Pegunigalsidase for treating Fabry disease

Slides for public
Contains no ACIC information

Technology appraisal committee B 06 July 2023

Chair: Charles Crawley

Lead team: Bushra Hasnie, Gabriel Rogers, Tony Wootton

External assessment group: BMJ Technology Assessment Group

Technical team: Raphael Egbu, Mary Hughes, Richard Diaz

Company: Chiesi Limited

Background on Fabry disease (1/2)

A progressive disease which leads to complications including organ damage

Cause

- Mutations to gene which produces an enzyme – alpha-galactosidase A (α-Gal A) – responsible for breaking down a fat called globotriaosylceramide (Gb3)
- Gb3 build up in the body leads to progressive organ damage
    - Progressive build-up of Gb3 often starts in childhood

Epidemiology

- Rare condition, 1 in 49,000 people estimated to have symptomatic Fabry disease (~1,150 people in England)

Classification

- Classic (usually more severe – symptoms start in children in multiple organs) and non-classic (later onset and slower progression)
- An X-linked condition – Men more likely to have classic Fabry disease, severity variable in women - some women can have mild or no disease activity

Gb3, globotriaosylceramide

Background on Fabry disease (2/2)

A progressive disease which leads to complications including organ damage

Symptoms

- Severe pain in hands and feet
- Fatigue and exhaustion
- Abdominal pain and altered bowel habits (reported in 60–80% of children)
- Altered temperature sensitivity and inability to sweat properly
- Tinnitus, vertigo, and angiokeratoma (tough lesions on the skin) is reported in 40% of children
- Progressive disease leading to complications such as heart and kidney failure
    - The Gb3 in cells may result in symptoms related to organ damage
        - May cause renal failure needing dialysis or transplant
        - May cause cardiovascular disease with frequent transient stroke

            → has both mental and physical impacts

NICE evaluations for Fabry disease

Enzyme replacement therapy (ERT) have been standard of care since 2001 but have not been appraised by NICE, migalastat was recommended in 2017

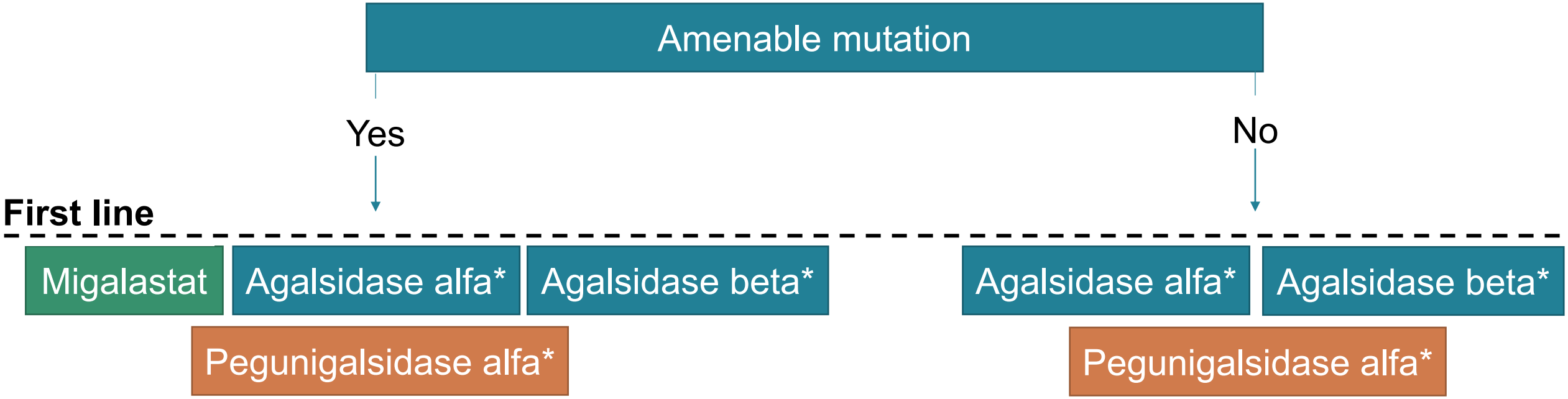
Highly specialised technology evaluation	Drug	Recommendation
NICE HST 4 (2017)	Migalastat	Recommended, within its marketing authorisation, as an option for treating Fabry disease in people over 16 years of age with an amenable mutation only if enzyme replacement therapy (ERT) would otherwise be offered

- Migalastat is an oral treatment (taken once every 2 days) designed to bind to the alpha-galactosidase A (α-gal A) enzyme as it is made, helping it to fold correctly and improving its function
- Need to fast for 2 hours before and 2 hours after taking migalastat (no food or caffeine)
- Not recommended for people with severe renal impairment (CKD stages 4-5)
- Around 30-50% of people with Fabry disease have an amenable mutation

ERT, enzyme replacement therapy; CKD, chronic kidney disease

Treatment pathway for Fabry disease

No cure, current treatments relieve symptoms and prevent progression



→ Alternative treatment not used earlier

*Enzyme replacement therapy (ERT)

NICE Is migalastat always used before ERTs for people with an amenable mutation?

Patient perspectives

Fabry disease has physical, social, and emotional impacts. A new treatment would benefit this population

Submission from patient expert

- Feel anxious about the disease progressing
- Receiving pegunigalsidase through clinical trial – it improved my kidney function, which was declining. This was invaluable for improving quality of life
- Well tolerated, administration takes planning but well-organised clinically and logistically

Anxiety compounded by experiencing mother and brother suffer from kidney failure due to Fabry disease

Submissions from Society for Mucopolysaccharide and Related Diseases (MPS Society)

- People with Fabry disease (FD) report the physical (stiff joints, pain and extreme fatigue) and emotional impact (anxiety)
- FD also affects children and this has a social impact
- Some people with Fabry disease currently not receiving treatment for reasons including intolerance. New treatment option would benefit this group

Having no control over your life. Not being able to plan from one day to the next

Hard socially as can't do the same activity as friends

Living with a lifelong condition that has no cure. It's scary and overwhelming but with hope

Equality considerations

No equality concerns were identified by the company, clinical experts or patient organisation submissions.

- At scoping, potential to define males with classic Fabry as a subgroup was discussed

  →Based on possibility treatment may be more cost-effective for this group

- Concluded this could potentially lead to inequity of access to treatment based on sex and agreed this should not be considered a separate subgroup

  →Committee to consider impact of recommendation on particular groups

Previous topics

- For HST4 (migalastat), the committee concluded no equality considerations needed to be discussed

  →At scoping, clinical experts noted that Fabry disease is X-linked but treatment decisions are based on organ damage not sex

  →both men and women would benefit from treatment

Key issues identified in EAG report

Issue	Resolved?	ICER impact
Should migalastat be included as a comparator?	No – for discussion	Unknown
Is it appropriate to assume pegunigalsidase and other ERTs are clinically equivalent? • Are data from the clinical trial generalisable to how it would be used in clinical practice? • Has clinical equivalence been statistically demonstrated? • In the modelling has uncertainty around clinical equivalence been adequately explored?	No – for discussion	Unknown
Are the transition probabilities externally valid?	No – for discussion	Unknown

→ The EAG further noted that the cost effectiveness of ERTs currently used in clinical practice has not been established

ERT, enzyme replacement therapy

Pegunigalsidase alfa (Elfabrio, Chiesi)

Technology details

Marketing authorisation (MA)	• UK MA through MHRA reliance route (pending) • EMA MA: long-term enzyme replacement therapy (ERT) in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase)
Mechanism of action	PEGylated alpha-galactosidase A with reported better stability, longer half-life (80 hours), improved biodistribution, and reduced risk of immunogenicity compared with existing ERTs
Administration	Intravenous infusion 1mg/kg every 2 weeks
Price	• List price: £1,255.19 per 20 mg vial • List price: £118,187 for 12 months of treatment • The company has a confidential PAS

EMA; European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; PEG, polyethylene glycol; ERT, enzyme replacement therapy; PAS, patient access scheme

Decision problem

Pegunigalsidase considered for a narrower population than in the final scope. Company considers people treated with an ERT includes people who cannot or choose not to have migalastat

	Final scope	Company	EAG comments
Population	Adults with Fabry disease	Adults with Fabry disease who would usually be treated with an ERT • Represents how pegunigalsidase will be used in clinical practice because migalastat is established for people with an amenable mutation	• Some people with an amenable mutation suitable for migalastat may still be treated with an ERT • Trial included only people with renal impairment and is not generalisable to whole UK Fabry disease population
Intervention	Pegunigalsidase	As per scope	Dosing weight in trial may be different to UK clinical practice

Decision problem

Comparators different from the final scope - migalastat excluded

	Final scope	Company	EAG comments
Comparators	• Agalsidase alfa • Agalsidase beta • Migalastat (for those aged over 16 years with an amenable mutation)	• Agalsidase alfa • Agalsidase beta Represents how pegunigalsidase will be used in clinical practice because migalastat is established for amenable mutation	• Migalastat still a relevant comparator • BALANCE trial only included agalsidase beta but equal efficacy assumed for agalsidase beta and agalsidase alfa
Outcomes	Excludes infusion premedication	Includes infusion premedication because this can sometimes lead to treatment discontinuation	None of the clinical efficacy data from BALANCE trial is used in the economic model

Key issue: migalastat excluded as a comparator (1/3)

Unclear if all the relevant comparators have been included

ICER Impact: Unknown

Background

- Company submission excludes migalastat as a comparator
- Migalastat is recommended by NICE (HST4) as an option for treating Fabry disease in people over 16 years old with an amenable mutation who would otherwise be offered ERT
- Pegunigalsidase alfa is licensed (in Europe) as an ERT for the whole Fabry disease population

Company

- Population optimised to reflect how pegunigalsidase alfa would be used in clinical practice, that is, for those being considered for ERT
- Migalastat is an established treatment for people with an amenable mutation
  - Pegunigalsidase would only be considered if migalastat is unsuitable
  - Indirect treatment comparison with migalastat unfeasible – data limited and heterogenous

ERT, enzyme replacement therapy; HST, highly specialised technology

Key issue: migalastat excluded as a comparator (2/3)

Unclear if all the relevant comparators have been included

ICER Impact: Unknown

EAG comments

- ERTs and migalastat are treatment options for people with an amenable mutation, pegunigalsidase is an additional option for this population
- Due to restricted population, some people with an amenable mutation currently eligible for migalastat would not be eligible for pegunigalsidase
- The EAG considers migalastat a comparator
- The EAG conducted an exploratory analysis of pegunigalsidase vs migalastat, notes:
  - assumed non-inferiority of pegunigalsidase vs migalastat (based on HST4)
  - limited compared with a full analysis by company with migalastat as true comparator.

Clinical experts at Scoping Workshop

- People with an amenable mutation could receive migalastat or ERT as first-line
- Decision led by clinician, taking into account: patient preference, symptoms, and suitability for oral vs intravenous treatment

NICE Would pegunigalsidase alfa be reserved for people for whom migalastat is unsuitable?

Key issue: migalastat excluded as a comparator (3/3)

ICER Impact: Unknown

Technical Engagement comments

MPS Society (patient organisation)

- People with an amenable mutation are a small subgroup [30-50%]. ERTs available to all. Reasonable to use ERT as comparator

Amicus (Migalastat)

- Critical not to ignore role of migalastat as unique oral therapy. EAG/NICE should decide comparators → although acknowledge lack of comparative data

Takeda (Agalsidase alfa)

- No evidence to suggest migalastat is used first line above ERTs in all amenable patients. ERTs and migalastat are options for this group. Migalastat should be a comparator

What are the relevant comparators? Should migalastat be included as a comparator?

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: BALANCE

The key clinical trial (BALANCE) included people with impaired renal function

Pegunigalsidase alfa clinical trial design and outcomes

	BALANCE
Design	Phase III, randomised (2:1), double-blind, active controlled study
Population	Adults (18 – 60 years) with Fabry disease and impaired renal function, previously treated with agalsidase beta
Intervention	Pegunigalsidase alfa 1mg/kg every 2 weeks (n=52)
Comparator	Agalsidase beta 1mg/kg every 2 weeks (n=25)
Duration	24 months (study completed July 2022)
Primary outcome	Annualised change (slope) in eGFR (a measure of renal function)
Key secondary outcomes	UPCR, LVMI, plasma and urine lyso-Gb3, plasma Gb3, quality of life (EQ-5D-5L)
Locations	12 countries including the UK
Used in model?	No (assumption of clinical equivalence based on this trial)

eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; LVMI; Left ventricular mass index; Gb3, globotriaosylceramide; Lyso-Gb3, globotriaosylsphingosine; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels

Non-inferiority criteria for primary outcome in BALANCE

- Trial protocol originally designed to assess non-inferiority at 12 months and superiority at 24 months, but amended to assess non-inferiority at 24 months
- For non-inferiority to be indicated, the lower limit of the 95% CI had to be greater than the prespecified non-inferiority margin of -3.0 (ml/min/1.73 m^2/year)
- Company prespecified criteria based on:
  - Natural history evidence suggesting untreated people show progressive kidney worsening with eGFR slope worse than -3 ml/min/1.73 m^2/year
  - Consensus of European panel of experts which consider stabilisation of kidney function achieved if GFR slope loss is ≤1–3 mL/min/1.73 m^2/year
  - Fabry disease being a rare condition, required sample size to detect small non-inferiority margin not feasible

eGFR, estimated glomerular filtration rate

BALANCE baseline characteristics (1/2)

Higher proportion of men and people with classic Fabry disease were in the comparator group

Summary of baseline characteristics for pegunigalsidase and agalsidase beta

	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)	Overall (n = 77)
Mean age, years ± SE	43.9 ± 1.4	45.2 ± 1.9	44.3 ± 1.1
Sex, n (%)			
Male	29 (55.8%)	18 (72.0%)	47 (61.0%)
Female	23 (44.2%)	7 (28.0%)	30 (39.0%)
Type of FD, n (%)			
Classic	27 (51.9%)	14 (56.0%)	41 (53.2%)
Non-classic	25 (48.1%)	11 (44.0%)	36 (46.8%)

Are the differences expected to impact treatment effect?

NICE

SE, standard error; FD, Fabry disease; eGFR, estimated glomerular filtration rate

BALANCE baseline characteristics: kidney function (2/2)

Higher proportion of people with the worse eGFR slope category were in the comparator group

BALANCE inclusion criteria: eGFR at screening of ≥ 40 to ≤ 120 ml/min/1.73 m^2

Summary of baseline characteristics for pegunigalsidase and agalsidase beta

	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)	Overall (n = 77)
eGFR (mL/min/1.73 m^2) at baseline			
Mean ± SE, years	73.3 ± 2.8	73.5 ± 4.0	73.3 ± 2.3
Range: min, max	30.2, 125.9	34.1, 107.6	30.2, 125.9
eGFR slope (mL/min/1.73 m^2/year) at baseline			
Mean ± SE, years	-8.07 ± 0.91	-8.48 ± 0.83	-8.21 ± 0.67
eGFR slope categories (mL/min/1.73 m^2/year), n (%) at baseline			
≤ -5	[redacted]	[redacted]	[redacted]
> -5	[redacted]	[redacted]	[redacted]

Is the baseline renal function similar for both treatment groups?

SE, standard error; FD, Fabry disease; eGFR, estimated glomerular filtration rate

EAG comments on BALANCE and baseline characteristics

- BALANCE only included people with impaired renal function, not all Fabry disease population has renal impairment
- Only included people pre-treated with agalsidase beta, the outcomes may not apply to people who are treatment naïve
- Slightly higher proportion of people with classic Fabry disease than in the general Fabry disease population
  - → Renal impairment is more common in classic Fabry disease than in non-classic Fabry disease
- Higher proportion of males received agalsidase beta (72%) than pegunigalsidase (56%)
- [redacted] proportion of people with eGFR slope category of ≤ -5 mL/min/1.73 m^2/year received pegunigalsidase alfa vs agalsidase beta [redacted]

eGFR, estimated glomerular filtration rate

Are these baseline characteristics generalisable to NHS clinical practice?

BALANCE trial results: ITT population (1/3)

Company: For non-inferiority, lower limit of the 95% CI should be greater than -3.0 (ml/min/1.73 m^2/year)

Company: pegunigalsidase non-inferior to agalsidase beta for annual change in renal function

	Pegunigalsidase alfa (n=52)	Agalsidase beta (n=25)	Difference
Median annual eGFR slopes (mL/min/1.73 m^2/year)			
12 months (95% CI)	[redacted]	[redacted]	[redacted]
24 months (95% CI)	-2.514 (-3.788; -1.240)	-2.155 (-3.805; -0.505)	**-0.359 (-2.444; 1.726)**
Mean annual eGFR slopes (mL/min/1.73 m^2/year)			
12 months (95% CI)	[redacted]	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]	[redacted]

Red font: below lower limit

ITT: received at least 1 dose

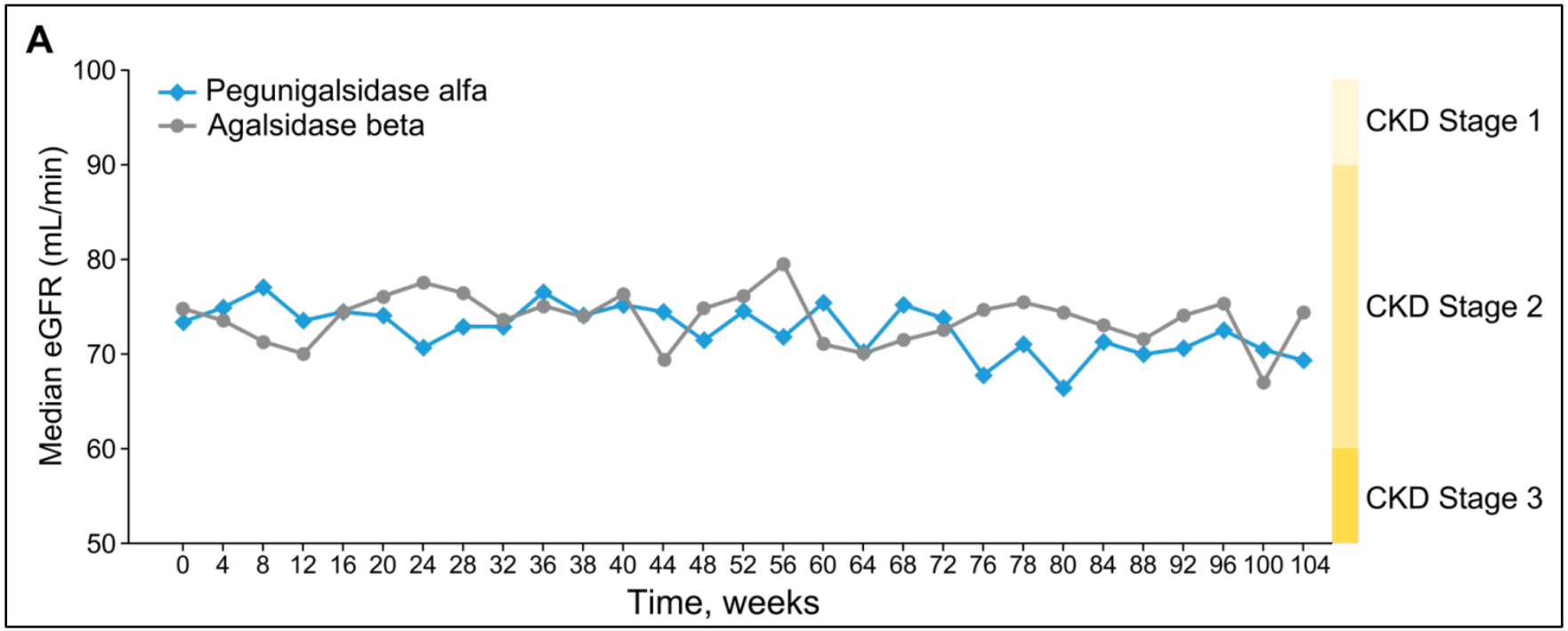
ITT, intention-to-treat; eGFR, estimated glomerular filtration rate

Is pegunigalsidase non-inferior to agalsidase beta? Are the differences clinically meaningful?

BALANCE trial results: ITT population (2/3)

Kidney function did not markedly differ with both treatments

Median eGFR in BALANCE



BALANCE inclusion criteria:

- eGFR at screening of ≥ 40 – ≤ 120 ml/min/1.73 m^2

eGFR, glomerular filtration rate; CKD; chronic kidney disease; ITT, intention-to-treat

Description of CKD stages	
stage 1	normal eGFR above 90ml/min, but other tests have detected signs of kidney damage
stage 2	slightly reduced eGFR of 60 to 89ml/min, with other signs of kidney damage
stage 3a	an eGFR of 45 to 59ml/min (mild to moderately impaired kidney function)
stage 3b	an eGFR of 30 to 44ml/min (moderately impaired kidney function)
stage 4	an eGFR of 15 to 29ml/min (severely impaired kidney function)
stage 5	an eGFR below 15ml/min (very severely impaired or kidney failure)

BALANCE trial results: subgroup analysis (3/3)

No difference in efficacy by subgroup was observed; wide confidence intervals are seen due to the small population

Subgroup analysis of the primary endpoint (change in eGFR slope) in BALANCE – ITT population

ADA, anti-drug antibodies; FD, Fabry disease; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio

Summary of additional pegunigalsidase trial with similar dose

Impaired renal function was not an inclusion criteria in BRIDGE

	BRIDGE (N=20)
Design	Phase III, open-label, single arm switchover study (people switched to pegunigalsidase alfa from agalsidase alfa [taken every 2 weeks for 2 years])
Population	Adults with symptomatic FD
Intervention	Pegunigalsidase alfa 1mg/kg every 2 weeks
Duration	12 months (up to 60 months for open label extension)
Primary outcome	Number of people with TEAE
Change in eGFR slope from baseline (mL/min/1.73 m^2/year)	
Mean (SE)	4.7 (2.3)
Used in model?	No

FD, Fabry disease; TEAE, treatment emergent adverse events

Overview of clinical effectiveness

Company makes case for clinical equivalence of pegunigalsidase alfa vs other ERTs

- BALANCE trial compared pegunigalsidase alfa vs agalsidase beta for non-inferiority
- No data for pegunigalsidase alfa vs agalsidase alfa, company states ITC not feasible
- Company assumes pegunigalsidase alfa, agalsidase beta and agalsidase alfa are clinically equivalent based on:
    - No statistical difference in 2 head-to-head RCTs of agalsidase alfa vs agalsidase beta, and systematic reviews

→Assumption: if RCTs show no difference in agalsidase alfa and beta, and BALANCE shows pegunigalsidase non-inferior to agalsidase beta then all three ERTs clinically equivalent

- Company presents cost comparison model (that is, assumes equal clinical effectiveness and quality of life)

ERT, enzyme replacement therapy; RCT, randomised controlled trial; ITC, indirect treatment comparison

Key issue: has clinical equivalence been demonstrated (1/3)

Company assumes clinical equivalence between pegunigalsidase and other ERTs

ICER Impact: Unknown

Company

- BALANCE showed pegunigalsidase alfa is non-inferior to agalsidase beta
- Naïve comparison of BRIDGE and BALANCE showed no significant difference in pegunigalsidase alfa eGFR slope in these trials
- Two RCTs support no statistical difference between agalsidase alfa and beta
  - Sirrs et al. 2014 and Vedder et al. 2007
- NICE HST4 (migalastat) assumed equal efficacy between agalsidase alfa and beta

EMA licence for pegunigalsidase alfa:

"No final conclusion on non-inferiority over agalsidase beta as measured by the annualised eGFR [based on primary endpoint at 12 months]… due to design and size of trial…Nevertheless, the median eGFR slopes [over 24 months]…appeared close"

eGFR, estimated glomerular filtration rate

Key issue: has clinical equivalence been demonstrated (2/3)

EAG: unclear if assumption of clinical equivalence between pegunigalsidase alfa and other ERTs is appropriate

ICER Impact: Unknown

EAG comments

- Protocol amendment to assess non-inferiority in BALANCE at month 24 (initially month 12) raises concerns
- EMA licence does not clearly support non-inferiority
- Unclear if data from BALANCE generalisable to whole FD population

→On evidence for equivalence of agalsidase beta and agalsidase alfa

- Sirrs et al. 2014 was underpowered, only 94 of the 294 people needed to detect a 10% difference in the outcome were included
- Vedder et al. 2007 not relevant because a lower dose of agalsidase beta was used (0.2 mg/kg instead of 1 mg/kg) compared with BALANCE. Also an open-label study
- HST4 did not aim to assess the efficacy of agalsidase alfa and beta

eGFR, estimated glomerular filtration rate; FD, Fabry disease; HST, highly specialised technology

Key issue: has clinical equivalence been demonstrated (3/3)

ICER Impact: Unknown

Non-company stakeholder technical engagement responses

MPS Society (patient organisation)

- Unclear why it is unreasonable to accept clinical equivalence [based on BALANCE, non-inferiority shown]. Always going to be uncertainties when evaluating treatments for small populations

Takeda (Agalsidase alfa)

- Despite meeting… non-inferiority [criteria in BALANCE] people receiving pegunigalsidase alfa had a greater [point estimate] decline in eGFR compared with agalsidase beta. Although a non-significant difference, by assuming equivalence in the economic analysis the results may be slightly biased to favour pegunigalsidase
- Greater proportion of males and people with classic FD in agalsidase beta arm. These groups generally have worse outcomes so may be biased to favour pegunigalsidase
- Acknowledge difficulties in evidence generation in this rare disease

Is it appropriate to assume pegunigalsidase and other ERTs are clinically equivalent?

NICE

eGFR, estimated glomerular filtration rate; FD, Fabry disease; HST, highly specialised technology

Adverse events in BALANCE (1/2)

A similar proportion of people had adverse events in each treatment arm.

Company did not include AE disutility in its cost utility results, EAG did not change this because the AEs are similar and not a key model driver

Summary of **all** treatment-emergent adverse events (TEAE)

	Pegunigalsidase (N = 52)		Agalsidase beta (N = 25)	
	People with ≥1 event n (%)	Number of events (rate*)	People with ≥ 1 event n (%)	Number of events (rate*)
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]

NICE

AE, adverse events

* Per 100 exposure years

Adverse events in BALANCE (2/2)

A similar proportion of people had adverse events related to treatment in each treatment arm, rate of treatment related adverse events was lower in the pegunigalsidase arm

Summary of treatment-emergent adverse events (TEAE) **related to treatment only**

	Pegunigalsidase (N = 52)		Agalsidase beta (N = 25)	
	People with ≥1 event n (%)	Number of events (rate*)	People with ≥ 1 event n (%)	Number of events (rate*)
TEAEs related to treatment 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]

* Per 100 exposure years

NICE

AE, adverse events

Should AE disutility be included in the modelling?

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Assumes equal clinical effectiveness and quality of life between treatment arms. Company base case is a cost comparison. Cost utility model presented but as same transition probability and health state utility values assumed, it only provides cost comparison

Model structure	Markov state transition model with 10 health states based on HST4 (migalastat) model
Population	Adults with Fabry disease
Intervention	Pegunigalsidase alfa every 2 weeks
Comparators	Agalsidase alfa or agalsidase beta every 2 weeks
Time horizon	60 years (mean starting age of 40 years)
Model cycle	1 year (with half-cycle correction applied)
Discount rates	3.5% applied to costs and QALYs
Perspective	NHS and Personal Social Services (PSS)

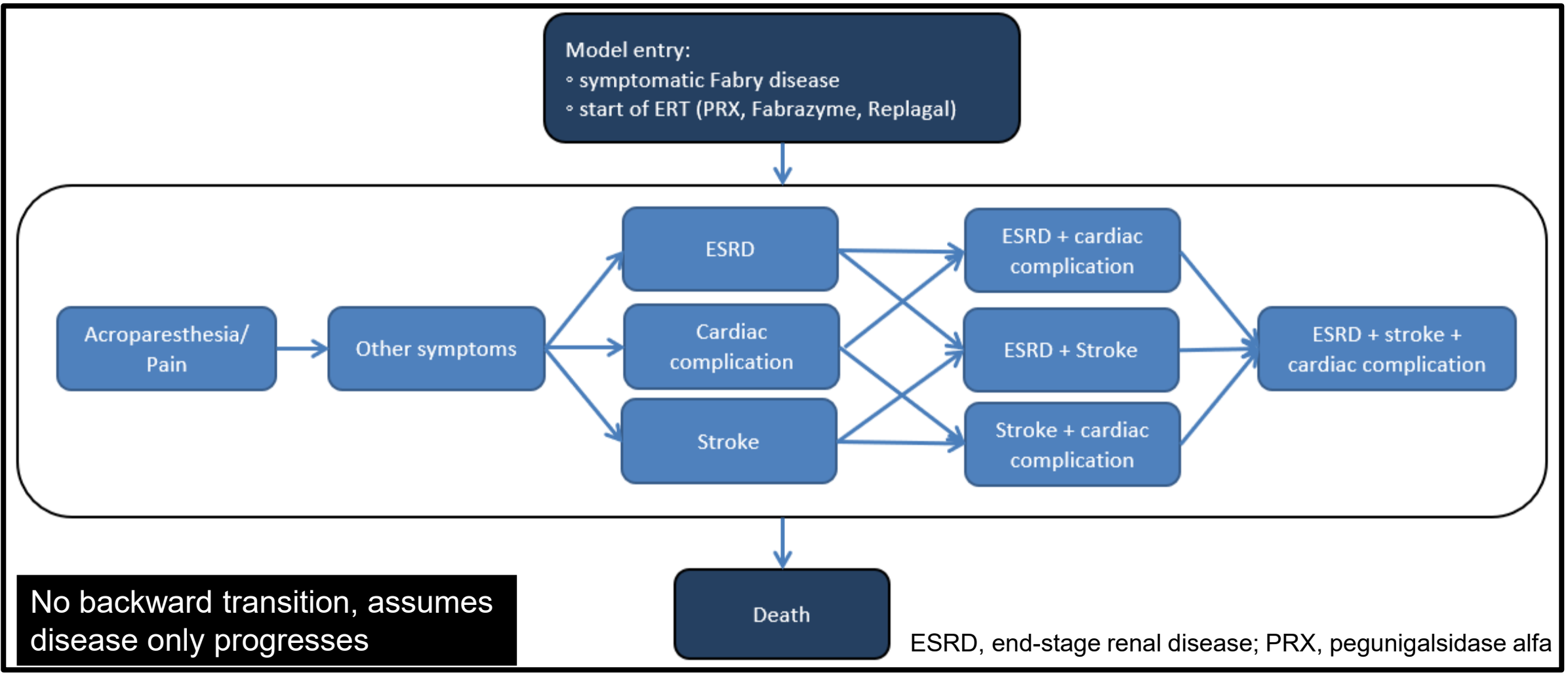
QALYs, quality-adjusted life year

Company's model overview

Models a progression of symptoms associated with worsening Fabry disease

- Technology affects **costs** by:
  - having lower unit price than standard treatment
- Technology does not affect **QALYs**:
  - equal efficacy to standard treatment is assumed
- Assumption with greatest effect on cost comparison:
  - Using life expectancy data by Waldek et al.

Model structure



No backward transition, assumes disease only progresses

ESRD, end-stage renal disease; PRX, pegunigalsidase alfa

How company incorporated evidence into model

Efficacy data from BALANCE were not used in the economic model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Fabry Registry (Waldek et al. 2009) and UK cohort study Malottki et al. (2022)
Intervention efficacy	Transition probabilities taken from Rombach et al. (2013), based on Dutch Fabry cohort. Not possible to use BALANCE data because starting health states not formally gathered in trial and no robust data for sufficient follow up
Comparator efficacy	
Costs	NHS reference costs 2020/2021, BNF, and Personal Social Services Research Unit. Confidential PAS applied
Resource use	Rombach et al. (2013), and clinical expert opinion

BNF, British National Formulary; PAS, patient access scheme

Key issue: external validity of transition probabilities (1/3)

Transition probabilities from 2013 Fabry disease cohort used in model

ICER Impact: Unknown

Background

- Company used transition probabilities from Rombach et al. 2013 (also used in HST4)
  - This is from a 2013 Dutch Fabry disease cohort (20% were children)
- For HST4, the EAG raised concerns about the generalisability of this population to UK clinical practice and high life expectancy

Company

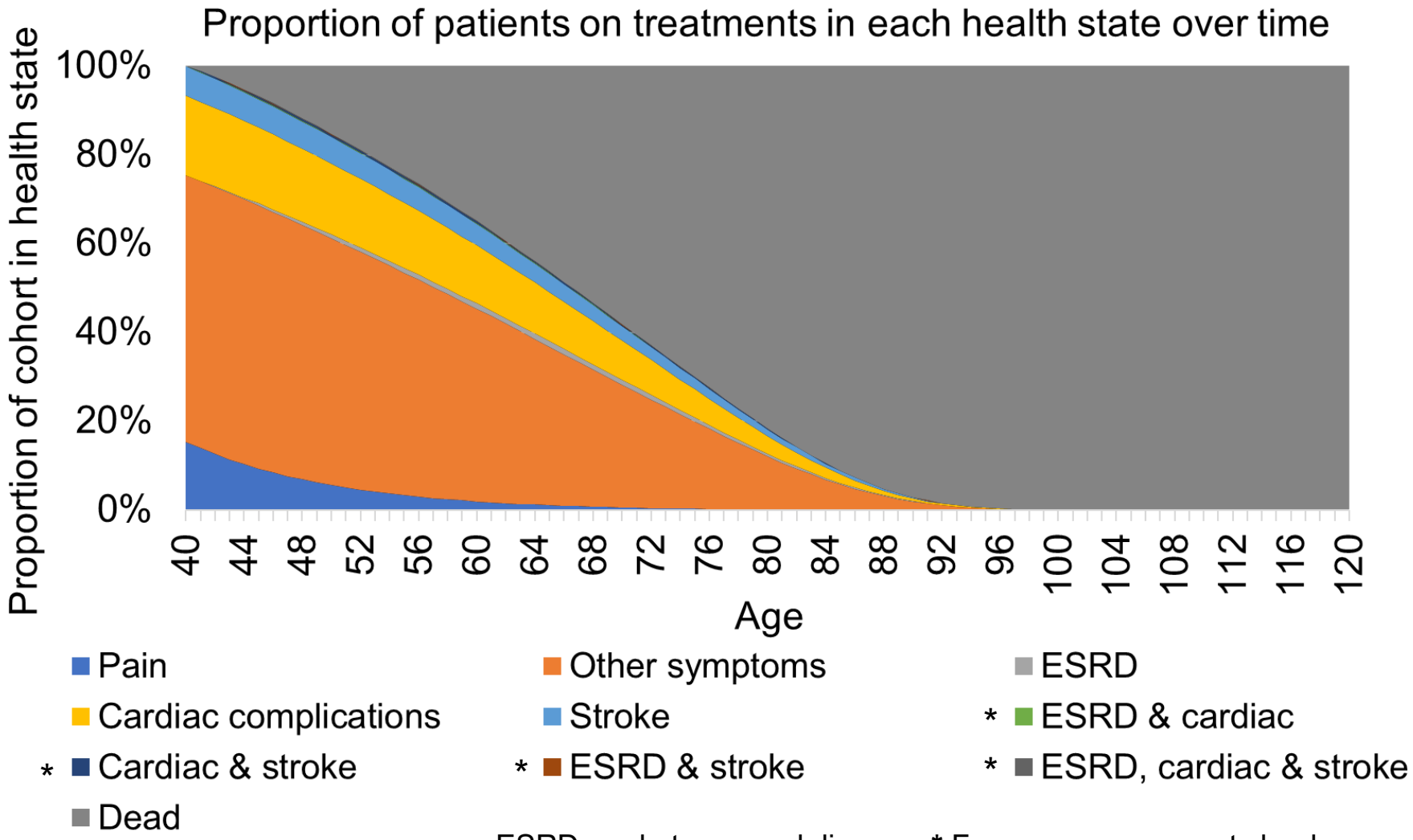
- Not feasible to derive transition probabilities from BALANCE and BRIDGE because the population was small and follow-up period not long enough
- Newer Fabry disease registry studies are available but are prone to selection bias related to the registry inclusion criteria
- Provided scenario using adjusted life expectancy data (Waldek et al. 2009): male - 58.2 years, and female - 74.7 years
- No explicit uncertainty around treatment effect in BALANCE which can be varied within the probabilistic sensitivity analysis (PSA)
- Transition probabilities were varied using the 95% CI included in the base case PSA

HST; highly specialised technology; CI, confidence interval; EAG, evidence assessment group; PSA, probabilistic sensitivity analysis

Model output – Pegunigalsidase Markov trace

EAG: validity of transition probability uncertain, Markov trace does not match the magnitude of progressive disease described by the company

Most people enter model with 'other symptoms'



ESRD, end-stage renal disease; * Few occurrences, not clearly seen in figure

Key issue: external validity of transition probabilities (2/3)

Transition probabilities from 2013 Fabry disease cohort used in model

ICER Impact: Unknown

EAG comments

- Transition probabilities do not match the progressive disease described by clinical experts, and company
- Almost half of the population die in their baseline health state
- Low number of people (0.79%) estimated to have more than one symptom (for example, ESRD and cardiac complication)
- Company did not provide requested scenario to use newer Fabry disease registry (from CPRD) for transition probabilities – it considered the newer registry prone to selection bias related to the registry inclusion criteria
- EAG base case uses adjusted life expectancy from Waldek et al. 2009
- Model does not account for uncertainty around difference in treatment effect between pegunigalsidase and the comparators
  - So, the PSA is not appropriate for decision making

ESRD, end-stage renal disease; CPRD, Clinical Practice Research Datalink; PSA, probabilistic sensitivity analysis

Do the transition probabilities lack external validity? Should data from BALANCE be used?

Key issue: external validity of transition probabilities (3/3)

ICER Impact: Unknown

Transition probabilities from 2013 Fabry disease cohort used in model

Comments from Technical Engagement

Company

- Robust transition probabilities difficult to achieve because:
  - Fabry disease is a rare condition (only about 1,000 people diagnosed in the UK)
  - Disease progression through health states occurs over a lifetime (about 60 years)
- Used data from Rombach et al., a 2013 Dutch Fabry study which included 142 people with Fabry disease, 72 received ERT → large sample size for a rare disease
- Also implemented changes suggested in HST4 (such as source of baseline characteristics)

EAG

- Impact on incremental costs minimal as affects both treatment arms equally due to clinical equivalence assumption
- Validity will be important for future FD appraisals where difference in outcomes is measured

MPS Society (patient organisation)

- In our opinion, the conclusion would be the same. Is this relevant to decision making?

Takeda (Agalsidase alfa)

- People occupy "other symptoms" health state for majority of the time
- Lack of granularity in disease progression prior to complication, and uncertainty in equal efficacy assumption limits ability to capture key aspect of quality of life

FD, Fabry disease

Resource and ERT costs used in the model

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

- Initial infusion: first 2 at hospital, next four at home all administered by nurse
- Maintenance infusions: 50% administered by nurse; 50% self –administered (1 nurse visit/year). If nurse-led, cost of 45 minutes for pre-infusion preparation and post-infusion monitoring
- Included costs of visits with GPs, physiotherapists, psychologist/psychiatrists and social worker
- 0.5% discontinuation rate of all ERTs
- Cost of acute complications used NHS Healthcare Resource Group costs

EAG comments on costs

Key model drivers include acquisition and administration cost of pegunigalsidase

- Technology acquisition and administration costs are main drivers of the incremental cost in the model
- EAG clinical experts noted most people not fully independent to deliver own IV treatment
    - Estimate 90% of people would require nurse to administer treatment, 10% would self-administer; EAG base case applies this assumption
- EAG excluded cost of social worker visits, considered this outside STA perspective
- Company used simple average rather than weighted average resource use estimates
- Company assumed all routine tests provided by the NHS, but experts noted in practice some are provided by companies. EAG conducted a scenario analysis including these costs

IV, intravenous

Which self-administration estimate is appropriate? Should a weighted average for cost be used? Should the modelling include the cost of routine tests?

EAG scenario comparing pegunigalsidase alfa with migalastat

- Used utility values from Arends et al.
  - Also used by company in its cost utility scenario for pegunigalsidase vs agalsidase alfa, and beta
  - Company: used this instead of HST4 values from Rombach et al. because more recent, had greater sample size, and more aligned to health states from model

  → EQ-5D-5L data was collected in BALANCE; not used in the model

  → but adjusted Arends et al. with BALANCE baseline utility (0.762)
- EAG cost-utility analysis assumptions:
  - Equivalent clinical effectiveness and adverse events affecting utility
  - Disutility of 0.025 applied annually for pegunigalsidase alfa for intravenous infusion
  - No administration costs for migalastat because it is an oral treatment taken every other day

NICE

Is a disutility for intravenous infusion (vs oral treatment) a plausible assumption?

Cost-effectiveness results

Company results

Deterministic base case results - cost-minimisation analysis

Technology	Total costs (£)	Total QALYs	Inc. QALYs	Inc. costs
Pegunigalsidase alfa	[redacted]	[redacted]		
Agalsidase alfa	[redacted]	[redacted]	0.00	-£476,243
Agalsidase beta	[redacted]	[redacted]	0.00	-£470,950

Probabilistic base case results - cost-minimisation analysis

Technology	Total costs (£)	Total QALYs	Inc. QALYs	Inc. costs
Pegunigalsidase alfa	[redacted]	[redacted]	-	-
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]

NICE Results are per person over a lifetime horizon (60 years)

Inc, incremental

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Require nurse-assisted infusion	50%	90%
Cost of acute complications	Simple average of HRG codes	Weighted average of HRG codes (taking into account activity for each included HRG code)
Cost of social work	Included	Excluded, outside STA scope
Mortality adjustment	As HST4	Adjusted to match Waldek et al. (using company scenario)
General management (including test frequency)	Expert opinion	Adjusted according to EAG clinical experts

EAG also made model corrections to formula for drug administration costs (such as homecare costs being included for people treated in hospital), and health state event costs (correct weighting for people in other symptoms health state - chronic kidney disease stage 1-4)

HRG Health Resource Group; STA single technology appraisal EAG, evidence assessment group

EAG preferred assumptions

EAG preferred model assumption (deterministic), results are cumulative

Preferred assumption	Inc. costs vs agalsidase alfa	Inc. costs vs agalsidase beta
Company base case		
	-£476,243	-£470,950
EAG corrected company base case		
	-£475,181	-£471,243
Increase the proportion of people requiring nurse assisted infusions to 90%		
	-£465,595	-£476,995
EAG estimation of acute complication costs		
	-£465,595	-£476,995
Removal of costs associated with social workers		
	-£465,595	-£476,995
Mortality adjusted to FD average life expectancy		
	-£386,796	-£396,288
EAG clinical expert assumptions for general management of FD		
	-£386,796	-£396,288

Inc, incremental; FD, Fabry disease

EAG base case results

EAG deterministic base case results - cost-minimisation analysis

Technology	Total costs	Incremental costs vs pegunigalsidase
Pegunigalsidase alfa	[redacted]	-
Agalsidase alfa	[redacted]	-£386,796
Agalsidase beta	[redacted]	-£396,288

EAG probabilistic base case results - cost-minimisation analysis

Technology	Total costs	Incremental costs vs pegunigalsidase	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

Results are per person over a lifetime horizon (60 years)

EAG deterministic scenario analysis

EAG scenario analyses (deterministic) – including the cost of the following routine tests for pegunigalsidase only but not the comparators:

- Plasma Lyso-Gb3
- Assay for alpha-galactosidase A
- GL-3G and Lyso-GL-3G
- Antibody test & neutralizing assay

Technology	Total costs	Incremental costs
Pegunigalsidase alfa	[redacted]	-
Agalsidase alfa	[redacted]	-£386,389
Agalsidase beta	[redacted]	-£395,881

Results are per person over a lifetime horizon (60 years)

*Increase of [redacted] compared with base case total cost

EAG deterministic scenario analysis

EAG scenario analyses (deterministic) - Migalastat cost utility analysis

- Migalastat has a confidential commercial discount. So, the results for this analysis are presented in Part 2
- The results are in the South-west quadrant, that is:
  → Pegunigalsidase alfa had lower cost and had fewer QALYs than migalastat

NICE National Institute for Health and Care Excellence

Thank you.

Back up

NICE National Institute for Health and Care Excellence

BALANCE trial results (PP population)

Company: For non-inferiority, lower limit of the 95% CI should be greater than -3.0 (ml/min/1.73 m^2/year)

	Pegunigalsidase alfa (n=52)	Agalsidase beta (n=25)	Difference
Median annual eGFR slopes (mL/min/1.73 m^2/year)			
12 months (95% CI)	-2.164 (-3.326; -1.002)	-1.767 (-2.847; -0.687)	**-0.397 (-1.863; 1.069)**
24 months (95% CI)	-2.515 (-3.666; -1.364)	-2.397 (-4.337; -0.457)	**-0.118 (-2.450; 2.213)**
Mean annual eGFR slopes (mL/min/1.73 m2/year)			
12 months (95% CI)	[redacted]	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]	[redacted]

Company: For non-inferiority to be indicated, the lower limit of the 95% CI had to be greater than the prespecified non-inferiority margin of -3.0.

PP: completed at least 24 months of treatment

PP, per protocol, eGFR, estimated glomerular filtration rate

BALANCE trial results

Secondary efficacy endpoints - biomarkers

	Pegunigalsidase (n = 52)	Agalsidase beta (n = 25)	Difference (95% CI) p-value
Plasma lyso-Gb3			
Mean (SE) change from baseline to Week 104	[redacted]	[redacted]	[redacted]
Adjusted means in change of log at Week 104, mean (95% CI)	[redacted]	[redacted]	[redacted]
Urine lyso-Gb3			
Mean (SE) change from baseline to Week 104	[redacted]	[redacted]	[redacted]
			[redacted]
Mean (SE) change from baseline to Week 104	[redacted]	[redacted]	[redacted]

Gb3, Globotriaosylceramide; Lyso-Gb3 Globotriaosylsphingosine; SE, standard error

BALANCE trial results

Secondary efficacy endpoints – quality of life

	Pegunigalsidase (n = 52)	Agalsidase beta (n = 25)	Difference (95% CI), p-value
Quality of life			
EQ-5D-5L			
Mean (SE) change from baseline to Week 104 in overall health score	[redacted]	[redacted]	[redacted]

EQ-5D-5L; EuroQol 5 Dimensions 5 Levels