Pegunigalsidase alfa for treating Fabry disease [ID3904]

STA Report

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All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

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.

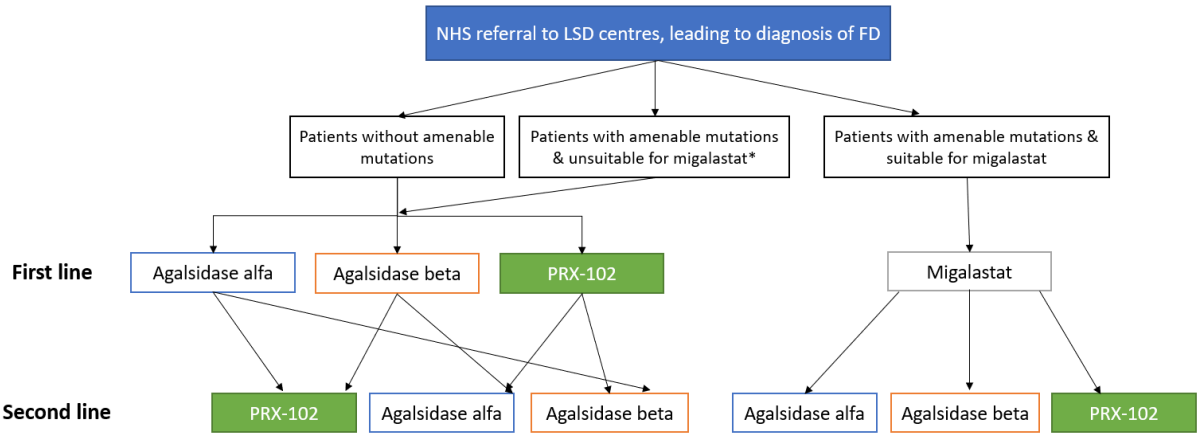
The EAG notes that pegunigalsidase alfa is indicated for long-term ERT in adult patients with a confirmed diagnosis of FD.[17] The company propose that pegunigalsidase alfa will be used as a treatment option for patients with symptomatic FD who would usually be offered ERT in line with BIMDG guidelines,[9] 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 $eGFR_{CKD-EPI}$, 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]

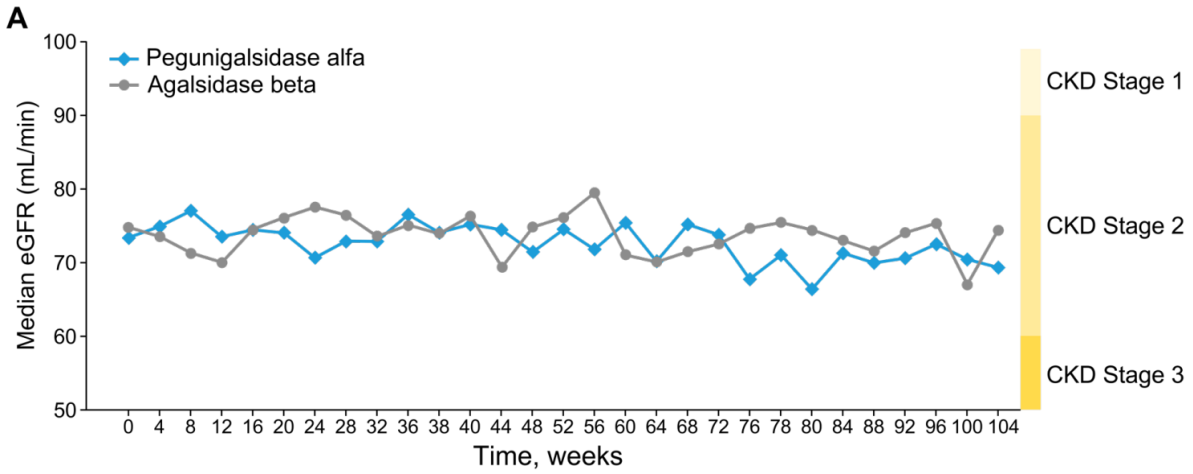
- For the analysis of the group difference in eGFR change from baseline using an MMRM model, the lower limit of the 95% CI for the difference between the groups at week 104 was [redacted], and so did not meet the criterion for non-inferiority (criterion was -6 as it was looking at

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

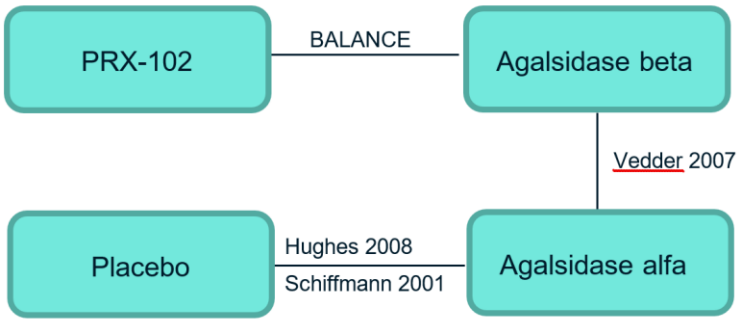
Key: E2W, every 2 weeks; ERT, enzyme replacement therapy; ITT, intention-to-treat; IV, intravenously; N, number of patients; NA, not applicable; NR, not reported; SLR, systematic literature review; SmPC, summary of product characteristics.

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

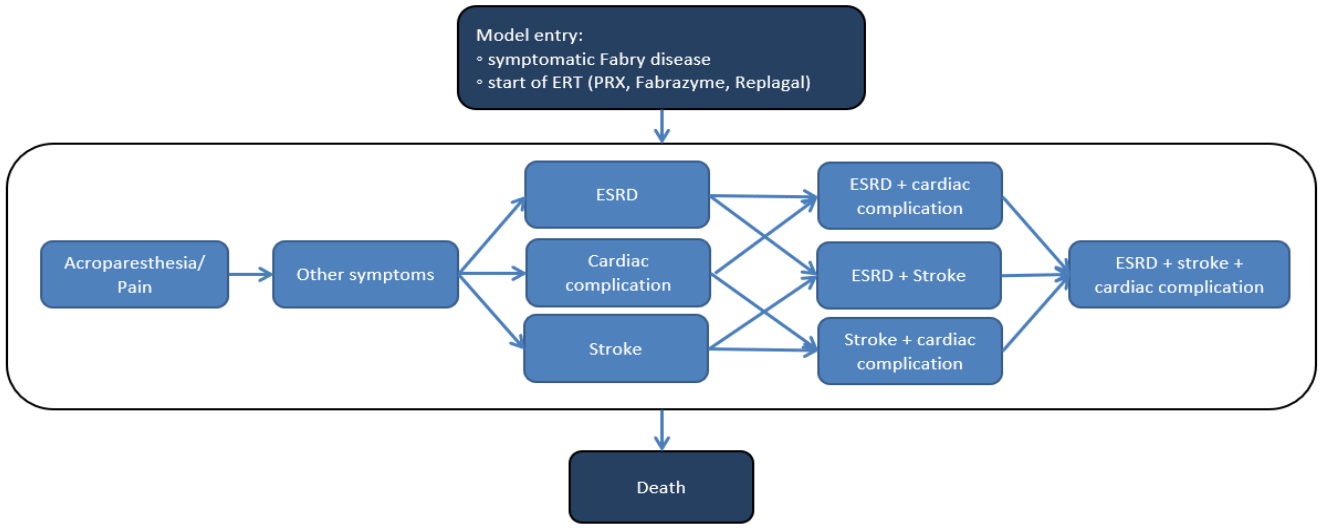
		with those from Arends *et al.*[46] adjusted to the baseline values of BALANCE used in the company base case. Scenarios using other sources were also explored due to the uncertainty around these values.
Source of preference data for valuation of changes in health-related quality of life	Representative 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.

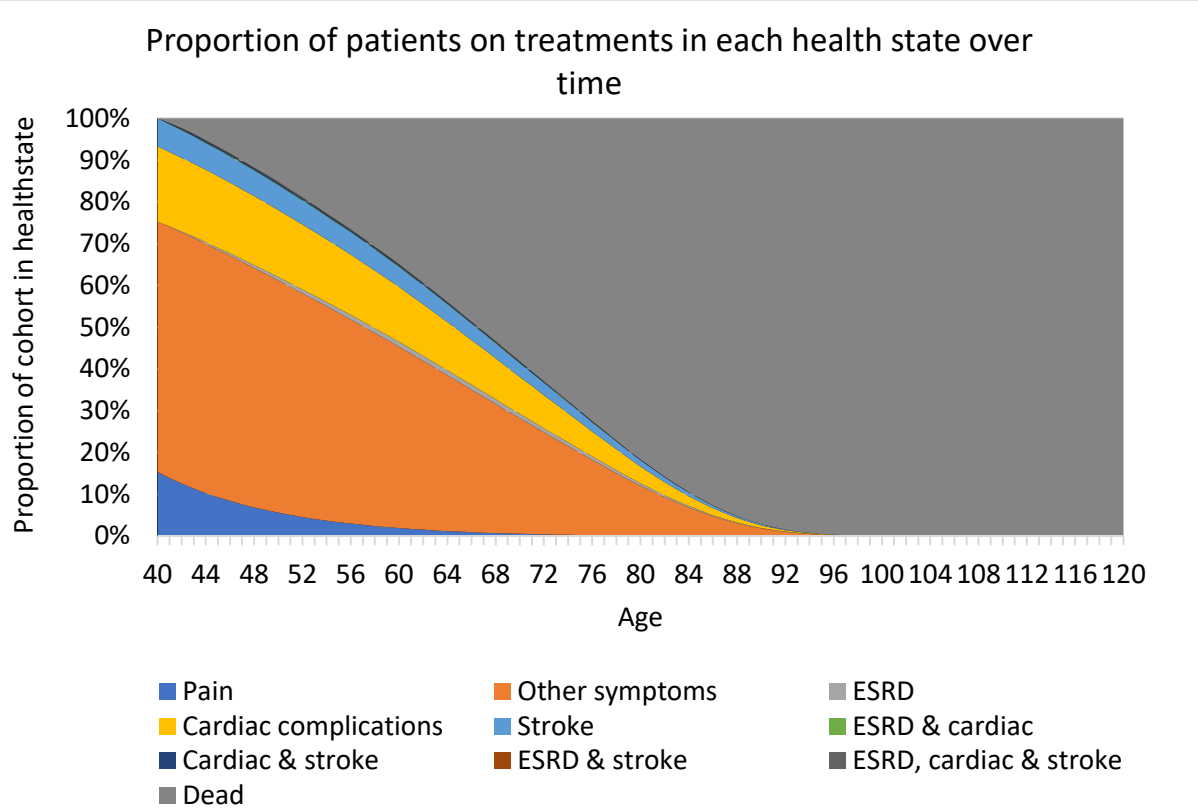
4.2.3.1 EAG critique

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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