has flagged concern there is potentially a population of patients who have an amenable mutation and who would be suitable for migalastat or an ERT, and therefore would not be eligible for PRX-102 due to the restricted positioning proposed by the company. We wish to reiterate that our positioning would not limit access to PRX-102 for these patients: if they choose not to be treated with migalastat for any reason, including

		patient/clinician choice, they would be able to receive PRX-102, as they would be deemed unsuitable for migalastat and so would be offered a choice of ERTs instead. As noted in the company submission, the ITC feasibility assessment concluded that the evidence base in FD is limited and heterogenous, therefore any statistical analysis would be associated with substantial uncertainty. As concluded for HST4, the addition of the available evidence base for migalastat would not change these conclusions and therefore any comparative effectiveness analysis between PRX-102 and migalastat would also be highly uncertain. Given the limitations of the evidence base, we consider the exploratory cost effectiveness analysis carried out by the EAG (page 97 of the assessment report) to be an adequate estimation of the likely cost-effectiveness of PRX-102 compared with migalastat, should the committee feel it necessary to include migalastat as a comparator despite the company positioning of PRX-102 in UK clinical practice.

Key issue 2: Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa.	Yes	We consider that BALANCE, the largest RCT ever conducted in FD, provides sufficient and robust evidence to support the conclusion of non-inferior efficacy between PRX-102 and agalsidase beta. In BALANCE, the pre-defined non-inferiority (NI) margin for the lower bound of the 95% CI for the difference in eGFR slopes between the treatment groups to support the non-inferiority conclusion was -3 ml/min/1.73 m^2/year. The decision to use this threshold as the NI margin was described in the responses to the EMA submitted as new evidence,[1, 2] and are summarised as follows: • Evidence derived from the natural history of FD suggests that untreated patients present with progressive kidney deterioration with an eGFR slope worse than -3 ml/min/1.73 m^2/year.[3] Therefore, a margin of -3 was considered a relevant eGFR slope threshold for assessing the benefit of a disease specific treatment, considering the large variability reported in the literature on the renal function in untreated and treated patients with FD. • Further support and validation of the NI margin used was provided from the consensus of a European panel of Fabry disease experts which noted that a stabilisation of kidney function decline is considered to have been achieved if a patient has a GFR slope loss ≤1–3 mL/min/1.73m^2/year.[4] Whilst this threshold refers

		primarily to the eGFR goal in an individual FD patient, consensus from these FD experts provides greater confidence in the clinical relevance of -3.0 ml/min/1.73m^2 per year as a non-inferiority margin for stability in kidney function decline for a new treatment when demonstrating non-inferiority to an approved therapy. • Required sample sizes for such a small NI margin and large SD are not feasible in rare diseases. Therefore the evaluation of a NI design in a rare disease field such as FD represents a challenge, and the choice of the margin for the NI analysis had to take into consideration the feasibility of the selected sample size in the context of the disease and the outcomes being assessed. Of note, the migalastat Phase III study was the only NI study in FD patients which evaluated eGFR slope.[5] Within this study to overcome the objective challenge related to feasibility in terms of patients numbers for enrolment to run a NI trial, NI was declared not based on the confidence interval approach, which is the typical statistical method in establishing NI, but rather by meeting the following two conditions: • Difference between the point estimates of the slopes which is smaller than 2.2 ml/min/1.73m^2/year; • At least 50% overlap between the individual confidence intervals. This is an easier bar for demonstrating NI than comparing the lower bound of the confidence interval to the pre-defined NI margin and hence it was possible to consider a margin of 2.2. In the migalastat EMA assessment report, the 95% CI for the treatment difference in eGFR slope is presented and its lower bound is - 2.57. During the appraisal HST4,[6] NICE accepted this data to support a conclusion of NI between migalastat and enzyme replacement therapies (ERTs). • It should be flagged that using the migalastat criteria for NI evaluation, BALANCE would have met NI criteria both at the interim analysis as well as at the final analysis. As per the request from the EAG and NICE at the technical engagement call, please find below a table outlining mean and median eGFR slope data at 12 months and 24 months,

which is also described in the response to Question 97 in the Day 120 EMA responses submitted as additional evidence:[2]

Table 1. Mean and Median eGFR slope at 12 months, and 24 months

	12 Months		**24 Months**	
	ITT	PP	ITT	PP
Number of subjects				
PRX-102	52	49	52	48
Agalsidase beta	25	25	25	24
Mean data: Estimated mean (95% CI) annual eGFR slopes (mL/min/1.73 m^2/year)				
Number of subjects considered in the analysis:				
PRX-102	53	49	51	48
Agalsidase beta	25	25	25	24
PRX-102	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]

		Difference in mean (PRX-102 - Agalsidase beta)	[redacted]	[redacted]	[redacted]a
		Median data: Primary model: Estimated median (95% CI) annual eGFR slopes (mL/min/1.73 m^2/year)			
		PRX-102	[redacted]	NR	-2.514 (-3.788; -1.240)	-2.515 (-3.666; -1.364)
		Agalsidase beta	[redacted]	NR	-2.155 (-3.805; -0.505)	-2.397 (-4.337; -0.457)
		Difference in medians (PRX-102 - Agalsidase beta)	[redacted]	NR	-0.359 (-2.444; 1.726)	-0.118 (-2.450; 2.213)
		Key: CI. Confidence interval; SE, standard error **Source:** Chiesi, BALANCE CSR[7]; Chiesi, Response to EMA Day 120 questions – question 97[2] **Notes:** Analysis is based on a quantile regression for the median with eGFR slope of each individual patient as dependent variable and treatment arm as covariate of the model. All observations are used including unscheduled visits. [a] For these 24-month mean data, confidence intervals were derived from the reported mean estimate and the standard error; these estimates have been calculated using aggregated data from the CSR as the patient-level data were not available not available within the timeframe for these responses but these data will need to be confirmed based on the patient-level data and an updated table will be provided			

		[b] For these median data, confidence intervals were derived from the reported median estimate and the standard error; these estimates have been calculated using aggregated data from the CSR as the patient-level data were not available within the timeframe for these responses, these data will need to be confirmed based on the patient-level data and an updated table will be provided In addition to the eGFR results, clinical equivalence between PRX-102 and agalsidase alfa is also supported by several other efficacy endpoints reported in the BALANCE study.[7] These include kidney function as assessed by urine protein to creatinine ratio (UPCR), the biomarker plasma-lyso Gb3, left ventricular mass index (LVMI), the Mainz Severity Score Index (MSSI) and pain severity as measured by the Brief Pain Inventory (BPI). While levels remained generally stable in the course of the study, small differences between groups in favour of PRX-102 (UPCR, LVMI, MSSI, and BPI) or in favour of agalsidase alfa (plasma-lyso Gb3) were observed, none of which were judged as clinically meaningful, thereby supporting clinical equivalence between the two treatments.
Key issue 3: External validity of transition probabilities unclear, given disease epidemiology.	No	We would like to highlight the challenge of developing transition probabilities for modelling a long-term progressive rare disease such as FD. Our model follows the progression of FD through 10 health states, with each state capturing the onset of a significant comorbidity. Disease progression through these health states does not occur rapidly, but over the lifetime of a patient that will live for more than 60 years on average.[8] Deriving transition probabilities is made even more difficult given the nature of FD as a rare disease. Based on the latest epidemiological data and clinical opinion, we estimated there are approximately 1,000 diagnosed FD patients in the UK, with approximately half of those receiving active treatment.[9] Combining both factors means that developing transition probabilities of the standard seen in other indications would require information on the majority of the English FD population over an extended period. A scenario that is likely unachievable. In light of this challenge, we believe that the transitions initially implemented by Rombach et al. provide a suitable dataset for decision making. The outcomes of 142 Dutch Fabry disease patients were collect both prospectively and retrospectively, 72 of these patients received an ERT, which is assumed to be clinically equivalent to PRX-102, providing a relatively large sample size for a specific treatment type in a rare disease.[10]

		The study reporting the transitions was identified using systematic literature review methods as is requested in the NICE method guide.[11] After identification we presented them to a UK advisory board, which could not provide any alternative sources that would provide superior quality of evidence. We believe that the use of these transitions in HST4 further validates our selection, given our SLR did not identify any superior evidence sources published since this appraisal. It is recognised that the ERG for HST4 raised similar limitations related to the transitions, which were noted by the committee. We have implemented the amendments proposed by the ERG to adjust the mean survival time of patients when using these probabilities. This mitigates some of the uncertainty associated with the transitions, and was considered sufficient for the committee to accept their use during HST4.[6]
Key issue 4: There is uncertainty in the assumption of non-inferiority translating to clinical equivalence in the model, because assuming non-inferiority of the treatments is already a key issue.	Yes	As noted in our response to Issue 2, we consider that BALANCE provides robust clinical evidence to support the non-inferiority of PRX-102 to agalsidase beta, and the extension of this conclusion to agalsidase alfa is supported by evidence in the literature and clinical opinion (provided within the CS). Non-inferiority has been deemed as sufficient evidence to support clinical equivalence in previous NICE appraisals. Technology appraisal (TA) 821 of avalglucosidase alfa for treating Pompe disease[12] and TA698 of ravulizumab for treating paroxysmal nocturnal haemoglobinuria[13] both presented results from Phase III non-inferiority randomized control trials and used this to support modelling of clinical equivalence. In both instances the committee concluded that the intervention and comparator had at least equivalent effectiveness and that cost comparison approaches were appropriate.
Key issue 5: Uncertainty about treatment effect of enzyme replacement therapies (ERTs).	No	As discussed with NICE/EAG at the technical engagement call, this issue sits outside of the scope of this appraisal. We do however want to reiterate that as FD is a rare disease it is important for patients with rare diseases to have access to additional treatment options with the same opportunity for access as patients with other diseases.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Assessing Fabry Disease as a rare disease	N/A	No	We would like to emphasise that this submission has been developed for the management of FD, which is a rare disease. FD met all of the criteria required for migalastat to be considered under the highly specialised technology process. These characteristics still exist, even if the availability of migalastat means that PRX-102 is being appraised under the single technology appraisal process.[6] We hope that the evidence presented in this submission and some of the areas of uncertainty highlighted by the EAG will be considered in this context by the committee, as is described in the NICE method guide.[11]
Additional issue 2: Acceptance of proposed PRX-102 positioning in other HTA	N/A	Yes	We would like to highlight that the National Centre for Pharmacoeconomics (NCPE) in Ireland have recently (May 2023) accepted the positioning of PRX-102 in patients who would usually be treated with an ERT and have concluded that a full HTA is not needed to assess PRX-102 versus other ERTs.[14]

Summary of changes to the company's cost-effectiveness estimate(s)

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Sensitivity analyses around revised base case
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3. Branton MH, Schiffmann R, Sabnis SG, et al. Natural History of Fabry Renal Disease: Influence of α-Galactosidase A Activity and Genetic Mutations on Clinical Course. *Medicine*. 2002; 81(2):122-38.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegunigalsidase alfa for treating Fabry disease [ID3904]

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Thank you for your time.

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	The MPS Society
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	The MPS Society has received funding from; Chiesi- £30k for its advocacy and mental health services and website development Takeda -£30k for its patient services (additional funds expected in June 2023 for patient services) Sanofi – Awaiting funds for patient services, mental health service and website (expected in June 2023) Amicus- £22k for its advocacy service, cost of living support (additional funds for literature review, MH and website expected June 2023)
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Exclusion of migalastat as a comparator.	Yes/No	It is unclear if this issue would even cause a meaningful impact on the ICER as such it would not change the decision. Migalastat is clinically viewed as an equal treatment option for patients with an ***amenable*** mutation; this is a small subgroup of patients, whereas ERT is available for all eligible patients. The intent of ERT and migalastat is also very different. With ERT you are infusing a functioning enzyme that is missing. Whereas for migalastat you are increasing enzyme activity by giving the correct set of instructions to enzymes that are not functioning properly. It therefore seems very reasonable just to use ERT as the comparator.
Key issue 2: Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa.	Yes/No	Clinical trial data indicates that pegunigalsidase alfa appears to be non-inferior to agalsidase beta in slowing kidney disease progression with similar trends seen against agalsidase alfa. It is unclear why, given data (accepted by the expert community) that pegunigalsidase alfa is not clinically equivalent and why it is unreasonable to infer clinical equivalence for the purpose of this assessment. There is always going to be uncertainties when evaluating treatments for small populations. Given there is no impact on the ICER, this uncertainty in our opinion

		is irrelevant to the decision-making, and therefore unclear why it is flagged as an issue.
Key issue 3: External validity of transition probabilities unclear, given disease epidemiology.	Yes/No	In our opinion, the conclusion would be the same. Is this relevant to decision making? It is unclear why this was raised as an issue.
Key issue 4: There is uncertainty in the assumption of non-inferiority translating to clinical equivalence in the model, because assuming non-inferiority of the treatments is already a key issue.	Yes/No	There is no indication that this uncertainty would change the directionality of the cost effectiveness assessment. Therefore, it is irrelevant to the assessment of existing ERTs. While we accept, a more precise estimate of cost effectiveness might be possible with reduced uncertainty this is unnecessary for the decision at hand and so unclear why this is raised as an issue.
Key issue 5: Uncertainty about treatment effect of enzyme replacement therapies (ERTs).	Yes/No	It is unclear why this has been included as a key issue. The plausibility of an MTA was discussed at scoping. Due to NICE not having the framework for this type of review a singular evaluation was the preferred route. It would therefore be inappropriate to discuss generic uncertainties about treatment effect of ERTs. As the ERG correctly stated this issue is outside of the scope of this evaluation, it therefore seems inappropriate for it to be raised as an Issue at all, let alone a key issue, within this process. Should the ERG wish to raises this, as they might reasonably do, it should be done outside this process, due to the nature of the scope of this review. And in the event the ERG do wish to raise this issue, in an appropriate manner (outside this process) then it is unclear why the ERG would choose to neglect to mention Migalastat as a comparator as they appear to believe it has a place as a comparator – see ERG note for Key Issue 1?

Additional issues

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Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

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Sensitivity analyses around revised base case
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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Amicus Therapeutics UK Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	n/a
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1. Exclusion of migalastat as a comparator	No	Amicus outlined our position on inclusion of migalastat as a comparator at the scoping stage of this appraisal. Amicus believes it is critical not to ignore the role of migalastat as a unique oral therapy for Fabry disease [1,2]. However, in the context of an assessment of pegunigalsidase alfa (PRX-102), we leave it to the EAG experts and NICE to decide on including migalastat as a comparator in the scope of this assessment, bearing in mind the paucity of comparative data.
Issue 2. Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa.	No	No comment
Issue 3. Transition probabilities lack external validity given disease epidemiology	No	No comment
Issue 4. The assumption of non-inferiority translating to clinical	No	No comment

equivalence in the model given the key issue of non-inferiority		
Issue 5. Treatment effects of ERTs	No	No comment

Additional issues

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Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The statement in the report: 'Treatments for FD such as migalastat, … have also been shown to be comparable to placebo in other studies,' with reference to Germain et al. (2016) [5]	Section 2.3.3 Comparators (page 36)	Yes – reference 4	Amicus believes that this statement in the EAR is inaccurate and recommends that it is removed. The primary objective of the study reported by Germain et al., 2016 was 'to compare the effect of migalastat with that of placebo on kidney GL-3 as assessed by histologic scoring of the number of inclusions in interstitial capillaries after 6 months of treatment' [3]. However, data on patients with both amenable and non-amenable mutations were taken into consideration for this primary analysis. Migalastat is a suitable treatment only for those FD patients with an amenable mutation. Notably, Germain et al., 2016 correctly report that although the primary analysis in patients with amenable or non-amenable mutations receiving migalastat therapy did not show a significant treatment effect, prespecified post-analyses in patients with amenable mutations provided evidence of a significant and durable reduction in kidney GL-3 levels, as expected with

			migalastat versus placebo [3]. After up to 24 months, the annualised rates of change in estimated GFR among migalastat-treated patients with amenable mutations at all baseline levels of urinary protein excretion were less than the decline in estimated GFR in published cohorts of untreated patients [3]. In contrast to the statement reported in the EAR, evidence from the literature shows that migalastat treatment in amenable FD patients is superior to placebo, with miglastat's clinical value and efficacy demonstrated in clinical trials (ATTRACT and FACETS) across multiple organ systems in the majority of amenable patients with varying disease severity [4,5]. Additionally, Germain et al., 2016 is more than 7 years old and a considerable amount of evidence for migalastat in the real-world setting has accumulated since then to show that migalastat treatment in amenable FD patients is superior to placebo. In summary, the statement regarding migalastat clinical efficacy compared to ERTs is incorrect and Amicus would like it removed from the document and not included in any future documents in this appraisal. Amicus has presented detailed reasons why this statement is incorrect and request that the EAG report is updated.
Additional issue 2: The EAG clinical experts state that 90% of ERT patients need a nurse to administer PRX-102 and ERT infusions.	Section 4.2.5.4 EAG critique (page 84)	Yes – reference 6	Amicus agrees with the EAG that the majority of ERT patients need a nurse to administer PRX-102 and ERT infusions. Based on a retrospective study of Fabry patients receiving ERTs, 54% of patients are fully dependent on nurse-assisted homecare, 27%

However, the company assumed nurse-led IV infusions in only 50% of patients in their submission.			are semi-dependent on nurse assistance and the remaining patients are nurse-independent [6]. Therefore, we believe the company should assume nurse-led IV infusions in 90% of patients in their submission.

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References

1. NICE. HST4: Migalastat for treating Fabry disease. [Accessed 15 May, 2023]. Available from: https://www.nice.org.uk/guidance/hst4/resources/migalastat-for-treating-fabry-disease-pdf-1394900887237

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3. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. N Engl J Med. 2016;375(6):545-555. doi:10.1056/NEJMoa1510198

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5. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet. 2017;54(4):288-296. doi:10.1136/jmedgenet-2016-104178

6. Finnegan N, Morris E, Forshaw-Hulme S, et al. Promoting independence and empowering patients on enzyme replacement therapy. Mol Genet Metab. 2020;129:S55-S56.

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We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **02 June 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Takeda UK Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Exclusion of migalastat as a comparator.	No	We agree that for patients with an amenable mutation, migalastat or ERTs would be relevant treatment options and thus Pegunigalsidase alfa would represent an additional treatment option for patients with an amenable mutation. There is no evidence to suggest Migalastat is used first line above ERTs in all amenable patients. We disagree that the eligible patient population would only include patients with an amenable mutation, in those who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). Therefore Migalastat should be included as a comparator.
Key issue 2: Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa.	No	Clinical equivalence is based on a study of pegunigalsidase alfa vs agalsidase beta in a population which is not representative of the Fabry UK population (renal impaired patients previously treated with ERT). There is also no head-to-head data comparing pegunigalsidase alfa with agalsidase alfa. The assumption of clinical equivalence between agalsidase beta and agalsidase alfa is not supported by a Cochrane review and 2 review publications as suggested

		by the company. Although the Cochrane review found no evidence identifying if the agalsidase alfa or agalsidase beta form is superior of ERT the data does not infer equivalence between the products, only that they may be similar when comparing data in clinical trials. The review publications offer no further information with regards to clinical equivalence. Clinical equivalence to agalsidase beta is based only on 24 months of clinical trial data. Both agalsidase alfa and agalsidase beta have long term data with regards to renal protection, cardiac function, event free survival and mortality. As Fabry is a long-term condition clinical equivalence could only be claimed following long-term data. Despite meeting the primary endpoint for non-inferiority in the BALANCE trial, patients receiving PRX-102 demonstrated a greater decline in eGFR compared to agalsidase beta. Although a non-significant difference, by assuming equivalence in the economic analysis, the results may be slightly biased in favour of PRX-102. Furthermore, there are some key imbalances in the BALANCE trial that potentially favour the PRX-102 treatment group. There is a greater proportion of male patients in the agalsidase beta group as well as a greater proportion overall who have a classical classification of Fabry. Male patients and those with a classical classification of Fabry are generally associated with worse outcomes. Therefore, the results of the trial may overly favour the PRX-102 group. We acknowledge the difficulties with robust evidence generation in this very rare disease population; however, it should be noted that there is uncertainty in the company's assumption of equal efficacy and their analysis may be overly favourable to PRX-102.
Key issue 3: External validity of transition probabilities unclear, given disease epidemiology.	No	A key limitation of the company's economic analysis is the lack of granularity in the disease progression prior to the complication health states. Given that patients occupy the "Other symptoms" health state for the majority of the time horizon, a lack of granularity in the disease progression within this state over time, and the

		uncertainty of over the assumption of equal efficacy, may limit the ability to capture a key aspect of patient's quality of life and the potential differential impact of each treatment. Relatively small differences observed in the short term trial periods could theoretically propagate through a long-term model into meaningful impacts over the patient's lifetime. Although we acknowledge the limitations of the evidence base, the limitations in the company's model result in key uncertainties in the economic analyses.
Key issue 4: There is uncertainty in the assumption of non-inferiority translating to clinical equivalence in the model, because assuming non-inferiority of the treatments is already a key issue.	No	We agree with the EAG's position that the treatment effects and the uncertainty around those effects should be included within the economic model so that the probabilistic analysis appropriately captures the evidence as observed in the trial. The simplistic assumption of equal efficacy may not adequately reflect the overall impact of all outcomes, as noted in Key Issue 2. Given this is a key source of uncertainty, the model should allow for this uncertainty to be tested. Despite this, we acknowledge the difficulties in generating robust economic analyses in this very rare disease population.
Key issue 5: Uncertainty about treatment effect of enzyme replacement therapies (ERTs).	No	For decades, enzyme replacement therapies (ERTs) have been the standard of care for patients with Fabry disease who require treatment. They are an essential, potentially life-preserving treatment for a very small group of patients who have no alternative.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage)
Technical engagement response form

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Baseline characteristics: Rapidly declining renal function	B.2.3.1.3 B.2.3.3.3	No	In both the BALANCE and BRIDGE studies the baseline eGRF slope for patients already on ERT is declining at a much greater rate than expected. For BALANCE the mean annualised slope was -8.1 mL/min/1.73 m2/year. For BRIDGE this was -5.9 mL/min/1.73 m2/year. The rate of renal decline in the non-Fabry population is approximately 1 mL/min/1.73 m2 per year for individuals over the age of forty years[1,2] The reported rate of decline in untreated Fabry males with rapidly progressing renal impairment* is −5.6 mL/min/1.73 m2 per year3 The baseline characteristics in both studies represent patients with rapidly declining renal function and therefore cannot be generalised to all Fabry patients. It may suggest that pegunigalsidase alfa could be reserved for situations where response to ERT has not been satisfactory.

			1. Wanner C, et al. Mol Genet Metab. 2018;124:189–203; 2. Weinstein JR, Anderson S. Adv Chronic Kidney Dis. 2010;17:302–307; 3. Wanner C, et al. Clin J Am Soc Nephrol. 2010;5:2220–2228;
Additional issue 2: Disutility for intravenous administration proposed by EAG	Section 6.2 Exploratory and sensitivity analyses undertaken by the EAG	No	The EAG have provided an analysis for the comparison against migalastat that assumes a utility decrement for the intravenous (IV) administration of ERTs. This assumption of reduced quality of life associated with IV administration has a number of uncertainties associated with it. Firstly, despite migalastat being an oral therapy, many patients may consider it to be more burdensome than a fortnightly IV administration given the high frequency of dosing (alternate days), and the requirement for patients to fast for a total of 4 hours for each dose (2 hours before and 2 hours after). In addition, each dose is required to be taken at the same time of day. This strict schedule of dosing requirements may actually be more impactful to a patient's quality of life than a twice weekly IV administration of ERT. In addition to this, difficulties in adhering to the strict migalastat dosing requirements stated above, may result in reduced effectiveness in a real-world setting that may not have been observed in a trial setting.

			Given these uncertainties, it may not be appropriate to assume a disutility for IV administration as the EAG have suggested.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

Technical engagement response form

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Pegunigalsidase alfa for treating Fabry disease [ID3904]

Technical engagement response

June 2023

Source of funding

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1 Introduction

This document provides the External Assessment Group's (EAG's) critique of the company's response to technical engagement (TE) for the appraisal of pegunigalsidase alfa for treating Fabry disease (FD). Each of the issues outlined in the TE report are discussed in detail in Section 2. For a summary of the EAG's assessment on each issue, see Table 1. The EAG notes that while the company were able to provide additional relevant information for key issue 2, this information was insufficient in resolving the issue. As such, all key issues presented in the EAG report remain unresolved and the company's and EAG's base case analyses are unchanged.

Table 1. Issues for TE and current status regarding issue resolution

Key Issue		Status according to the EAG	Company approach	EAG approach
1	Exclusion of migalastat as a comparator	Unresolved	Restricted positioning of pegunigalsidase alfa.	Inclusion of migalastat as a potential comparator.
2	Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa	Unresolved	BALANCE provides sufficient and robust evidence to support the conclusion of non-inferior efficacy between pegunigalsidase alfa and agalsidase beta.	Likely to be unresolvable based on the clinical evidence available at this time.
3	Transition probabilities lack external validity given disease epidemiology	Unresolved	Use of transition probabilities derived from the Rombach *et al.* 2013[1] data set.	Likely to be unresolvable given the lack of additional robust datasets.
4	The assumption of non-inferiority translating into clinical equivalence in the model given the key issue of non-inferiority	Unresolved	Incorporating the same random variation in treatment effectiveness parameters between treatments in the PSA. Leading to no difference in overall treatment outcomes	The company was asked to incorporate the uncertainty in treatment effects measure in the BALANCE trial in the PSA. However the company stated, *"there is no explicit uncertainty around the treatment effect*

			between treatments.	*identified in BALANCE that can be varied within the probabilistic sensitivity analysis".* Therefore, the EAG was unable to take a different approach.
5	Cost effectiveness of ERTs	Unresolved	Lies outside of the scope of this indication and so the company did not address this issue.	Given the issue lies outside the scope of this STA the EAG recommends that an MTA be conducted for all FD treatments.

Abbreviations: EAG, external assessment group; ERT, enzyme replacement therapy. FD, Fabry disease. MTA, multiple technology appraisal. PAS, probabilistic sensitivity analysis.

2 Issues for technical engagement

2.1 Key Issue 1: Exclusion of migalastat as a comparator

As discussed in the external assessment group (EAG) report, migalastat was deemed not to be a relevant comparator by the company, but based on clinical expert advice, the EAG considers it to be a relevant comparator for patients with an amenable mutation. The EAG's clinical experts reported that for patients with an amenable mutation, migalastat or enzyme replacement therapies (ERTs) would be relevant treatment options and thus pegunigalsidase alfa would represent an additional treatment option for patients with an amenable mutation.

In the company's response to technical engagement, the company reports no change in their proposed positioning of pegunigalsidase alfa (PRX-102) in the UK treatment pathway; the company consider pegunigalsidase alfa would be used as a treatment option for patients with symptomatic Fabry disease (FD) who would be treated with an ERT. The company also acknowledge that this eligible patient population is smaller than the full marketing authorisation and would include patients without an amenable mutation for migalastat, but also patients with an amenable mutation who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). The company report that this proposed positioning was supported by an advisory board comprising 4 UK clinical experts and is consistent

with the positioning of pegunigalsidase alfa as described by NHS England in its budget impact submission. The EAG did not have access to the budget impact submission but notes that the company considers the only relevant comparators for this appraisal are the other ERTs, agalsidase alfa and agalsidase beta.

The EAG is concerned that there is potentially a population of patients who have an amenable mutation and who would be suitable for migalastat or an ERT, and therefore would not be eligible for pegunigalsidase alfa due to the restricted positioning proposed by the company. The company argues that any patients not treated with migalastat, even if due to patient/clinician choice, would be eligible for pegunigalsidase alfa as they would be deemed unsuitable for migalastat and so would be offered a choice of ERTs instead.

The company reported that any comparative effectiveness analysis between pegunigalsidase alfa and migalastat would be highly uncertain due to the limitations of the evidence base. However, the company also stated that they, "*consider the exploratory cost effectiveness analysis carried out by the EAG (page 97 of the assessment report) to be an adequate estimation of the likely cost-effectiveness of PRX-102 compared with migalastat, should the committee feel it necessary to include migalastat as a comparator despite the company positioning of PRX-102 in UK clinical practice*". The EAG would like to reiterate that the exploratory analysis conducted by the EAG is for illustrative purposes and was underpinned by multiple assumptions and simplifications such as clinical equivalence in treatment effects between migalastat and pegunigalsidase alfa. The EAG reiterates that there is no direct clinical evidence to support this assumption, only that in HST4 migalastat was considered clinically equivalent to ERTs and the company has concluded through BALANCE that pegunigalsidase alfa is clinically equivalent to ERTs. The EAG would like to explicitly state that BALANCE aimed to provided evidence for non-inferiority between pegunigalsidase alfa and agalsidase beta and not clinical equivalence which is being assumed in the model and scenario. For this reason, the exploratory analysis is limited compared to a cost-effectiveness analysis conducted by the company where migalastat is considered a true comparator and further sensitivity analysis and assumption testing are performed. If the committee considers that there is any uncertainty around the assumption of clinical equivalence between migalastat and pegunigalsidase alfa then the exploratory analysis may be directly unsuitable for decision making purposes. If however, given that the costs of the exploratory analysis are generalisable, then a minimal difference in treatment effectiveness required for cost-effectiveness can be inferred, the attainability of which may aid decision making.

The EAG notes that there was mixed feedback on this key issue from the three additional stakeholder responses to TE (Table 2).

Table 2. Stakeholder responses to Key Issue 1: Exclusion of migalastat as a comparator

Stakeholder	Comment
The MPS Society	It is unclear if this issue would even cause a meaningful impact on the ICER as such it would not change the decision. Migalastat is clinically viewed as an equal treatment option for patients with an amenable mutation; this is a small subgroup of patients, whereas ERT is available for all eligible patients. The intent of ERT and migalastat is also very different. With ERT you are infusing a functioning enzyme that is missing. Whereas for migalastat you are increasing enzyme activity by giving the correct set of instructions to enzymes that are not functioning properly. It therefore seems very reasonable just to use ERT as the comparator.
Amicus Therapeutics UK Ltd.	Amicus outlined our position on inclusion of migalastat as a comparator at the scoping stage of this appraisal. Amicus believes it is critical not to ignore the role of migalastat as a unique oral therapy for Fabry disease.[2, 3] However, in the context of an assessment of pegunigalsidase alfa (PRX-102), we leave it to the EAG experts and NICE to decide on including migalastat as a comparator in the scope of this assessment, bearing in mind the paucity of comparative data.
Takeda UK Ltd	We agree that for patients with an amenable mutation, migalastat or ERTs would be relevant treatment options and thus Pegunigalsidase alfa would represent an additional treatment option for patients with an amenable mutation. There is no evidence to suggest Migalastat is used first line above ERTs in all amenable patients. We disagree that the eligible patient population would only include patients with an amenable mutation, in those who are unsuitable for treatment with migalastat for any reason (due to issues with adherence, tolerance, patient or clinician choice, or any other reason). Therefore Migalastat should be included as a comparator.

Abbreviations: ERT, enzyme replacement therapy; ICER, incremental cost effectiveness ratio.

In conclusion, the EAG notes that the company is proposing a restricted positioning of pegunigalsidase alfa in the UK population which limits its use to patients without an amenable mutation for migalastat or patients with an amenable mutation who are unsuitable for treatment with migalastat. However, the EAG is concerned that ERTs and migalastat are both potential treatment options for patients with amenable mutations and therefore migalastat should potentially be included as a comparator for pegunigalsidase alfa, with clinical effectiveness and cost-effectiveness results presented.

2.2 Key Issue 2: Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa

The EAG remains concerned about the lack of robust clinical evidence to draw conclusions of clinical equivalence between pegunigalsidase alfa and any of the comparators in this appraisal. However, in

response to TE, the company has provided mean and median data for both the 12 and 24 month analyses of annual eGFR slopes in BALANCE (pegunigalsidase alfa compared with agalsidase beta [Table 3]). As discussed in the EAG report, the EAG is concerned about the robustness of the company's claims of non-inferiority for pegunigalsidase alfa compared with agalsidase beta and notes that there was a change in the primary assessment endpoint of BALANCE as a result of a protocol amendment, from assessment of non-inferiority at 12-months to assessment of non-inferiority at 24-months. In the draft SmPC it is stated: "[redacted]".

In BALANCE, the pre-defined non-inferiority (NI) margin for the lower bound of the 95% CI for the difference in eGFR slopes between the treatment groups to support the non-inferiority conclusion was -3 ml/min/1.73 m^2/year. In response to TE, the company provided a summary of the rationale for the selection of this threshold as the NI margin. In addition, the company reported that in the migalastat Phase III study[4] used in HST 4,[2] NI was not based on the confidence interval approach, but instead two criteria were required to be met:

- A difference between the point estimates of the slopes which is smaller than 2.2 ml/min/1.73m^2/year; and
- At least 50% overlap between the individual confidence intervals.

The company considered that using the migalastat criteria for NI evaluation in BALANCE meant NI was achieved at both the interim and final analyses but the EAG considers it important to highlight that these criteria are for a different study.

The EAG also notes that in HST 4: "*The committee concluded that, despite some important uncertainties in the clinical evidence, migalastat may provide similar outcomes to ERT.*"[2]

Table 3. Mean and Median eGFR slope at 12 months, and 24 months (Reproduced from company response to TE, BALANCE_F20 NICE Table 1 updated 07JUNE2023_CORRECTED)

	12 Months		24 Months	
	ITT	PP	ITT	PP
Number of subjects				
PRX-102	52	49	52	48
Agalsidase beta	25	25	25	24
Mean data: Estimated mean (95% CI) annual eGFR slopes (mL/min/1.73 m^2/year) Based on random intercept and random slope (RIRS) model				
Number of subjects considered in the analysis:				

PRX-102	52	49	52	48
Agalsidase beta	25	25	25	24
PRX-102	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]
Difference in mean (PRX-102 - Agalsidase beta)	[redacted]	[redacted]	[redacted]	[redacted]
Median data: Primary model: Estimated median (95% CI) annual eGFR slopes (mL/min/1.73 m2/year) Based on quantile regression (QR) model				
Number of subjects considered in the analysis:				
PRX-102	51	49	51	48
Agalsidase beta	25	25	25	24
PRX-102	[redacted]	[redacted]	-2.514 (-3.788 to -1.240)	-2.515 (-3.666 to -1.364)
Agalsidase beta	[redacted]	[redacted]	-2.155 (-3.805 to -0.505)	-2.397 (-4.337 to -0.457)
Difference in medians (PRX-102 - Agalsidase beta)	[redacted]	[redacted]	-0.359 (-2.444 to 1.726)	-0.118 (-2.450 to 2.213)
Key: CI. Confidence interval; SE, standard error.				

The additional stakeholder responses to TE provide opposing views for Key Issue 2 (Table 4).

Table 4. Stakeholder responses to Key Issue 2: Uncertainty around the assumption of clinical equivalence between agalsidase alfa, agalsidase beta and pegunigalsidase alfa

Stakeholder	Comment
The MPS Society	Clinical trial data indicates that pegunigalsidase alfa appears to be non-inferior to agalsidase beta in slowing kidney disease progression with similar trends seen against agalsidase alfa. It is unclear why, given data (accepted by the expert community) that pegunigalsidase alfa is not clinically equivalent and why it is unreasonable to infer clinical equivalence for the purpose of this assessment. There is always going to be uncertainties when evaluating treatments for small populations. Given there is no impact on the ICER, this uncertainty in our opinion is irrelevant to the decision-making, and therefore unclear why it is flagged as an issue.
Amicus Therapeutics UK Ltd.	No comment
Takeda UK Ltd	Clinical equivalence is based on a study of pegunigalsidase alfa vs agalsidase beta in a population which is not representative of the Fabry UK population (renal impaired patients

	previously treated with ERT). There is also no head-to-head data comparing pegunigalsidase alfa with agalsidase alfa. The assumption of clinical equivalence between agalsidase beta and agalsidase alfa is not supported by a Cochrane review and 2 review publications as suggested by the company. Although the Cochrane review found no evidence identifying if the agalsidase alfa or agalsidase beta form is superior of ERT the data does not infer equivalence between the products, only that they may be similar when comparing data in clinical trials. The review publications offer no further information with regards to clinical equivalence. Clinical equivalence to agalsidase beta is based only on 24 months of clinical trial data. Both agalsidase alfa and agalsidase beta have long term data with regards to renal protection, cardiac function, event free survival and mortality. As Fabry is a long-term condition clinical equivalence could only be claimed following long-term data. Despite meeting the primary endpoint for non-inferiority in the BALANCE trial, patients receiving PRX-102 demonstrated a greater decline in eGFR compared to agalsidase beta. Although a non-significant difference, by assuming equivalence in the economic analysis, the results may be slightly biased in favour of PRX-102. Furthermore, there are some key imbalances in the BALANCE trial that potentially favour the PRX-102 treatment group. There is a greater proportion of male patients in the agalsidase beta group as well as a greater proportion overall who have a classical classification of Fabry. Male patients and those with a classical classification of Fabry are generally associated with worse outcomes. Therefore, the results of the trial may overly favour the PRX-102 group. We acknowledge the difficulties with robust evidence generation in this very rare disease population; however, it should be noted that there is uncertainty in the company's assumption of equal efficacy and their analysis may be overly favourable to PRX-102.

Abbreviations: ERT, enzyme replacement therapy; ICER, incremental cost effectiveness ratio; PRX-102, pegunigalsidase alfa.

In conclusion, the EAG considers this issue is likely to be unresolvable based on the clinical evidence available at this time.

2.3 Key Issue 3: Transition probabilities lack external validity given disease epidemiology

As discussed in Section 4.2.3 of the EAG report, the EAG is concerned that the transition probabilities used in the model do not reflect the disease epidemiology outlined by the EAG's clinical experts. Fabry disease is a progressive condition associated with the accumulation of symptoms; however, almost half of the patients entering the economic model die in the health state they are initially assigned to and very little progress to develop the accumulation of different symptoms described by the EAG's clinical experts.

In the company's TE response, the company highlight the challenge of developing transition probabilities for FD patients given the rarity of the condition and subsequent lack of available data. Additionally the company reiterate their view that the transition probabilities initially implemented

by Rombach *et al.* 2013,[1] based on the 72 Dutch Fabry disease patients who received ERTs, are suitable for decision making.

The EAG appreciates the considerable challenge faced by the company in trying to derive transition probabilities generalisable to UK FD patients from the limited data available. The issue lies not in the company's approach, who are considered to have used the most appropriate data set available, but of the external validity of the dataset and derived values when compared to FD epidemiology outlined by the EAG's clinical experts, and how the issue of validity translates to uncertainty in the economic model.

One response from a stakeholder on this key issue stated, *"…In our opinion, the conclusion would be the same. Is this relevant to decision making…"*. As the company assumes that pegunigalsidase alfa and ERT treatments are clinically equivalent the impact of this uncertainty is indeed minimal as all patients move through the model equally independent of their treatment. However, the key issue around the validity and generalisability of the Rombach dataset and derived transition probabilities used in the economic model will be of crucial importance for future FD treatments appraisals, where a difference in clinical outcomes is measured, and so this a key issue.

2.4 Key Issue 4: The assumption of non-inferiority translating into clinical equivalence in the model given the key issue of non-inferiority

As described in Section 4.2.3 in the EAG report, the same estimates of treatment effectiveness have been applied to pegunigalsidase alfa and other ERT treatments in the economic model. As such any uncertainty around the difference in treatment effectiveness between treatments is not captured, with this being especially true for the PSA for which the same random parameter variation is applied to each treatment. Given the uncertainty around the assumption of non-inferiority, and therefore clinical equivalence, the EAG considers that this uncertainty has not been addressed by the company and is critical for decision making.

In the TE response, the company reiterated that BALANCE provided robust clinical evidence to support conclusions of non-inferiority of pegunigalsidase alfa against agalsidase beta and by extension to agalsidase alfa. The company noted how non-inferiority was deemed sufficient to support clinical equivalence in previous NICE appraisals (TA821 and TA698) and how in both cases the committee concluded that the intervention and comparator had at least equivalent effectiveness. As a result, a cost comparison was deemed appropriate.

The EAG notes that, given the reasons provided in the EAG's critique of key issue two, there remains considerable uncertainty around the question of non-inferiority between pegunigalsidase alfa and ERTs and therefore the appropriateness of assuming clinical equivalence in the economic model. The EAG concludes that the issue is therefore unresolved.

2.5 Key Issue 5: Cost effectiveness of ERTs

As stated in the EAG report, the EAG is concerned that pegunigalsidase alfa is being compared to treatments that have not been evaluated for cost-effectiveness and the inherent subsequent problems that causes for this appraisal and any subsequent appraisals.

The company states in their TE response that this issue sits outside of the scope of this appraisal. The EAG agrees with the company and that this this issue does lie outside the scope of an STA; however, the EAG considers that that the committee should be aware of this issue in decision making for this appraisal and its implications for future FD appraisals.

3 Stakeholder comments on the EAG report

As a result of stakeholder response, the EAG would like to clarify that in the study by Germain *et al.*2016 [5] mentioned in the EAG report, although migalastat was found to have treatment effects comparable to placebo, the study failed to take into account amenable mutation status. In prespecified post-analyses, patients with amenable mutations treated with migalastat were found to experience a significant treatment effect compared to placebo.

4 References

1. Rombach SM, Hollak CE, Linthorst GE, Dijkgraaf MG. Cost-effectiveness of enzyme replacement therapy for Fabry disease. *Orphanet J Rare Dis* 2013; **8**: 29.
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Final draft guidance

Pegunigalsidase alfa for treating Fabry disease

1 Recommendations

1.1 Pegunigalsidase alfa is recommended, within its marketing authorisation, as an option for treating Fabry disease in adults (also known as alpha-galactosidase deficiency). It is recommended only if the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Usual treatment for Fabry disease is migalastat or enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta. Pegunigalsidase alfa is another ERT.

Clinical trial evidence shows that pegunigalsidase alfa works as well as agalsidase beta. There is no direct clinical trial evidence comparing pegunigalsidase alfa with agalsidase alfa or migalastat. But, clinical experts advised that pegunigalsidase alfa is also likely to work as well as these 2 treatments.

Economic evidence suggests that pegunigalsidase alfa is cost saving when compared with the other ERTs and migalastat. So, it is recommended.

2 Information about pegunigalsidase alfa

Marketing authorisation indication/anticipated marketing authorisation indication

2.1 Pegunigalsidase alfa (Elfabrio, Chiesi) is indicated for 'long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for pegunigalsidase alfa.

Price

2.3 The list price of pegunigalsidase alfa is £1,225.19 per 20-mg vial (excluding VAT; company submission January 2023). The annual treatment cost is £118,187 (based on an average dosing weight of 72.2 kg).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes pegunigalsidase alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Chiesi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Symptoms of Fabry disease include:

- short-term severe pain (lasting for minutes to days) or burning sensation starting at the extremities and spreading throughout the body (referred to 'Fabry crisis')
- gastrointestinal symptoms such as diarrhoea, nausea, and abdominal pain
- headaches
- hypohidrosis (an inability to sweat properly)
- vertigo (feeling off balance) and

- hearing impairment.

As Fabry disease progresses, it can lead to complications such as heart and kidney failure, and an increased risk of stroke. The clinical experts noted that it is uncommon for people to have a single complication only, and symptoms accrue as the condition progresses and as organ damage occurs. The committee heard from clinical experts that the presentation of the condition can vary between people. Because it is an X-linked condition, men tend to have the more severe 'classic' form in which symptoms appear earlier and progress more quickly than non-classic Fabry disease. Women may have milder symptoms. The committee heard from the patient expert that the symptoms of Fabry disease have physical and emotional impacts, which negatively affect quality of life. Gastrointestinal symptoms and heat intolerance can prevent people going out and all symptoms impact work and relationships. The patient expert stated that because the condition may not be physically obvious, it can be difficult to talk about. They also noted that because the disease is progressive and has no cure, they had a constant feeling of anxiety. Their feeling of anxiety was compounded by knowing that family members had died from complications of Fabry disease. The patient expert also noted that, because the condition is hereditary, parents of people with Fabry disease may feel guilt knowing that they have passed it on to their children. The patient and clinical experts highlighted that current treatments reduce the progression of kidney impairment, which provides hope. The committee concluded that the symptoms of Fabry disease are progressive and have a large impact on quality of life.

Clinical management

Treatment options and comparators

3.2 There is no cure for Fabry disease, but treatments are available that relieve the symptoms and slow progression of damage to the kidneys and heart. In the UK, people with Fabry disease typically start treatment when

one of the criteria outlined in the British Inherited Metabolic Disease Group guidelines are met. These include evidence of Fabry-related general symptoms (such as uncontrolled pain) and kidney and cardiac disease. The clinical experts explained that treatment options include infusion with agalsidase alfa or agalsidase beta, which are enzyme replacement therapies (ERTs) that replace the non-functioning enzyme, or migalastat. NICE has not evaluated ERTs but does recommend migalastat (taken orally) as a treatment option for Fabry disease in people over 16 with an amenable mutation (see NICE's highly specialised technology guidance on migalastat for treating Fabry disease, from here HST4). The committee noted that the company considered that people with amenable mutations would be offered migalastat first if it is suitable. For this reason, the company did not consider migalastat to be a relevant comparator for this appraisal. The clinical experts stated that if a person had an amenable mutation either migalastat or an ERT can be offered first, and the choice is based on the person's preference. The clinical experts also noted that people who have amenable mutations tend to have milder Fabry disease. They highlighted that many people with an amenable mutation may choose migalastat because it is taken orally. But, they also noted that some people may not choose to have migalastat because of the need to fast for 2 hours before and 2 hours after having it. It is also taken every 2 days, so some people may have difficulty remembering to take the treatment consistently. The clinical experts shared that it is possible for people to switch treatment from ERT to migalastat and vice versa. They stated that the current treatments slow disease progression but there is an unmet need for further treatment options for Fabry disease. The committee concluded that pegunigalsidase alfa would be an additional ERT for people with and without an amenable mutation, and migalastat, agalsidase alfa and agalsidase beta were relevant comparators.

Clinical effectiveness

Data sources and generalisability

3.3 The company's key clinical evidence is from BALANCE, an international, randomised, double-blind, phase 3 clinical trial with 24-month follow-up. The trial was done in adults (aged 18 to 60 years) with Fabry disease and impaired kidney function, who had previously had agalsidase beta. The trial was designed to test whether pegunigalsidase alfa was statistically non-inferior in clinical effectiveness to agalsidase beta. The EAG noted that not everyone with Fabry disease has kidney impairment or would have already had treatment with agalsidase beta. So, the results may not be generalisable to people who have not had a previous treatment or do not have kidney impairment. In addition, the EAG noted that kidney impairment is more common in people with classic Fabry disease than those with non-classic Fabry disease. The clinical experts stated that deterioration in kidney function tends to be late in the disease progression, so people with kidney impairment have worse treatment outcomes. The clinical experts expected that the assessment of non-inferiority of pegunigalsidase alfa compared with agalsidase beta in BALANCE would be generalisable to the whole population who would have an ERT. The EAG also noted that there was a higher proportion of men (72% versus 56%) and people with classic Fabry disease (56% versus 52%) in the agalsidase beta arm compared with the pegunigalsidase alfa arm. Also, more people in the poorer kidney function group (that is, estimated glomerular filtration rate [eGFR] slope of less than −5 ml/minute/1.73 m^2/year compared with a slope greater than −5 ml/minute/1.73 m^2/year) had agalsidase beta. The clinical experts agreed that there were some imbalances but considered that this would likely have less of an impact on the analysis because kidney impairment was a predefined inclusion criterion and people in both arms of the trial would have similar kidney function. The clinical experts did not consider the difference in the proportions of people in the kidney function subgroups to be significant or to impact the results. The committee acknowledged the imbalances in the baseline characteristics but concluded that for the purpose of its decision making, data from

BALANCE could be considered generalisable to the whole population who would have pegunigalsidase alfa.

Clinical trial outcomes

3.4 The primary outcome in BALANCE was annual rate of change (slope) in eGFR, which is a measure of declining kidney function over time. The trial was intended to measure if pegunigalsidase alfa is non-inferior to agalsidase beta. The committee noted the EAG's concerns that the trial's statistical analysis plan changed over the course of the clinical trial. It heard from the company that this related to its FDA regulatory submission and the protocol amendment happened after the last patient entered the trial and before the trial database was locked. The median eGFR slope difference between pegunigalsidase alfa and agalsidase beta after 24 months was −0.359 ml/minute/1.73 m^2/year (95% confidence interval −2.444 to 1.726). The company's prespecified criteria for non-inferiority was that the lower limit of the 95% confidence interval had to be greater than −3.0 ml/minute/1.73 m^2/year. Based on this, it considered the non-inferiority criteria met. The mean value at 12 months did not conclusively meet the criteria but the later data cut (24 months) did. Subgroup analysis did not show any difference in eGFR slope based on gender or form of Fabry disease (see section 3.3), although the confidence intervals were wide due to the small population in the clinical trial. The committee concluded that based on the available evidence it considered pegunigalsidase alfa non-inferior to agalsidase beta.

Clinical equivalence assumption

3.5 There was no direct comparison of pegunigalsidase alfa with agalsidase alfa in a randomised clinical trial. In its submission, the company assumed all 3 ERTs were clinically equivalent. The company's assumption was based on 2 randomised controlled trials (Sirrs et al. and Vedder et al.) that showed no statistical difference between agalsidase alfa and agalsidase beta, and on the BALANCE trial, which showed that pegunigalsidase alfa was non-inferior to agalsidase beta. The company noted that an indirect

comparison for the treatments was not feasible, and any analysis would be uncertain because of the heterogenous evidence base. The EAG raised concerns regarding the company's assumption of clinical equivalence. It noted that Sirrs et al. included only around one-third (94 out of 294) of the people needed to observe the prespecified difference in outcome. Also, in Vedder et al. people were treated with only one-fifth (0.2 mg/kg versus 1 mg/kg) of the dose of agalsidase beta used in BALANCE. So, these trials do not provide supportive evidence for clinical equivalence of pegunigalsidase alfa compared with agalsidase alfa and agalsidase beta. The clinical experts noted that clinical trials for rare diseases can sometimes be underpowered because of the difficulty with recruiting people from a small population. The clinical experts also stated that there is no strong evidence of pharmacological difference between agalsidase alfa and agalsidase beta, and in clinical practice they are broadly considered to be similarly effective. The clinical experts noted that because pegunigalsidase alfa contains the polyethylene glycol molecule, it would be expected to be broken down less quickly in the body. This would potentially lead to longer exposure time, which would be beneficial to people having the treatment. But, they noted that this potential benefit in exposure time had not translated into better outcomes in BALANCE. The committee noted that the company had not presented a comparison of pegunigalsidase alfa with migalastat and had stated in response to technical engagement that an indirect comparison was unfeasible. The committee was aware that HST4 concluded that it was reasonable to assume clinical equivalence between migalastat and ERTs, although the data used to determine clinical equivalence in HST4 also had limitations. The committee heard from clinical experts that, in practice, whether a person has ERT or migalastat would depend on that person's choice of administration method rather than any difference in clinical effectiveness (see section 3.2). The committee concluded that, overall, the limitations of the data meant it was not possible to conclude that pegunigalsidase alfa and its comparators were clinically equivalent. But, it was reasonable to

assume for the purpose of this appraisal that pegunigalsidase alfa, agalsidase alfa, and agalsidase beta were similarly clinically effective.

Adverse events

3.6 In BALANCE, a similar proportion of people who had pegunigalsidase alfa and agalsidase beta experienced an adverse event. But, the company noted that the overall number of events (rate per 100 exposure years) was lower for people who had pegunigalsidase alfa. The committee asked the clinical experts if pegunigalsidase alfa would be expected to provide fewer adverse events than other ERTs. The clinical experts responded that early data suggests that people in the pegunigalsidase alfa group had fewer anti-drug antibodies, which reduce treatment efficacy. They speculated that this may result in benefits for pegunigalsidase alfa in the longer term. The clinical experts noted that the adverse event of interest in BALANCE is infusion-related reaction and the rate of this event was lower (by about 3 cases per 100 infusions) in the pegunigalsidase alfa arm than the agalsidase beta arm. The EAG noted that in BALANCE, slightly more people in the agalsidase beta arm had treatment for 24 months than in the pegunigalsidase alfa arm. This may have affected the observed rates of adverse events. The committee further noted that people in BALANCE had all previously had agalsidase beta and may have tolerance to it. This might have biased the adverse event outcomes against pegunigalsidase alfa. The committee concluded that pegunigalsidase alfa was a similarly tolerable treatment to agalsidase beta.

Economic model

Company's modelling approach

3.7 The company made a case for a cost-minimisation analysis (an approach that assumes equivalent outcomes and compares costs only) rather than a cost-utility analysis to assess the cost effectiveness of pegunigalsidase alfa compared with agalsidase alfa and agalsidase beta. This was because the company stated that there was no difference in clinical effectiveness or quality of life of the 3 treatments, so it was appropriate to

compare only the costs. The EAG also presented an exploratory cost-utility assessment between pegunigalsidase alfa and migalastat. The EAG's assessment assumed clinical equivalence between both treatments, with a decrease in quality of life associated with taking an intravenous rather than an oral treatment. The company confirmed at technical engagement that if migalastat were considered a comparator, it agreed with the EAG's approach to measure cost effectiveness. The committee acknowledged the rarity of Fabry disease and the potential difficulty of gathering robust utility evidence in rare conditions (see section 3.11). It concluded that cost minimisation was appropriate for the comparison with the ERTs. This was because it was satisfied that the clinical effectiveness and quality of life would be similar, and it would use the EAG's analysis for the comparison with migalastat in its decision making.

Company's model structure

3.8 The company used a Markov state transition model with 10 health states capturing symptoms and complications related to Fabry disease. These included pain, end-stage kidney disease and cardiac complications. The modelled cohort had a mean age of 40, had symptomatic Fabry disease and included the same proportion of men and women. The cohort were modelled for 60 years. The model structure was similar to that used in HST4. This was in turn based on a model from a Dutch study (Rombach et al. 2013) that evaluated the cost effectiveness of ERTs and standard care in a Dutch Fabry disease cohort. In the model, people progressed to worse health states or died. The distribution of the modelled cohort at entry across the health states was based on the global Fabry Registry. But, the model excluded people with end-stage kidney disease because they were not considered appropriate to start a new treatment. The EAG noted that at baseline, people could only have a single symptom health state. The EAG stated that this did not align with its clinical expert's opinion that at 40 years, multiple complications would likely have already developed. The committee heard from clinical experts that it is uncommon

for people to have a single health state complication (see section 3.3). But overall, the model structure was reflective of Fabry disease in terms of kidney and cardiac symptoms occurring later as the disease progressed. The committee concluded that, although the health states in the model may not reflect the combinations of symptoms people may have, the model structure was reasonable for decision making.

Transition probabilities

3.9 The company's submission included transition probabilities (the chance of moving between health states) from Rombach et al., the same dataset used for HST4. The model had different transition probabilities for men and women. The company noted that it was not feasible to derive transition probabilities from the pegunigalsidase alfa trials because they did not follow a large enough population over a long enough period to generate robust transition probabilities. The company added that robust estimates of transition probabilities are difficult to achieve because Fabry disease is a rare condition and disease progression through health states occurs over a lifetime (about 60 years). So, it considered Rombach et al., which included 72 people having ERT, to be the most robust dataset. The EAG considered that the transition probabilities did not reflect the rate or extent of disease progression described by its clinical expert or by the company. It noted that in the model, around half of the population die in their baseline health state and less than 1% of people are estimated to have more than 1 symptom (for example, end-stage kidney disease and cardiac complication). The clinical experts during the committee meeting agreed that the transition probabilities did not reflect the progression seen in clinical practice. In particular, the clinical experts highlighted that more people would be expected to have cardiac and kidney complications than were modelled. The committee was aware that newer data may be available from the Fabry disease registry (Clinical Practice Research Datalink), which was identified in the company submission. The company noted that Rombach et al. had 11 years of data from a single patient centre. The data is therefore less heterogenous and may also be less

subject to bias than the Fabry disease registry, in which people were enrolled without clear exclusion criteria. The company stated that this meant that the characteristics of people enrolled in the registry may vary from centre to centre. The clinical experts did not have concerns about selective enrolment, noting that the majority of people with Fabry disease in the UK are enrolled in a registry. One clinical expert noted that people under their clinical care are enrolled in a registry containing around 450 people. They considered this registry appropriately captures the Fabry disease population across all health states. The EAG considered the uncertainty around the model's transition probabilities unresolved. But it noted that the impact of using different transition probabilities on the incremental costs would likely be minimal. This is because the treatment arms would be affected equally because of the company's assumption of clinical equivalence between the modelled treatment arms (see section 3.5 and section 3.7). But, the EAG noted that external validity would be important for future Fabry disease appraisals where measured differences in outcomes are used in the model. The committee concluded that the transition probabilities likely lacked external validity. But it noted that because of the clinical equivalence assumption (see section 3.5), using a different source of transition probabilities might have limited impact on the incremental cost estimates.

Mortality data source

3.10 For HST4, the committee concluded that the mortality probability data used in the model led to an unexpectedly high life expectancy (83.4 years) for people with Fabry disease. For the current pegunigalsidase alfa submission, the company used Fabry Registry data (Waldek et al. 2009), which estimates the life expectancy for men and women to be 58.2 years and 74.7 years respectively. The EAG could not validate this adjustment in the company's base-case results but applied the mortality adjustment in its own base-case. The committee concluded that the Fabry Registry is an appropriate data source for estimating mortality.

Utility values

Source of utility values

3.11 Although the company presented a cost-minimisation analysis as its base case, which did not include utility values, it also presented a cost-utility scenario analysis. This scenario assumed equal clinical effectiveness and quality of life between each treatment arm and no disutility for adverse events between treatment arms. It therefore produced the same results as the company base case. The cost-utility model used utility values for each health state from Arends et al. (2018) and adjusted by the mean baseline utility value in BALANCE (0.762). The committee was aware that the company collected EQ-5D-5L data from BALANCE, which was mapped to EQ-5D-3L using crosswalk regression method described by Hernández Alava et al. (2017). However, the company reported that it could not estimate robust utilities for every health state. This was because of the low number of Fabry clinical events, and utility data from BALANCE could only be derived for 2 of the 10 health states: pain and other symptoms. The EAG preferred the company's original base-case approach (that is, Arends et al. adjusted with the BALANCE baseline utility value for all health states), if the complete utility values for all health states could not be obtained from BALANCE. In the EAG's exploratory analyses comparing pegunigalsidase alfa with migalastat, the EAG assumed a disutility of 0.025 associated with having an intravenous treatment rather than an oral treatment. This was based on HST4 in which the committee had determined a disutility of 0.5 was too high and 0.025 was plausible. The patient experts stated that it was not possible to say whether the exact assumed value was plausible, but taking an intravenous rather than an oral treatment was expected to have a minimal effect on quality of life. The committee noted that it can be difficult to generate utility values for rare conditions such as Fabry disease. It concluded that it would have preferred robust utility data from BALANCE but given the assumption of clinical equivalence the company's base-case dataset is sufficient for

decision making. It further concluded that the disutility assumed in the EAG exploratory analysis was reasonable.

Costs

Administration costs

3.12 The company sourced its administration costs from NHS Reference Costs 2020/2021, and Personal Social Services Research Unit 2021. For the maintenance treatments, the company assumed 50% of people would need nurse-assisted administration while the other 50% would self-administer and only have 1 nurse visit per year. The EAG's clinical expert reported that around 90% of people would likely need nurse-assisted administration because they are not fully independent to deliver their own infusion. The EAG applied this assumption in its exploratory base case. The clinical experts at the committee meeting stated that not everyone who self-administers their treatment does so independently; some people may still need nurse assistance for preparation and other support. They estimated that around 10% to 20% of people with Fabry disease would be fully independent and require no nurse-assisted administration. The company also included the costs of other healthcare professionals such as GPs, physiotherapists, psychiatrists and social workers, as part of the follow-up costs. The EAG's clinical expert noted that the cost of social worker visits would not be funded by the NHS. So, in its base case the EAG excluded the cost of social worker visits. The committee concluded that social worker costs should be captured in the model as part of personal social service costs that are in the NICE reference case, but it preferred the EAG's estimates of the cost of administration.

Resource use

3.13 The company obtained costs for acute complications from NHS Reference Costs 2020/2021. The EAG noted that the company used simple averages rather than weighted average for cost categories that included multiple codes representing varying severity. The EAG also noted that the company assumed all tests (including anti-ERT antibody tests) in the

general management of Fabry disease are paid for by the NHS. Whereas, the EAG's clinical expert and the experts at the committee meeting stated that some tests are currently paid for by manufacturers of current standard care. The company stated that it would also cover these costs for pegunigalsidase alfa. The EAG's expert further noted that the annual number (frequency) of some of the routine management tests was different to the company's estimates. The EAG conducted a scenario using its clinical expert's estimates, which had a minor impact on the incremental costs. The committee concluded that the EAG's frequency estimates are appropriate. The committee also noted the company's statement that it will cover the cost of similar tests currently paid for by manufacturers of current standard care.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.14 The company's base-case deterministic incremental cost estimates suggest that pegunigalsidase alfa is cost saving compared with agalsidase alfa (saving £476,243) and agalsidase beta (saving £470,950). The results represent costs over the lifetime of 1 person with Fabry disease. The probabilistic estimates were also cost saving, but the results are considered confidential by the company and cannot be reported here. The EAG applied its preferred assumptions in its base case by:

- Increasing the number of people needing nurse-assisted treatment infusion to 90% (see section 3.12).
- Using weighted average for estimating the cost of acute complications (see section 3.13).
- Removing costs of social care visits (see section 3.12).
- Adjusting mortality to reflect average life expectancy in people with Fabry disease (see section 3.10).
- Using the EAG's clinical expert's general management resource use estimates (see section 3.13).

With the EAG's preferred assumptions, the deterministic base-case incremental cost estimates suggest that pegunigalsidase alfa is cost saving compared with agalsidase alfa (saving £386,796) and agalsidase beta (saving £396,288). The EAG's additional scenario analysis, which compared pegunigalsidase alfa with migalastat, assumed:

- non-inferiority between the treatments
- no difference in disutilities related to adverse events
- an annual disutility of 0.025 (based on HST4) applied for people having pegunigalsidase alfa, which is an intravenous infusion, and
- no administration cost for migalastat because it is an oral treatment.

The EAG considered the analysis illustrative only and noted that a full analysis by the company would be preferable. Migalastat has a confidential discount, so the results cannot be reported here. However, the results showed that pegunigalsidase alfa provides fewer quality adjusted life years (QALYs) but is less costly than migalastat.

Uncertainty in the cost-minimisation estimates

3.15 The company's model applied a single treatment discontinuation rate of 0.5% across treatment arms, which was also used in HST4. The committee noted that the number of discontinuations in BALANCE for pegunigalsidase alfa and agalsidase beta (5 people versus 1 person) was low. But it raised concerns that subsequent treatment costs for people who switch treatment from pegunigalsidase alfa were not included in the model. The committee was concerned that if people switched to more expensive treatments after pegunigalsidase alfa these costs could affect any potential cost savings in the modelled pegunigalsidase alfa treatment arm. The committee noted that omitting subsequent treatments from the model and using an assumption of treatment discontinuation rates meant that the exact cost savings associated with pegunigalsidase alfa were uncertain but it remained reasonable to conclude that pegunigalsidase alfa is cost saving compared with its comparators. In addition, the

committee shared the EAG's concerns that the cost effectiveness of agalsidase alfa and agalsidase beta have not been evaluated by NICE and it could not exclude the possibility that pegunigalsidase alfa was being compared with cost-ineffective treatments. However, it recognised that agalsidase alfa, agalsidase beta, and migalastat represent established treatments for Fabry disease and that pegunigalsidase alfa was cost saving compared with these treatments.

Conclusion

Recommendation

3.16 The committee concluded that pegunigalsidase alfa was cost saving compared with agalsidase alfa, agalsidase beta, and migalastat. Although there were fewer modelled QALYs with pegunigalsidase alfa compared with migalastat, this was driven by the different ways the treatments are administered rather than a difference in clinical effectiveness or adverse events. Overall, the committee concluded that pegunigalsidase alfa was similarly clinically effective, as tolerable as the treatments used in the NHS, and costs less. Therefore, the committee recommended pegunigalsidase alfa for treating Fabry disease.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide

funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Fabry disease and the healthcare professional responsible for their care thinks that pegunigalsidase alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Raphael Egbu

Technical lead

Mary Hughes

Technical adviser

Leena Issa and Vonda Murray

Project managers