Pegzilarginase for treating arginase-1 deficiency [ID4029]

For PUBLIC– contains no confidential information

Highly Specialised Technology Appraisal Committee [18th September 2025]

3rd committee meeting

Chair: Paul Arundel

External assessment group: Sheffield Centre for Health and Related Research

Technical team: Lauren Elston, Alan Moore, Richard Diaz

Company: Immedica

Pegzilarginase for treating arginase-1 deficiency

- ✓ **Background and overview of key issues**
- ❑ Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

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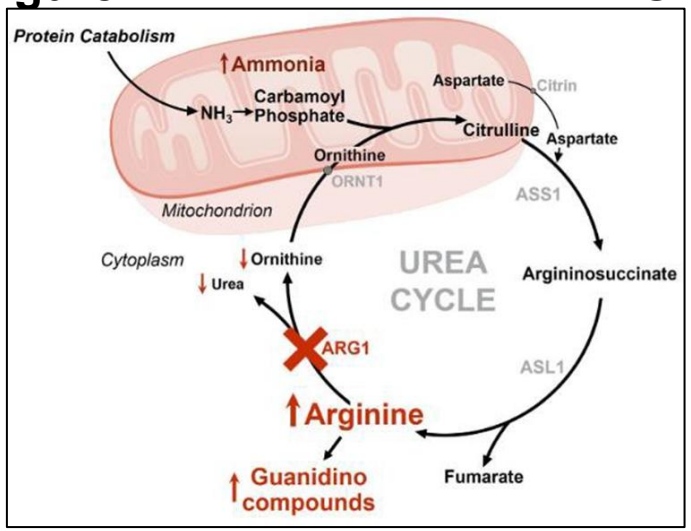
Background on arginase-1 deficiency (ARG1-D)

Ultra-rare inherited metabolic condition caused by mutations in the ARG1 gene

Causes

- Urea cycle disorder. The body is unable to process arginine (an amino acid used to build protein)
- Lack of arginase in liver and red blood cells leads to hyperammonaemia and hyperargininaemia

Figure: Metabolic effects of ARG1-D



Source: Company submission (CS), Figure 2

Epidemiology

- Presents in early childhood
- Occurs in approximately 1 in 300,000 to 1,000,000 births
- Prevalence of 0.58 cases per 1,000,000 in the UK

Diagnosis and classification

- Routinely available assessment of red blood cell arginase levels, plasma arginine, or genetic analysis. Newborn screening for ARG1-D is not routine in the NHS

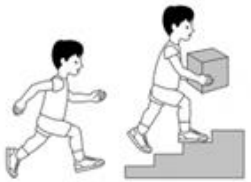
Symptoms and prognosis

- Increased mortality and reduced quality of life ➔ Median age of death is ~17 years few patients survive beyond 35 years of age
- Clinical features include spastic paraparesis, progressive neurological and motor deterioration affecting mobility, growth and developmental delays, cognitive delays and seizures

More ECM1 recap in appendix

GMFCS categorisation

Figure: The company's representation of the GMFCS (and used in economic model)

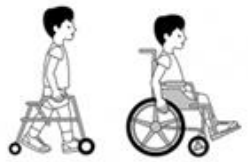


GMFCS Level I

- Can walk indoors and outdoors and climb stairs without using hands for support
- Can perform usual activities such as running and jumping
- Has decreased speed, balance and coordination

GMFCS Level II

- Has the ability to walk indoors and outdoors and climb stairs with a railing
- Has difficulty with uneven surfaces, inclines and crowds
- Has only minimal ability to run or jump



GMFCS Level III

- Walks with assistive mobility devices indoors and outdoors on level surfaces
- Maybe able to climb stairs using a railing
- May propel a manual wheelchair (may require assistance for long distances or uneven surfaces)

GMFCS Level IV

- Walking ability severely limited even with assistive devices
- Uses wheelchair most of the time and may propel their own power wheelchair
- May participate in standing transfer

GMFCS Level V

- Has physical impairment that restricts voluntary control of movement and the ability to maintain head and neck position against gravity
- Is impaired in all areas of motor function
- Cannot sit or stand independently, even with adaptive equipment
- Cannot independently walk, though may be able to use powered mobility

Source: EAR, Figure 2

GMFCS: Gross Motor Function Classification System

Equality issues

Equality considerations

- Patient carer submission: **Metabolic Support UK**
    - ARG1-D is a genetic condition with a reported higher prevalence in communities where consanguineous marriage is more prevalent. Special consideration must be given to communities where consanguineous marriage is/was common.

- **Draft guidance section 3.24:** The committee considered this issue. It also considered that its recommendation applies equally and difference in condition prevalence does not in itself represent an equality issue. The committee concluded that there were no equalities issues that could be addressed by its recommendations.

- No further potential equality issues have been raised during the 2nd draft guidance consultation

Pegzilarginase (Loargys, Immedica)

Marketing authorisation	MHRA approval granted on 20 December 2023: "for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older."
Mechanism of action	Substitutes the deficient human arginase 1 enzyme activity in patients with ARG1-D. This has shown to rapidly and sustainably reduce plasma arginine and convert it to urea and ornithine
Administration	Intravenous or subcutaneous injection • 0.1mg/kg once weekly, preceded by increase or decrease of 0.05mg/kg increments to achieve therapeutic goals • Doses above 0.2 mg/kg per week have not been studied in clinical trials in ARG1-D

Price	• The list price for pegzilarginase is £4,690.00 per 2 mg vial.
	  • A dose of 2 vials equates to £487,760 per patient per year
	  • A dose of 4 vials equates to £975,520 per patient per year
	• Company has a confidential PAS discount in place

MHRA: Medicines & Healthcare Products Regulatory Agency; PAS: Patient access scheme

More ECM1 recap in appendix

Draft guidance recommendation

Pegzilarginase is not recommended, within its marketing authorisation, for treating arginase-1 deficiency in people 2 years and over.

Why the committee made these recommendations

- Clinical evidence showed that pegzilarginase + usual treatment reduced levels of arginine in the blood compared with placebo + usual treatment; evidence in mobility and mental processing improvements were less certain.

- Key uncertainties in the economic model included:
  - Whether the condition can get worse on pegzilarginase treatment
  - Assumptions on life expectancy and quality of life for people who have pegzilarginase
  - How pegzilarginase affects body weight and how weight is modelled
  - How long people stay on pegzilarginase treatment

- The most likely ICERs were substantially above the acceptable range for HSTs.

ICER: incremental cost-effectiveness ratio.

ECM2 committee conclusions (1/4)

DG section	Committee conclusion
3.4 Clinical outcomes	Pegzilarginase reduces plasma arginine levels, an important outcome in pathogenesis of ARG1-D. However, life extension with pegzilarginase uncertain, given lack of longer-term data
3.5 Company's modelling approach	Model starting age of 13 years acceptable for decision making. But it may have represented a younger age than that seen in the current NHS England population
3.6 Starting distributions by GMFCS health states	Distributions in each GMFCS health state informed by European burden of illness survey, but assuming 50% of people in GMFCS-2 health state would be in GMFCS-3 instead
3.7 Transition probabilities for pegzilarginase	Everyone in pegzilarginase arm remaining in same GMFCS health state after 3 years but this is uncertain given lack of longer-term data

ARG1-D: arginase-1 deficiency; DG: draft guidance; GMFCS: Gross Motor Function Classification System; GMFM-DE: Gross Motor Function Measure

ECM2 committee conclusions (2/4)

DG section	Committee conclusion
3.8 Transition probabilities for standard care arm	− Using mean of PEACE, Study 101A and Study 102A as starting GMFM-DE score in GMFCS-1 health state. − A reduction in GMFM-DE score of 2.66 per year. − Converting inverse of time in GMFCS health state to probability.
3.9 Transition from GMFCS-2 and -3 to GMFCS-5 after hyperammonaemic crisis	EAG's preferred analysis that 5% of people per year transition from GMFCS-2 and -3 health states to GMFCS-5 after hyperammonaemic crisis in people under 16 years, in both pegzilarginase and standard care arms.
3.10 + 3.11 Life expectancy	Standardised mortality rates (SMRs) for pegzilarginase arm and standard care using EAG's preferred analysis, with GMFCS-2 health state for pegzilarginase having a SMR equal to 25% of standard care. - Committee noted SMRs were highly uncertain, may have underestimated cost-effectiveness results and affects the QALY weighting, and requested more information on this issue.

DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System, QALY: Quality Adjusted Life Year

ECM2 committee conclusions (3/4)

DG section	Committee conclusion
3.12 Distribution of peak ammonia levels during hyperammonaemic crisis	Company's updated analysis, in which distribution of high levels of peak ammonia in pegzilarginase arm were between values used in company's base case and EAG's scenario analysis was appropriate.
3.13 Source of utility values	GMFCS health-state utility values used in company's original base case.
3.14 Utility gain associated with improved diet	Utility gain associated with improved diet with pegzilarginase treatment is applied to 48.5% of people.
3.15 Disutility associated with cognitive disability	Treatment-specific cognitive disutility applied in GMFCS-1 to GMFCS-3 health states (as in company original base case).

DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; QALY: quality-adjusted life-year

ECM2 committee conclusions (4/4)

DG section	Committee conclusion
3.16 Carer disutility	Carer disutility as applied in company's base case but not applying additional carer disutility for carers with more than 1 child with condition
3.17 Pegzilarginase dosing and drug wastage	Company's adherence rate, a dosing amount of 0.14 mg/kg and a 10% threshold for drug wastage
3.18 Pegzilarginase weight-based dosing costs	Adults having pegzilarginase would weigh 90% of general population weight, and 50% of people with condition are expected to be female
3.19 Pegzilarginase treatment discontinuation	Used EAG's log-logistic distribution for pegzilarginase treatment discontinuation (noting high uncertainty)
3.20 Criteria for applying a QALY weighting	Applied a QALY weighting equal to 50% of the QALY weighting implied by economic model using committee preferences, due to high levels of uncertainty

DG: draft guidance; EAG: external assessment group; QALY: quality-adjusted life-year

Stakeholder responses to Draft Guidance

Submissions from Metabolic Support UK and 3 clinical experts (combined submission):

- Remain concerned that by not recommending pegzilarginase, committee has not fully understood high level of unmet need, or high physical and psychological burden of ARG1-D on patients and carers
- The clinically meaningful impact of pegzilarginase on patients, and their families, as detailed in previously provided evidence by patients, carers, clinical experts and company, have not been fully taken into account
- Several uncertainties highlighted by committee are inherent to rare diseases and cannot be addressed by current state of real-world data
- Results associated with mobility, mental processing and quality of life outcomes are clinically significant despite not being statistically significant

"This progressive disorder has a marked effect on people living with ARG1d and their families and we have sadly seen disease onset, worsening and lost members of the community while this assessment process has been on-going."

Note: Stakeholder responses also discussed in later key issue slides
ARG1-D: Arginine-1 deficiency

ECM3 key issues for discussion

Key issue	Impact on ICER
Utility gain associated with improved diet	**Moderate**
Pegzilarginase weight-based dosing costs • Proportion of female/male patients • Weight ratio to the general population • Distribution of weight	**Large**
Criteria for applying a QALY weighting	**Large**

See appendix for overview of changes to ECM2 key issues

DG: draft guidance; EAG: external assessment group; ICER: incremental cost-effectiveness ratio; IDM; individualised disease management; PSA; probabilistic sensitivity analysis.

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Moderate impact

Key issue: Utility gain associated with improved diet (1/2)

Recap (DG 3.14):

- Company base case: 83.3% of people get utility gains from a liberalised diet.
- Committee conclusion: Value in company's base case was too high because a placebo effect should also be modelled. EAG scenario applying a utility gain to 48.5% of people with diet liberalisation is appropriate.

Company (response to DG)

- Maintain utility gains from a liberalised diet should be applied to 83.3% of people with no placebo effect (placebo effect is not supported by clinical practice).
- Real-world data show that 83.3% of patients experienced improved dietary protein tolerance, not just those meeting the >15% threshold.
  - This is a meaningful and sustained improvement in daily life and should be reflected in the utility gains.

DG: draft guidance; EAG: external assessment group.

Moderate impact

Key issue: Utility gain associated with improved diet (2/2)

EAG comments

- No new data provided by company.
- Individual data (Arnoux et al.) not available for 12 patients with data on natural protein increases, so it's unclear whether all 10 patients had clinically meaningful improvements.
- Utility gain (0.04 per person; half the difference between strict diet and general population utilities for FCS from HST13) is likely to be a function of threshold of increased protein.
  - Reducing threshold for improved diet could be associated with a lower utility gain.
- Company scenarios analyses: indicated that % of people with an improved diet (83.3%, 66.7%, 48.5%) was not a large driver of ICER.

Stakeholder comments (Metabolic Support UK)

- Assumption that only 48.5% of people will liberalise diet is implausible; all 9 HCPs in clinical survey indicated they would expect to liberalise diet. This is aligned with CS and published literature (Arnoux et al. 2024, Singh et al. 2024).
- A utility gain should also be included for reduced requirement for ammonia scavengers, as no hyperammonaemia episodes reported and this is a "most feared symptom".

What utility gain should be applied?
What proportion of people should utility gains for improved diet be applied to?

CS: company submission; EAG: external assessment group; FCS: familial chylomicronaemia syndrome; HCP; health care practitioner; ICER: incremental cost-effectiveness ratio.

Pegzilarginase drug costs – summary of key issues

There are several issues which impact on estimation of pegzilarginase costs

Pegzilarginase drug cost estimation issues
Proportion of males/females with the condition assumed
Weight of people on treatment with pegzilarginase over their lifetime
How weight is modelled (average weight versus distribution of weight)

NICE technical team: These issues can interact with each other and make the impact of each of these issues on the cost-effectiveness results larger

Large impact

Key issue: Proportion of females and males in the model

Background:

- NICE technical team: proportion of males/females in model should be 50/50.
- Systemic review (Bin Sawad et al. 2022): equal split of females/males with ARG1-D.
- Committee conclusion: 50% of people with condition are expected to be female.

Company (DG response)

- Committee preferred baseline GMFCS states informed by European ARG1-D BOI study.
- To be consistent, company prefers % of females from BOI study data – 76% - consistent with clinical expert feedback that most UK patients are female.

EAG comments

- Agree with the company: 0.76 appropriate as consistent with BOI study.

NICE technical team

- GMFCS states are informed by BOI study and NHS clinical input (from survey).
- McNutt et al. 2025 reports 52% are female. Current NHS % may be different (clinical input helpful). Impact of issue increased due to how company model patient weight.

What proportion of females and males should be assumed in the model?

ARG1-D: Arginine-1 deficiency; BOI: burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System.

Large impact

Key issue: Weight of people on pegzilarginase over lifetime (1/3)

Recap (DG 3.15):

- ECM2 company base case: average weight ratio of 0.782 for all patients, based on trial baseline data; average weight mainly applied to 10-year age ranges (e.g. 16-24 years).
- NICE tech team: Company's position on weight on pegzilarginase inconsistent. If patients do not benefit from growth/healthier weight, high utility utilities values lack validity.
- Responses to 1st draft guidance consultation from Metabolic UK and clinical experts stated only a few people with the condition in England are currently underweight.
  - Also, results from a healthcare professional survey stated that several people gained weight on pegzilarginase treatment, including people who were underweight at baseline.
- Committee conclusion: people on pegzilarginase weigh 90% of general population weight.

Company (DG response)

- Agrees with committee that using 0.782 for all patients may underestimate average weight. However, committee preferred assumption of 0.9 overestimates weight.
- Suggests weight ratio of 0.84 (average of 0.782 and 0.9) for all patients; as proportion of patients below vs above 13 yrs when starting treatment in model is equal.

DG: draft guidance

Large impact

Key issue: Weight of people on pegzilarginase over lifetime (2/2)

EAG comments

- Simply averaging committee and company preferred weight ratios may not be correct.
- Results from Delphi panel appears more supportive of a higher value (90%).
- Company has not provided any new data regarding this key issue.

Stakeholder comments (Metabolic Support UK)

- All community respondents to a survey reported that weight of the individuals living with ARG1-D is impacted by the disorder. This varied over from being underweight to obese.
- Limited impact of pegzilarginase on weight was reported.
- This was also supported by the findings from the clinical survey.

NICE technical team comments

- Pegzilarginase modelled to give substantial quality of life gains – not compatible with assuming underweight population (implies lower health).

NICE

What is the most appropriate weight ratio to use?

ARG1-D: Arginine-1 deficiency; EAG: external assessment group.

Large impact

Key issue: How weight is modelled (1/3)

Background:

- NICE technical team: using average weight to estimate number of vials is incorrect. Impacted by % of female patients assumed, and weight-ratio used.

NICE Technical Team:

- Use of 10-year age ranges in company analysis further increases impact of issue.
- Some weights close to vial threshold, particularly early in model (impacts more: discounting), but over time some may require a 6th vial (later in the model).

EAG comments

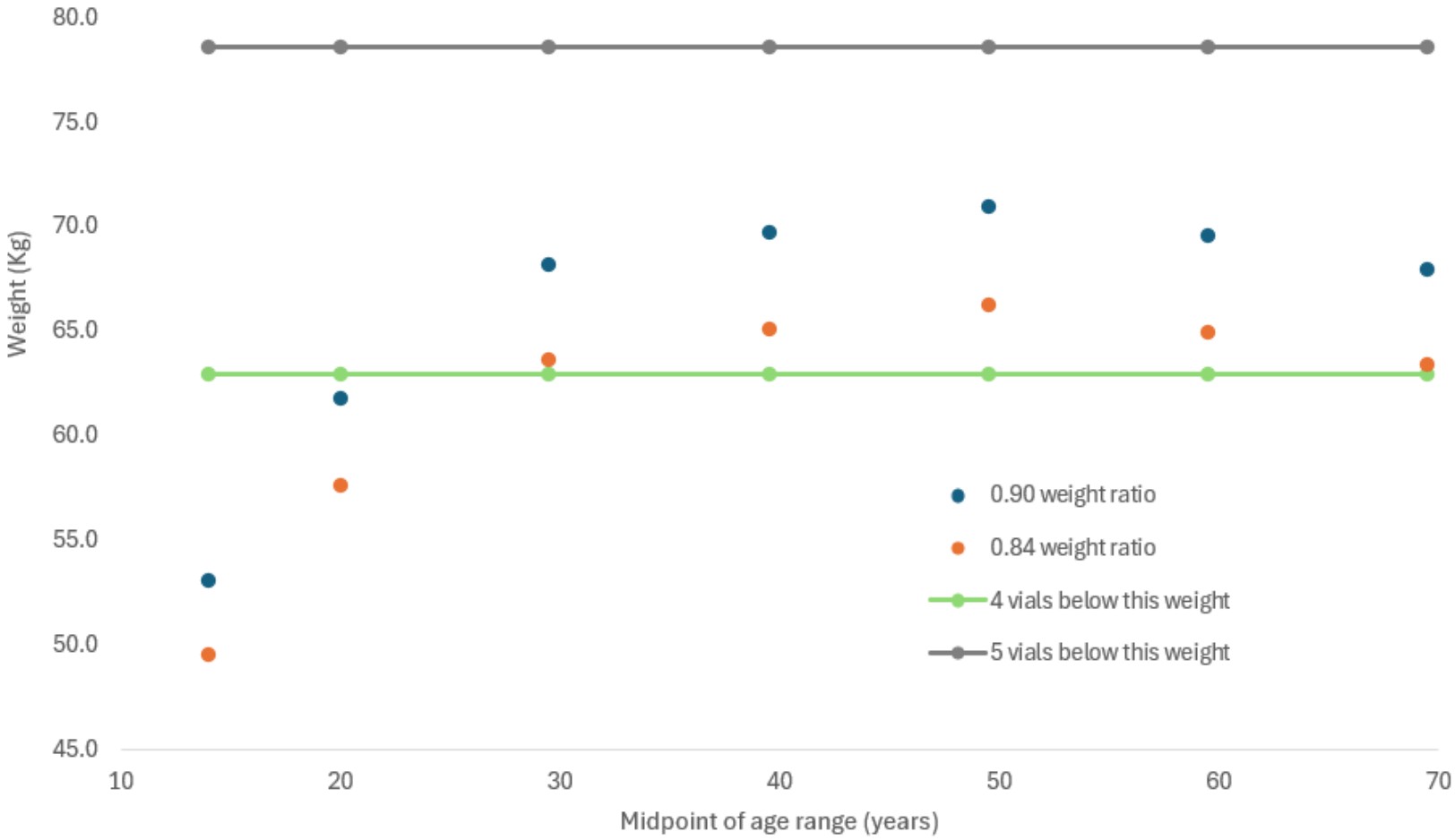
- Use of a point estimate for weight can cause inaccuracy in costing estimates where the point estimate lies close to a threshold weight for an additional vial (see next slides).
- EAG scenarios: analysis assuming drug costs:
  - Decreased by 5% for 76% female and 0.84 weight ratio (company base case), and for 50% female and 0.90 weight ratio (committee preferred),
  - Increased by 5% for 76% female, weight ratio of 0.90 (EAG preferred).
- Distribution preferred, but sensitive to proportion of female/male patients.

EAG: external assessment group; ICER: incremental cost-effectiveness ratio.

Key issue: How weight is modelled (2/3)

Large impact

Figure: Comparison of point estimate of weights and thresholds for number of vials of pegzilarginase assuming 76% of population are female



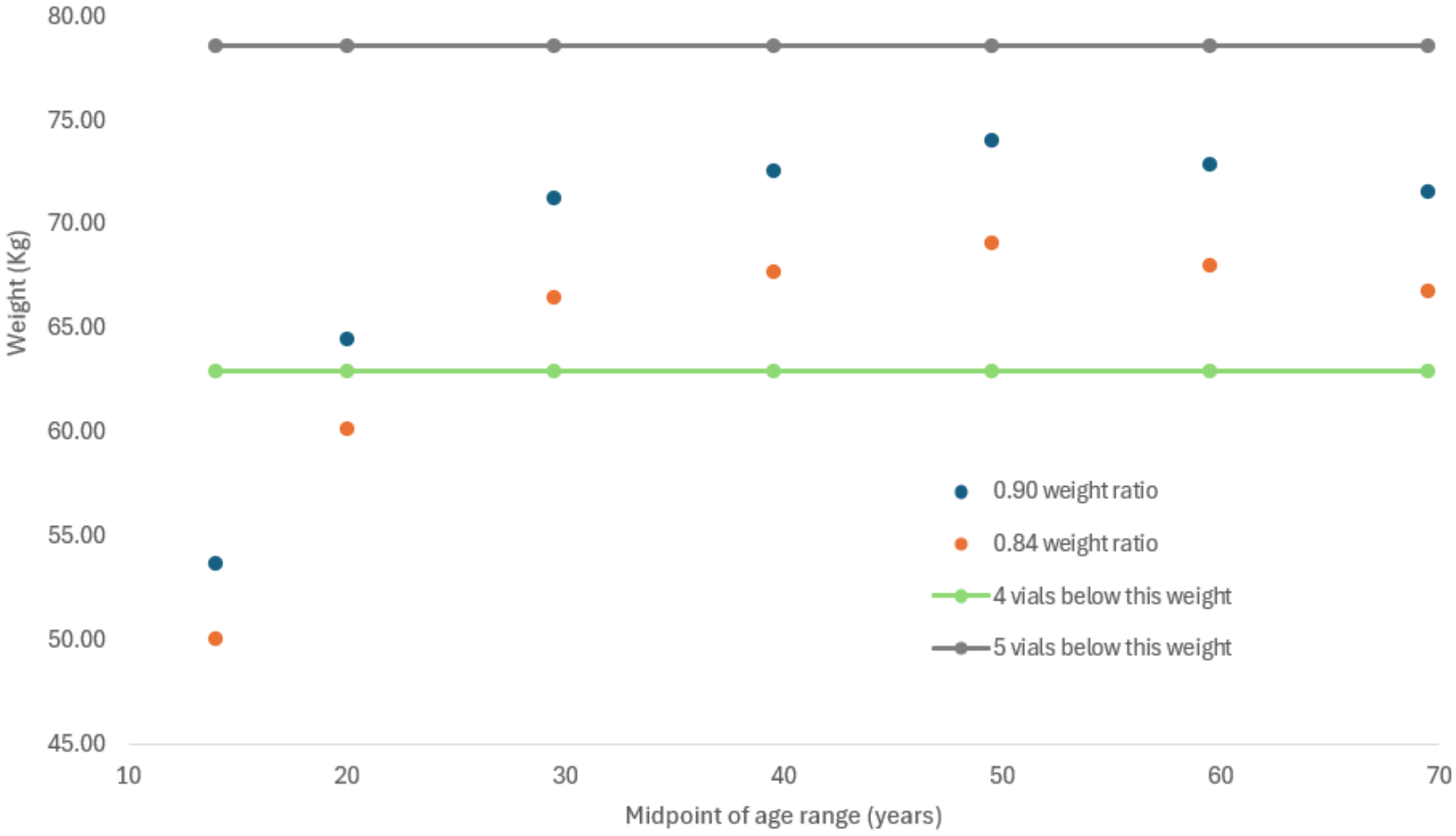
EAG comments continued

- 0.84 weight ratio at 25-34 years just over 4 vial threshold; overestimates costs when it is likely a significant proportion of patients would weigh under the threshold.
- 0.90 weight ratio may underestimate costs at 16-24 years (inaccuracy in younger ages will be more influential due to impacts of discounting).

Key issue: How weight is modelled (3/3)

Large impact

Figure: Comparison of point estimate of weights and thresholds for number of vials of pegzilarginase assuming 50% of population are female (committee preferred)



EAG comments continued

- With 50% female population, inaccuracy on costs appears smaller.
- Mainly impacts the 16-24 years group; underestimates costs for the 0.84 ratio and potentially overestimates costs with 0.90 ratio.

Should costs be adjusted due to average weight use?

Key issue: QALY weighting (1/3)

High impact

Recap (DG 3.17)

- Methods guide: "*For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY. To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains".*
- Committee conclusion: Applied a QALY weighting equal to 50% of the QALY weighting.

NICE Technical Team:

- Many scenarios show substantial undiscounted QALY gains.
- Relies on several model inputs/assumptions; committee could not apply full QALY weighting at ECM2, primarily due to very high uncertainty around:
  - Long life expectancy on pegzilarginase treatment (SMRs from 2 different sources used in the model; high impact on ICER See appendix for scenario analysis)
  - Whether disease progression occurs with pegzilarginase
  - High utility while on pegzilarginase treatment and low QALYs in standard of care arm (below zero [negative QALYs])
  - Long time on treatment with pegzilarginase.
- Committee noted there was enough evidence to apply a partial QALY weighting (50%).

DG: draft guidance; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Large impact

Key issue: QALY weighting (2/3)

Company (response to DG)

- Clarification, evidence and scenario analyses addressing key uncertainties raised by committee has been provided in company's response to DG.
- This should support application of full QALY weighting, as estimated by the model.

EAG comments

- There is little new data presented, as would be expected given longer-term data would need to come from pivotal clinical studies, but more reiterations of likely long-term benefits of pegzilarginase provided.

Stakeholder comments (Metabolic Support UK and 3 clinical experts)

- The QALY weighting applied in this technology appraisal depends considerably on whether disease progression occurs in patients on treatment.

DG: draft guidance; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Key issue: QALY weighting (3/3)

Company (response to DG continued)

- Arginine key driver of disease; sustained reductions in plasma arginine associated with disease stabilisation and lowering elevated arginine concentrations give meaningful clinical benefit.
- Sustained arginine control should be interpreted as a key indicator of disease stabilisation.
- Pegzilarginase trials show arginine levels can be reduced to normal level for all patients, and kept within normal levels over time.
- Hyperammonaemia reduced with pegzilarginase and less frequent, less severe HAC events.
- Trials show reduced arginine levels, to within normal level, associated with clinically relevant improvements in motor function with some patients reaching normal level of function.
- Improvement in symptoms or avoidance of any/further progression expected to increase survival.
- Very few patients are expected to discontinue pegzilarginase treatment.
- Improved protein tolerance = meaningful quality of life benefits. May enhance growth also.
- Patient utility values strongly correlated with symptom severity, reaching negative values when both motor function and cognition are severely impacted.
- Patients treated with pegzilarginase will experience more years with improved QoL/utilities.

What QALY weighting should be applied?

DG: draft guidance; HAC: hyperammonaemic crisis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; QoL: quality of life

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Company base case and EAG preferences

Issue	Company base case	EAG preferred
Utility gains: % improved diet	83.3%	48.5%
Weight	0.84 weight ratio (10% margin for wastage)	0.90 weight ratio (10% margin for wastage) **Scenarios:** • 5% decrease in drug costs for company base case (0.84 weight ratio 76% female), + 0.9 ratio and 50% female (committee preferred) • 5% increase for 0.9 ratio and 76% female (EAG preferred)
% of female patients	76% (BOI study)	76% (BOI study) **Scenario:** 50% female
SMR	Same as ECM2 Pegzilarginase: GMFCS I-II (1.16 and 1.32), GMFCS III+ half of IDM SMR	Same as company **Exploratory analysis:** SMRs from HST18 (ECM1 company base case)
QALY weighting	Full QALY weighting	N/A (committee decision)

ARG1-D: Arginine-1 deficiency; BOI: burden of illness; GMFCS: Gross Motor Function Classification System; ICER: Incremental cost-effectiveness ratio; IDM: individualised disease management; QALY: quality-adjusted life-year; SMR: Standardised mortality ratio

Overview of EAG analyses

EAG undertook exploratory analyses for 16 scenarios combining committee preferences and company's proposed changes:

- The % of patients with an improved diet resulting in utility gains
- The assumed weight ratio between people treated with pegzilarginase and the general population
- The % of pegzilarginase-treated patients that are female
- QALY weighting (50% v full).

Table: Preferred scenarios

	Company	Committee	EAG
% with improved diet	0.833	0.485	0.485
Weight ratio	0.84	0.90	0.90
% female	0.76	0.5	0.76

EAG: external assessment group; ICER: incremental cost-effectiveness ratio

EAG exploratory analysis results (1/2)

Table: Deterministic results

	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight[2]
Company base case	[redacted]	[redacted]	32.09	[redacted]	£98,804	[redacted]
Committee preferred assumptions base case	[redacted]	[redacted]	32.22	[redacted]	£165,807	[redacted]

Table: Probabilistic results

	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight[2]
Company base case	[redacted]	[redacted]	32.42	[redacted]	£102,186	[redacted]
Committee preferred assumptions base case	[redacted]	[redacted]	31.71	[redacted]	£169,650	[redacted]

Results include confidential commercial discount for pegzilarginase.

NOTE: company ICERs have full weighting; committee have 50% weighting (preferred at ECM2).

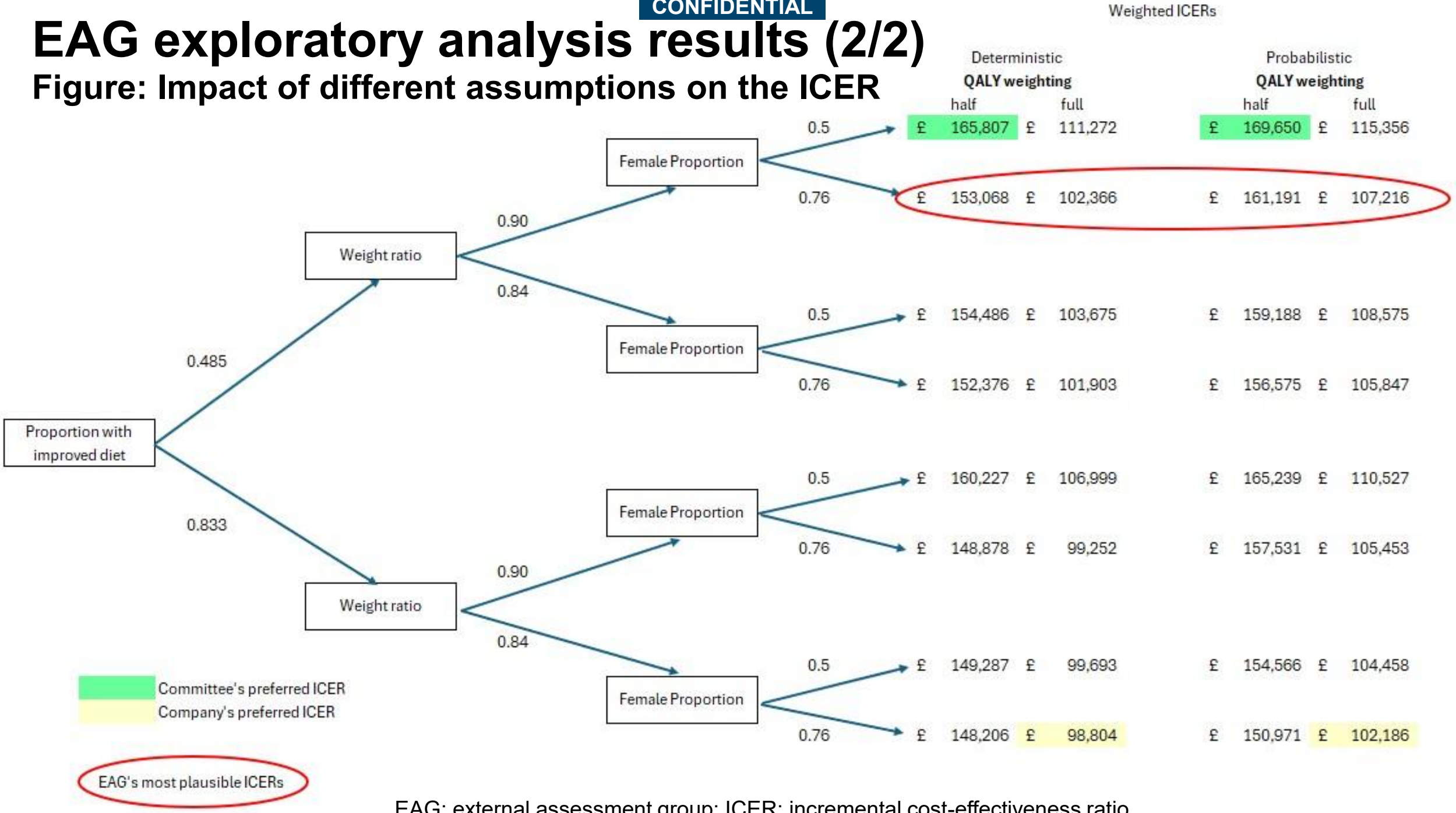
[1]Undiscounted

[2]Calculated using undiscounted QALY gains

EAG: external assessment group; ICER: incremental cost effectiveness ratio; LYGs: life years gained; QALYs: quality-adjusted life-years

EAG exploratory analysis results (2/2)

Figure: Impact of different assumptions on the ICER



EAG: external assessment group; ICER: incremental cost-effectiveness ratio

Overview of additional EAG analyses

EAG also explored impact of two additional factors:

- Adjusting pegzilarginase costs to explore impact of assuming that weight distributions (rather than fixed average weight) would result in some patients needing different numbers of vials. (see weight key issue):
  - 5% reduction in costs for 0.84 weight ratio, 76% female (company base case).
  - 5% reduction for 0.90 weight ratio, 50% female (committee preferred ECM2).
  - 5% increase for 0.90 weight ratio, 76% female (EAG preferred).

- Applying SMRs used in original company base case, based on SMRs for metachromatic leukodystrophy (HST18, see appendix).

EAG: external assessment group; ICER: incremental cost-effectiveness ratio

Additional EAG analyses: Weight modelling

Table: Probabilistic ICERs from selected scenarios when the estimated acquisition costs are modified

	Weight Ratio	Female Proportion	QALY weighting	Assumed change in total costs	Probabilistic ICER
Company's preferred scenario	0.84	0.76	Full	-5%	£97,672
Committee's preferred scenario	0.90	0.50	Half	-5%	£162,629
Committee's preferred scenario, full QALY weighting	0.90	0.50	Full	-5%	£110,898
EAG's most plausible scenario 1	0.90	0.76	Half	+5%	£167,523
EAG's most plausible scenario 2	0.90	0.76	Full	+5%	£113,080

ICER: Incremental Cost Effectiveness Ratio; QALY: quality-adjusted life years

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Other considerations

Potential for managed access

- Managed access not proposed by the company

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ECM3 key issues for discussion - recap

Key issue	Question for committee	Impact on ICER
Utility gain associated with improved diet	• What utility gain should be applied? • What proportion of people should utility gains be applied to?	**Moderate**
Pegzilarginase weight-based dosing costs • Proportion of female/male patients • Weight ratio to the general population • Distribution of weight (vial wastage)	• What proportion of females/males should be assumed in the model? • What is the most appropriate weight ratio to use? • Should costs be adjusted due to averaged weight use?	**Large**
Criteria for applying a QALY weighting	• What QALY weighting should be applied?	**Large**

DG: draft guidance; EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALY; quality-adjusted life-year; SMR: standardised mortality ratio.

Pegzilarginase for treating arginase-1 deficiency

Supplementary appendix

NICE National Institute for Health and Care Excellence

Patient and carer perspectives (1/2)

ARG1-D has significant impact on quality of life of patients and carers and high demand on the NHS

Submissions from Metabolic Support UK and 2 patient experts:

- ARG1-D has a profound impact on patients, parents and carers, including physical and mental health and social and work life ➔ For patients, it leads to premature death

"Before the onset of the symptoms, [he] enjoyed life fully, was very active and an outdoor person, made friends and socialised. [He] can no longer do any of the above and lost confidence and feels confined and not able to participate with others."

"On two occasions the arginase-1 deficiency condition has also led to extremely traumatic temporary loss of eyesight 'cortical blindness' for the patient (where the patient was asking if she was still alive)"

"I have had to step back from an Executive/Director level career, utilise annual leave days for appointments and furthermore work longer hours to juggle priorities."

- High demand on healthcare system ➔ Regular medical appointments with various specialists and hospitalisations, including for life-threatening emergencies

"Unplanned visits can vary year on year, from not frequent, to, very common and frequent in our experience sometimes, up to 3 - 4 a year."

"Their care needs now are extremely high. They go to day centres, but the care outside of that is non-stop: they require fulltime personal care. Each of them is a wheelchair user, none of them can walk. For all of them, their speech deteriorated with time, my brother lost his speech, and my two sisters have speech difficulties but they can still speak and have gone to speech therapy.

Patient and carer perspectives (2/2)

Pegzilarginase could potentially fulfil the unmet need for disease-modifying treatments for ARG1-D

Submissions from Metabolic Support UK and 2 patient experts:

- Significant unmet need for disease-modifying treatments for ARG1-D ➔ Currently, only managed by strict dietary management plans and ammonia scavengers and low protein diet can be extremely burdensome
- Delays can occur in diagnosis of condition

"All we could do was maintain a strict diet, and give Ravicti to slow down the disease."

"low protein diet is based on the weight of the person with ARG1d which is very demanding for caregivers. Additionally, accessing low protein food can also be challenging. None of the staple food items can be bought in the supermarket. All are prescribed. There have been numerous occasions where the pharmacy has not been able to supply bread or milk."

- Pegzilarginase has potential to fulfil this unmet need ➔ Disease modifying treatment, improves clinical outcomes and improves quality of life of patient and carers

"The true value of this treatment is in the improvement it provides to the lives of patients with Arginase Deficiency and the impact of this on family and carers."

"we know that some families saw symptoms reserve, with physical improvements most commonly observed.

- Lifelong treatment, travelling to specialised centres and product unavailability could be potential disadvantages of pegzilarginase

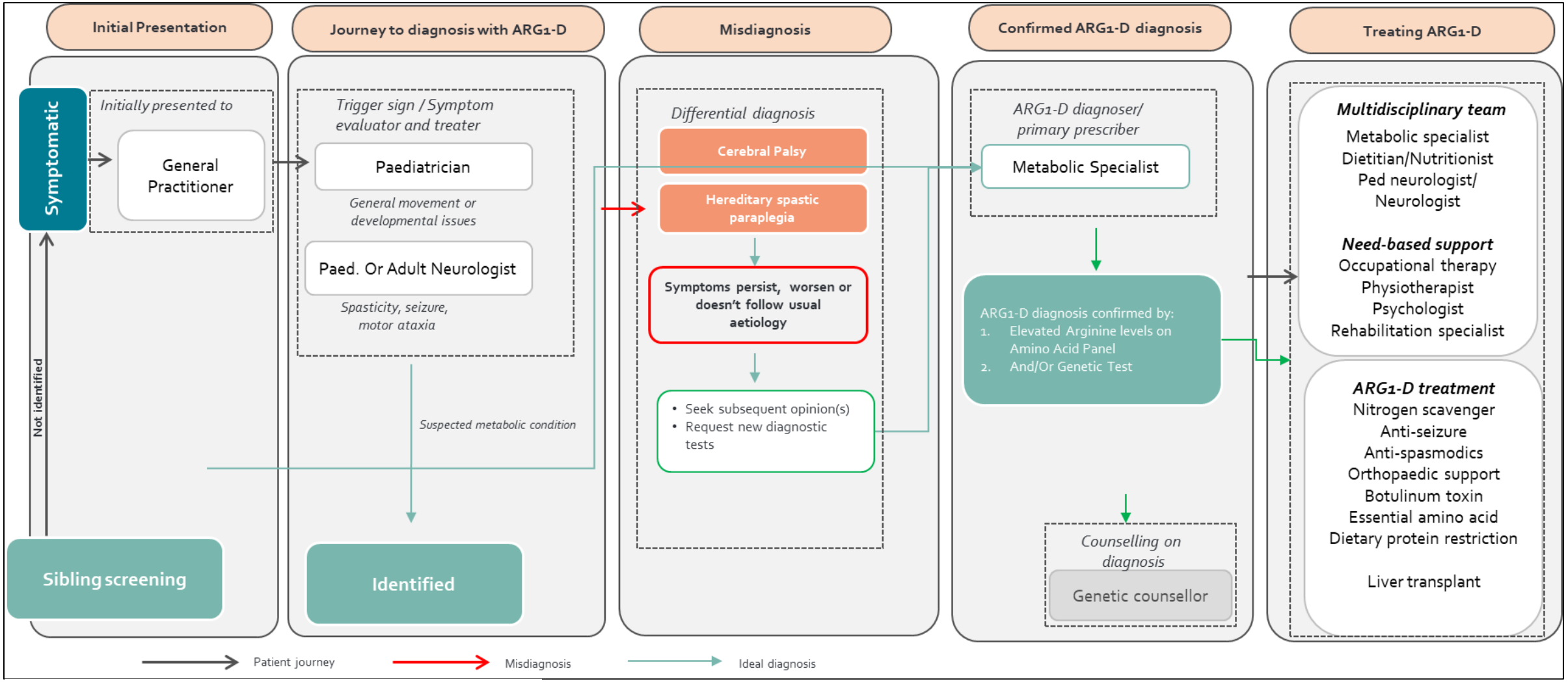
Clinical expert perspectives

Pegzilarginase is a step change treatment for ARG1-D

- Aims of ARG1-D treatment are to reduce arginine levels, prevent disability, delay progression and improve health related quality of life
- Multiple complications of ARG1-D including hyperargininemia, osteoporosis, pancytopenia and hepatic adenomas ➔ Some people may need liver transplant
- Current standard treatment for ARG1-D is dietary management plans and ammonia scavengers
  - Reduction of plasma arginine to target levels is almost never attained
  - Progression is common with physical and cognitive deterioration
  - Dietary management is extremely restrictive and difficult to adhere with
- Pegzilarginase is a step change treatment
  - Reduces arginine to within target levels, potentially stabilises disease and improves functional mobility
  - Additional benefits include liberalising extremely restrictive diet, or reduce or stop medications
- There are some considerations for starting pegzilarginase
  - More frequent blood tests would be required for arginine and ammonia level to get the optimum dose
  - People with non-reversible disabilities and who do not have high ammonia may not benefit from this treatment

Treatment pathway

Figure: Current clinical care pathway for ARG1-D patients in England



Source: Company submission, Figure 10

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ARG1-D: Arginase-1 deficiency

ECM2 key issues

Key issues from ECM2	Resolved?
3.5 Company's modelling approach	Yes
3.6 Starting distributions by GMFCS health states	Yes
3.7 Transition probabilities for pegzilarginase	Yes
3.8 Transition probabilities for standard care arm	Yes
3.9 Transition from GMFCS-2 and -3 to GMFCS-5 after hyperammonaemic crisis	Yes
3.10 + 3.11 Life expectancy	Yes
3.12 Distribution of peak ammonia levels during hyperammonaemic crisis	Yes
3.13 Source of utility values	Yes
3.14 Utility gain associated with improved diet	No
3.15 Disutility associated with cognitive disability	Yes
3.16 Carer disutility	Yes
3.17 Pegzilarginase dosing and drug wastage	Yes
3.18 Pegzilarginase weight-based dosing costs	No
3.19 Pegzilarginase treatment discontinuation	Yes
3.20 Criteria for applying a QALY weighting	No

DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio

Clinical effectiveness evidence: BOI study

Table: BOI study design

Design	Cross-sectional, international, multi-centre survey
Population	Patients with ARG1-D (n=43) and their caregivers. Patients receiving pegzilarginase as part of a short term early access program were eligible; those receiving longer-term treatment (i.e. in clinical trials) were excluded. Mean age: 16.7 for patients and 44 for caregivers 76% of patients and 63% of caregivers were female
Survey design	Web-based questionnaire with 12 questions; Part 1 concerned the patient and Part 2 concerned the caregiver. Questions included: • demographics • symptoms (using GMFCS) • ability to work • health-related quality of life (EQ-5D-5L) • caregiver burden.
Method of data collection	Invited to participate either at clinic or over the phone, and then given an invitation letter. The questionnaire was completed by the patient and/or caregiver at the clinic or at home using a link from the letter.
Locations	France, Portugal, Spain, UK

Source: Olofsson et al. 2024

ARG1-D: Arginase-1 deficiency; BOI: burden of illness; GMFCS: Gross Motor Function Classification System

Clinical effectiveness evidence: Overview

Table: PEACE and Study 101A/102A design and outcomes

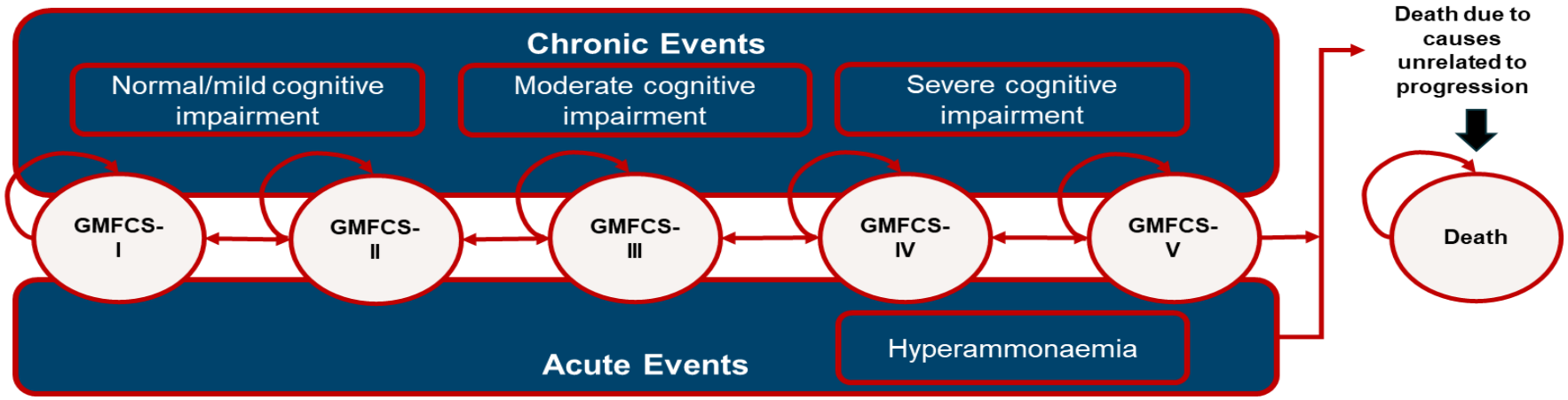
	PEACE	Study 101A	Study 102A
Design	Phase 3, randomised, double-blind, placebo-controlled, multicentre	Phase 1/2, open-label, multicentre	Phase 2, open-label, multicentre, long term extension (LTE) of Study 101A
Population	Patients aged 2 years and older with ARG1-D		
Intervention	Pegzilarginase plus individualised disease management (IDM)		
Comparator	Placebo plus IDM	NA	NA
Duration	24 weeks placebo controlled randomised followed by 150 weeks single arm LTE	20 weeks	Up to 3years
Primary outcome	• Plasma arginine concentration • Level of ornithine and guanidino compounds • Mobility • Adaptive behaviour	• Neurocognitive function • Adverse effects of treatment • Health-related quality of life • Overall response rate	
Locations	US, UK, France, Canada, Austria, Germany and Italy	US, UK Portugal, Canada	

- Evidence from PEACE is main data source used in economic model, whilst evidence from Study 101A/102A is also used
- Evidence from a burden of illness (BOI) survey (a European survey of resource use and health related quality of life in people with ARG1-D and their caregivers) is used to inform utility values in the model

ARG1-D: Arginase-1 deficiency; NA: Not applicable

Company's model structure (ECM1)

Figure 4: Model structure



Source: adapted from EAR, Figure 10

Model structure	Cohort-level Markov
Time horizon and perspective	Lifetime (87 years) NHS and PSS perspective
Discount rate	3.5% per annum for both health outcomes and costs

NICE Technical Team:

- Update to structure from ECM1: people in GMFCS-I and –II can transition to GMFCS-V following severe HAC.

GMFCS: Gross Motor Function Classification System; HAC: hyperammonaemic crisis; PSS; Personal social services

NICE technical team issue: SMRs in the model

Large impact

NICE technical team comments

- Inconsistent use of HST18 SMRs – company argue MLD is a valid proxy condition, but only use low SMRs from HST18 in states 1 and 2.
- Unclear why company changed base case from ECM1 (where all HST SMRs were used) – case for change not compelling (and not requested by committee).
- Company use very high SMRs in health states 3-5 – assuming pegzilarginase has very high effectiveness in health states 1 and 2 but very low efficacy in health states 3-5.
- Reverting to ECM1 company base case increases ICER substantially (see next slide).

Table: The SMRs applied in different analyses

Health State	ECM2 company base case		EAG exploratory analyses/ECM1 company base case		Committee preferred at ECM2/ECM3 company base case	
	IDM	Peg	IDM	Peg	IDM	Peg
GMFCS-I	67.42	1.16	67.42	1.16	88.89	1.16
GMFCS-II	83.71	1.32	83.71	1.32	101.15	25.29*
GMFCS-III	193.22	96.61	193.22	1.80	137.94	68.97
GMFCS-IV	1414.46	707.23	1414.46	1.80	137.94	68.97
GMFCS-V	118.12	59.06	118.12	8.14	623.47	311.74

*calculated as 25% of IDM

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EAG: external assessment group; GMFCS: Gross Motor Function Classification System; HST: highly specialised technology; IDM: individualised disease management; SMR: standardised mortality ratio.

Additional EAG analyses: SMR

Table: Probabilistic results when SMRs from HST18 are used

	Preferred scenario	SMRs from HST18
Company's base case, full QALY weighting	£102,186	£113,110
Committee, half QALY weighting	£169,650	£126,048
Committee, full QALY weighting	£115,842	£189,892
EAG, half QALY weighting	£161,191	£178,765
EAG, full QALY weighting	£107,216	£121,293

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ICER: Incremental Cost Effectiveness Ratio; QALY: quality-adjusted life years