For PRESENTATION – confidential information redacted

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Highly Specialised Technology Appraisal Committee [22nd May 2025]

2nd committee meeting

Chair: Paul Arundel

External assessment group: Sheffield Centre for Health and Related Research

Technical team: Lauren Elston, Alan Moore, Rich Diaz

Company: Immedica

Pegzilarginase for treating arginase-1 deficiency

- ✓ **Background and key issues**
- ❑ Key issues – transitions/effectiveness
- ❑ Key issues – utilities
- ❑ Key issues – drug usage
- ❑ Other Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

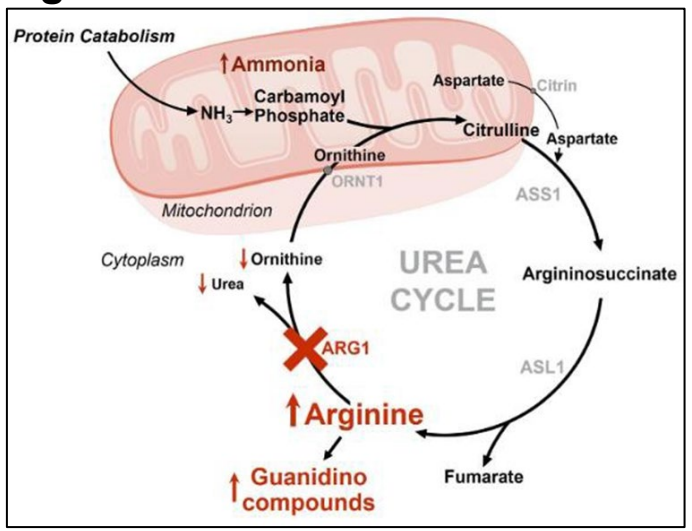
Background on arginase-1 deficiency (ARG1-D)

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

Causes

- A urea cycle disorder in which 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 hyperargininemia

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

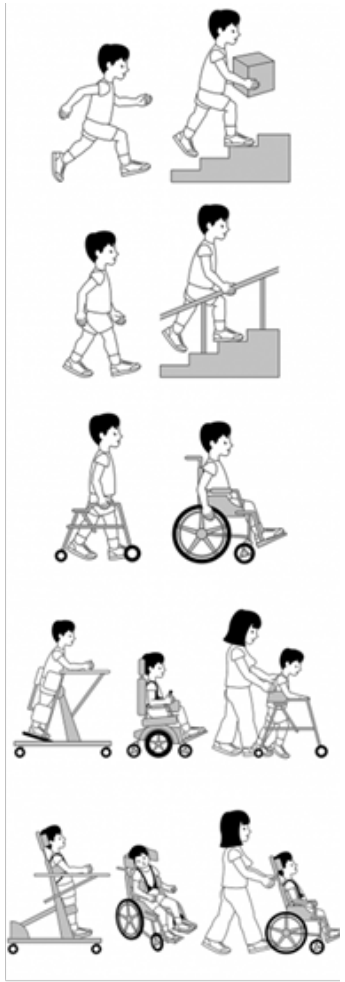
Symptoms and prognosis

- Increased morbidity and mortality and reduced quality of life ➔ Median age of death is ~17 years with very few patients surviving 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



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 3.21:** 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.

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

*More ECM1 recap in appendix

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

Draft guidance recommendation

Pegzilarginase is not recommended, within its marketing authorisation, for treating arginase-1 deficiency (also called hyperargininemia) 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
- Uncertainties in the economic model included:
    - Whether the distributions by disease severity represented NHS clinical practice
    - Assumptions on mean age at the start of each GMFCS group for NHS clinical practice
    - How pegzilarginase affects body weight and levels of ammonia in the blood
    - How long people stay on pegzilarginase treatment, treatment effect, and life expectancy gains
- The most likely ICERs were substantially above the acceptable range for HSTs

ICER: incremental cost-effectiveness ratio.

Stakeholder responses to Draft Guidance

Submissions from Metabolic Support UK, 1 patient expert and 2 clinical experts (combined submission):

- In not recommending pegzilarginase, the committee has not fully understood or taken into account the high level of unmet need, or the high physical and psychological burden of ARG1-D on patients and carers.
- ARG1-D is associated with progressive neurological deterioration and people continue to decline without therapy.
- Evidence from patients and carer demonstrates that pegzilarginase has hugely beneficial impact on patients' and their families' quality of life.
- People on pegzilarginase had improved mobility and cognitive ability; they were able to live a more normal life for their age, come out of isolation and socialise, hugely improving mental wellbeing for patients, carers and family members.

"Patients and families are holding onto hope for ARG1-D treatment and improvement in health and quality of life, that is only possible from receiving pegzilarginase treatment."

Note: Stakeholder responses also discussed in later key issue slides

ARG1-D: Arginine-1 deficiency

ECM1 committee conclusions (1/3)

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	Committee would like to see results of an alternative modelling approach as a scenario analysis, in which mean starting age varies according to GMFCS health state. This would likely be a more appropriate modelling of the condition.
3.6 Starting distributions by GMFCS health states	Starting distributions of people across each GMFCS health state informed by European burden of illness survey was most appropriate option.
3.7 Transition probabilities for pegzilarginase	Assuming people in pegzilarginase arm remain in same GMFCS health state after 3 years is appropriate for decision making, but this was associated with high levels of uncertainty.
3.8 Transition probabilities for standard care arm	EAG's base-case approach to model transition probabilities for standard care more reflective of clinical expert estimates of time taken to progress to more severe GMFCS health states; • mean of PEACE, Study 101A and Study 102A used as the starting GMFM-DE score for people in the GMFCS 1 health state • reduction in GMFM-DE score of 2.66 per year • inverse of time spent in a GMFCS health state converted to a probability.

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

ECM1 committee conclusions (2/3)

DG section	Committee conclusion
3.9 Life expectancy	Requested further analyses around mortality, including scenario analyses around standardised mortality rates (SMRs) and life years gained by GMFCS health state. The scenario analysis in which nearly all people in the standard care arm die at age 50 is appropriate.
3.10 Distribution of peak ammonia levels during hyperammonaemic crisis	Likely that a few incidences of high levels of peak ammonia may still occur with pegzilarginase but values in EAG's scenario were potentially too high.
3.11 Source of utility values	Health state utility values used in the company's base case are appropriate for decision making.
3.12 Utility gain associated with improved diet	Company's assumed utility gain associated with improved diet in the pegzilarginase arm is appropriate for decision making.
3.13 Disutility associated with cognitive disability	Company's approach to applying treatment-specific cognitive disutility for GMFCS health states 1 to 3 is uncertain. But it also recognised that this approach is supported by clinical expert advice and may be conservative. The committee concluded it is appropriate to apply treatment-specific cognitive disutility in GMFCS-1 to GMFCS-3 health states.

DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

ECM1 committee conclusions (3/3)

DG section	Committee conclusion
3.14 Carer disutility	Uncertainty in carer disutility values but concluded that values used in the base-case model are acceptable for decision making.
3.15 Pegzilarginase dosing and drug wastage	• NICE technical team's scenario analyses using heavier weights are more plausible, that is, assuming adults would weigh 95% of the expected general population weight on pegzilarginase treatment. • The level of drug wastage, including 10% weight margin, is uncertain.
3.16 Pegzilarginase treatment discontinuation	A 2% pegzilarginase annual discontinuation is appropriate, but uncertain. The committee also concluded that the absence of an analysis based on responders and non-responders to pegzilarginase treatment in the model is acceptable because this would be difficult to implement with the available data.
3.17 Criteria for applying a QALY weighting	The committee could not apply a QALY weighting at this stage because of high uncertainty around key model parameters. It requested further input on these from consultation with stakeholders.

DG: draft guidance; QALY: quality-adjusted life-year

ECM1 committee requests (Draft Guidance)

Committee requests from ECM1	Updated?	Resolved?	ICER impact
3.6 Starting distributions by GMFCS health states Further details on the current population with the condition in the NHS in England.	No	No	Large
3.5 Company's modelling approach An alternative modelling approach which varies mean age according to the GMFCS health state (scenario).	Yes	No	Moderate
3.9 Life expectancy Further analyses around mortality, including further scenario analyses around standardised mortality rates and life years gained by GMFCS health state.	Yes	No	Large
3.15 Pegzilarginase dosing and drug wastage (and weight) The committee requested data (from trials and clinical expert opinion) on the impact of pegzilarginase on weight over someone's lifetime.	Yes	No	Large
3.16 Pegzilarginase treatment discontinuation It concluded that a 2% pegzilarginase discontinuation is appropriate, but uncertain.	Yes	No	Large
3.9 and 3.11-3.14 clinical input on the relevance of metachromatic leukodystrophy and familial chylomicronaemia syndrome to arginase-1 deficiency	No	No	Large

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

Key additional changes from company

Changes from ECM1 (EAG response section)	Impact on ICER
Adjusting the compliance assumed for those receiving pegzilarginase treatment (2.1)	Large
Including additional disutility for carers with more than one child with ARG1-D (2.5)	Moderate
Altering the methodology used to determine the utility of patients in each GMFCS health state and the impact of cognitive impairments (2.8)	Large
Increasing the proportion of patients who receive a utility gain due to an improved diet whilst on pegzilarginase treatment to 83.3% (2.9)	Moderate
Revising time spent in each health state for patients on IDM (2.10)	Large
Assuming that each year 5% of patients move from GMFCS-II and -III to GMFCS-V (2.11)	Moderate

ARG1-D: Arginine-1 deficiency; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio; IDM; individualised disease management; PSA; probabilistic sensitivity analysis.

Changes not up for discussion

The EAG and the NICE technical team did not identify these changes as key issues

Changes from ECM1	Impact on ICER
Distribution of peak ammonia levels during hyperammonaemic crisis (response to DG 3.10)	Small (but EAG highlight uncertainty in PSA)
Adding in costs associated with death (EAG response section 2.3)	Small
Adjusting the costs associated with diet management for patients receiving pegzilarginase (EAG response section 2.4)	Small
Correcting a minor error in the trace for pegzilarginase and IDM when applying cognitive disutilities (EAG response section 2.14)	Small

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

Key issues

Key issues	
Transitions	**Impact**
Starting distribution by GMFCS state	LARGE
Company's modelling approach to starting age	MODERATE
Time spent in GMFCS states for patients on IDM	LARGE
5% patients move from GMFCS-II and II to IV	MODERATE
Disease progression with pegzilarginase	LARGE
Life expectancy	LARGE
Utilities	
Changed methodology on utilities for cognitive impairment	LARGE
Increased proportion of patients receiving improved diet utility	MODERATE
Additional carer disutility for more than 1 child	MODERATE
Cost of pegzilarginase	
Pegzilarginase dosing per kg	LARGE
Weight thresholds for use of additional vials (wastage)	LARGE
Weight of people on pegzilarginase over lifetime	LARGE
How weight is modelled	LARGE
Compliance with pegzilarginase	LARGE
Treatment discontinuation rate	LARGE
Other issues	
QALY weighting	LARGE

GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio; IDM; individualised disease management; PSA; probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

Overview of EAG analyses

- EAG undertook exploratory analyses to address the key issues identified; EAG base case not possible.
- Many changes related to using alternative plausible assumptions, rather than fundamental disagreement with company assumptions.
- Grouped into 3 categories: C1, C2, C3

Table: Classification of EAG changes

Group	Description
C1	Where the EAG believes that their alternative assumptions, or values, that are likely to be strongly preferable to those used by the company in its base case
C2	Where the EAG believes that alternative assumptions are plausible, but there is no clear reason to strongly prefer these to one of the company's assumptions or the assumptions used in a C1 EAG sensitivity analyses. However, these should be given due consideration by the Appraisal Committee
C3	Where the EAG believes it unlikely that the assumptions are preferable to that in the company's base case, but believes that the analyses may be useful for the Appraisal Committee in determining upper or lower bounds of the ICER based on changing these assumptions in isolation

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

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ✓ **Key issues – transitions/effectiveness**
- ❑ Key issues – utilities
- ❑ Key issues – drug usage
- ❑ Other Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Large impact

Key issue: Starting distribution by GMFCS states

Recap (ECM1, see DG 3.6):

- Company uses pooled data from PEACE, Study101A/102A and BOI survey to inform starting distribution across GMFCS states in base case.
- EAG: Clinical advice suggests distribution of patients across GMFCS states may be more representative in European BOI survey than in clinical studies where more severe patients may be underrepresented.
- NICE technical team: clinical expert input could be informative for NHS population.
- Committee: starting distributions informed by European BOI survey most appropriate option; requested further details on current population with the condition in the NHS in England.

Company (response to DG)

- Disagrees with committee's conclusion that European BOI more representative than company approach.
- Results from Delphi study showed consensus that company approach reflects UK clinical practice.

EAG comments

- EAG analysis includes starting distributions as in the BOI study.

NICE Technical Team:

- Starting distribution should reflect current NHS population eligible for pegzilarginase.
- Stakeholder responses to draft guidance suggest more severe population currently in NHS compared to company's modelling.

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio

Large impact

Starting distributions between GMFCS health states - Company revised base case and EAG analysis

Stakeholder comments (Clinical experts, based on clinician survey with support from Metabolic UK)
Clinician survey (of 12 clinicians, 7 from England), English patients;

- Paediatrics (n=9): GMFCS level 1 = 7/9, level 2 = 1/9, level 3 = 0/9, level 4 = 0/9, level 5 = 1/9
- Adults (n=12): GMFCS level 1 = 2/12, level 2 = 1/12, level 3 = 3/12, level 4 = 2/12, level 5 = 4/12

Table: Starting distributions by GMFCS health states

	I	II	III	IV	V	Source
Company base case	48.44%	34.38%	3.13%	12.50%	1.56%	**Pooled data from the PEACE study, study 101A/102A, and BOI survey (n=[redacted])**
Committee preferred	50.00%	31.25%	0.00%	12.50%	6.25%	**BOI survey (n=[redacted])**
Clinical experts DG comments	~43%	~10%	~14%	~10%	~23%	**Clinician survey (clinical experts) – distribution based on English patients (n=21)**

What distribution by GMFCS health states should be assumed at the start of the model?

NICE

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

Moderate impact

Key issue: Company's modelling approach to starting age

Recap (ECM1, see DG 3.5):

- In company base case, the same starting age was used across all GMFCS health states (13 years).
- Committee: current approach does not match clinical practice. Requested alternative scenario where mean age varies by health state.

Company (response to DG)

- Average ages for each health state determined by consensus in Delphi panel.
    - GMFCS I: 11 years
    - GMFCS II: 12 years
    - GMFCS III: 16 years
    - GMFCS IV: 25 years
    - GMFCS-V: 15 years; this is lower than GMFCS-IV due to people who transition from GMFCS-II and –III due to severe HACs resulting in permanent and substantial decline in health.

EAG comments

- Used company's proposed ages; explored limitations in company's modelling approaches (in other issues)

NICE Technical Team:

- Starting model age appears young given that high proportion of current NHS population are adults

Are the proposed ages for each health state appropriate?
Is a modelled starting age of 13 years appropriate?

BOI: Burden of illness; DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

Large impact

Key issue: Time spent in GMFCS states for IDM

Recap (DG 3.8):

- Company original base case: GMFM-DE scores used to model long-term progression for IDM, using midpoints between lower CI for better health state and upper CI for the worse health state. An annual reduction of 1.45 in the GMFM-DE score was assumed.
- Committee conclusion: EAG base case more reflective (reduction of 2.66 in the GMFM-DE score).

Company (response to DG)

- Annual decrease changed from 2.66 to 3.17; assumes linear reduction from maximum GMFM-DE score of 111 to minimum score of 0 over a 35-year period
- GMFM-DE cut-offs for GMFCS states are redefined to ensure the average age (based on Delphi panel) occurs halfway through the time spent in each GMFCS state

EAG comments

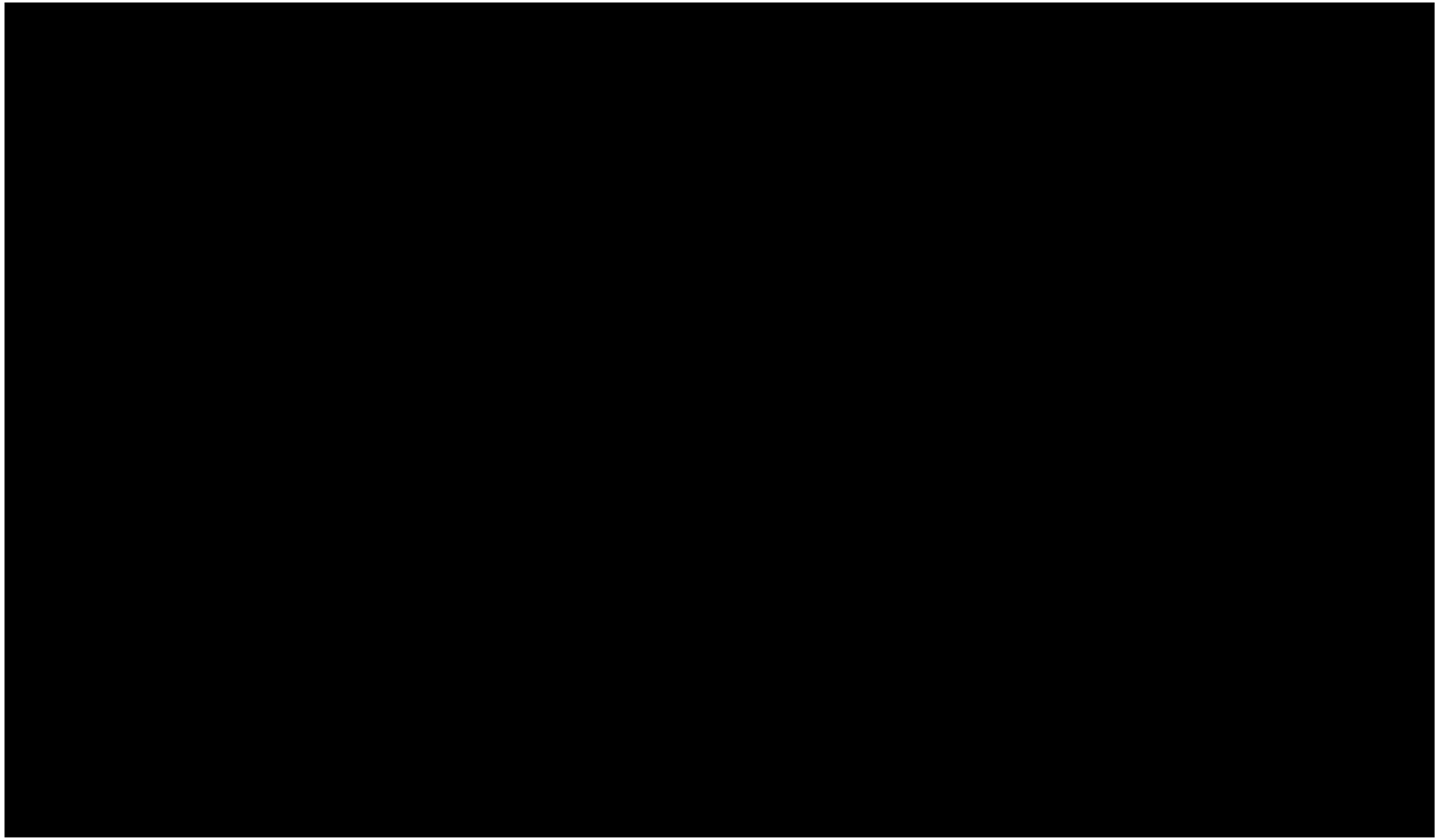
- No rationale was provided for the change in GMFM reduction
- New approach is reliant on several assumptions that are uncertain; no clear reason to think it is superior to the original EAG base case
- Average ages from Delphi panel should have been used rather than GMFM-DE score ranges (applied in EAG C1 analyses); indicate slower progression through GMFCS-II and III.

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; GMFM-DE: Gross Motor Function Measure; IDM; individualised disease management;

Large impact

Key issue: Time spent in GMFCS states for patients on IDM (1/2)

Figure: Assumed linear relationship between age and GMFM-DE score with mean age distribution across GMFCS health states



NICE

GMFM-DE: Gross Motor Function Measure; GMFCS: Gross Motor Function Classification System; IDM; individualised disease management

Large impact

Key issue: Time spent in GMFCS states for patients on IDM (2/2)

Table: GMFM-DE score cut-off and estimated progression probability for patients receiving IDM

	Observed GMFM-DE score (n=22), mean (95% CI)	EAG analysis (ECM1)			Company's new submission		
		Cut-off of GMFM-DE	Estimated time spent within each health state (years)	Transition probability per cycle	Cut-off of GMFM-DE	Estimated time spent within each health state (years)	Transition probability per cycle
GMFCS-I	[redacted]	104-92	4.5	[redacted]	78–75	1.0	[redacted]
GMFCS-II	[redacted]	92-58	12.8	[redacted]	75–67	2.5	[redacted]
GMFCS-III	[redacted]	58-24	12.8	[redacted]	67–46	6.5	[redacted]
GMFCS-IV	[redacted]	24-6	6.9	[redacted]	46–21	8.0	[redacted]

Is the company's updated approach to time spent in each GMFCS state appropriate? If not, what analysis should be used for decision-making?

EAG: external assessment group; GMFM-DE: Gross Motor Function Measure; GMFCS: Gross Motor Function Classification System; IDM; individualised disease management

Moderate impact

Key issue: 5% patients move from GMFCS-II and III to V

Recap (DG 3.8):

- Company original base case: sequential progression through GMFCS health states until reaching GMFCS-V or death.

Company (response to DG)

- Updated assumption that patients in GMFCS-II and -III could move straight to GMFCS-V after a severe HAC.
- Delphi consensus: 5-10% patients progress from GMFCS-II to GMFCS-III per year.
- Conservative approach: 5%.

EAG comments

- Two key concerns:
  - Company assumed transitioning from GMFCS-II and –III to GMFCS-V in pegzilarginase arm does not happen.
  - Clinicians explicitly said transition would happen in early childhood; company modelled for all ages.
- C1 analyses: transition is not possible for ages 16 and over; transition can occur in pegzilarginase arm.

Should any updated transitions be included in committee preferences?

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

Key issue: Disease progression with pegzilarginase

Large impact

Recap (DG 3.7):

- Company original base case: For pegzilarginase, company assumed no disease progression after 3 years; all patients remain in GMFCS state that they were in at 3 years.
- Clinical advice to EAG: remaining in same state after 3 years plausible; but EAG noted uncertainty due to lack of clinical evidence (PEACE study had short follow-up)
- Committee conclusion: Assuming people in pegzilarginase arm remain in same GMFCS health state after 3 years is appropriate for decision making, but associated with high levels of uncertainty.

NICE technical team:

- Highly uncertain if pegzilarginase prevents disease progression in all cases over the lifetime
- Committee may want to consider impact of scenarios of assuming some disease progression on treatment as cost-effectiveness results are highly sensitive to this assumption

EAG comments:

- Included scenarios (C2) changing transition probabilities for pegzilarginase so that after 3 years of treatment risk to transition to next worse GMFCS state is 10% of that associated with IDM and 20% of that associated with IDM.

Stakeholder comments (Metabolic UK)

- Some people continue to experience HACs while on pegzilarginase (based on responses from community survey and HCPs).

Should any disease progression be assumed for some people treatment with pegzilarginase?

EAG: external assessment group; GMFCS: Gross Motor Function Classification System; HCP; health care practitioner; IDM; individualised disease management, HAC; Hyperammonaemic crisis

Large impact

Key issue: Life expectancy (1/3)

Recap:

- Company's original base case: nearly all patients receiving IDM die by 35 years of age; applied SMRs from MLD (HST 18) for pegzilarginase (modified to remove treatment toxicity) and applied multiplier to obtain SMRs for IDM.
- EAG: Clinical advice suggests all dying by 35 unlikely and 1 person in BOI study was 49. Scenario analysis assuming nearly all patients died before 50.
- Committee concluded this scenario was appropriate but requested further scenarios to address uncertainty including the appropriateness of using MLD SMRs.

Company (response to DG):

- Did not accept committee-preferred (EAG) scenario; instead, used Delphi panel to recalibrate SMRs.
- Company state there is Delphi consensus on 3 points: diagnosis occurs ~5.1 years; mortality distribution in IDM arm by GMFCS state; 90% receiving IDM die by 32.
- New base case:
  - All patients in model were assigned GMFCS-I with starting age 5.1 years
  - Multiplication factor applied so that at 50 years, 99% of IDM-treated patients had died
  - Individual multipliers for each health state based on Delphi panel distribution of deaths (exc. HACs); pegzilarginase SMRs: GMFCS I-II from previous submission, GMFCS III-V set to half of IDM.
  - GMFCS-V further adjusted so 90% mortality by 32 years.

DG: draft guidance; EAG: external assessment group GMFCS: Gross Motor Function Classification System; HAC: hyperammonaemic crisis; ICER: incremental cost-effectiveness ratio; IDM: individualised disease management; MLD: Metachromatic leukodystrophy; SMR: Standardised mortality ratio

Large impact

Key issue: Life expectancy (2/3)

EAG:

- Many limitations around company's new approach, including uncertainty in:
  - Delphi panel estimates - proportion of responses were 'somewhat agree', whether this = consensus is debatable; uncertainty compounded by having this issue in all 3 components.
  - Methodology used to calibrate SMR for GMFCS-V to be markedly lower than GMFCS-IV; would expect higher SMR in a more severe state, which raises concerns over face validity & methods to derive SMRs.
  - Cannot determine if approach to pegzilarginase-treated patients are conservative (as company state) due to uncertainty in long-term OS; increasing SMR in more severe states likely benefits pegzilarginase.
- EAG analysis:
  - IDM: common multiplier applied to each health state so that 10% alive at 32 and 0.05% alive at 50 (C1);
  - Pegzilarginase: all SMRs are half that of IDM-treated patients to show impact on all GMFCS states (C2).

NICE Technical Team:

- 1.16 and 1.32 SMRs suggests almost a cure in stages 1 and 2 – most people are assumed to remain in stages 1 and 2 on pegzilarginase in the company model
- Company state in other key issues that some impact from disease will occur before pegzilarginase treatment
- DG stakeholder responses stated that HACs still occurred for some treated with pegzilarginase
- Company have not provided further evidence, as requested by the committee, on the appropriateness of using HST18 (MLD) SMRs for this condition, NICE notes HST18 refers to a gene therapy treatment for MLD
- In company base case, it is estimated that the average life years gained from pegzilarginase is >44 years compared to IDM

EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: Incremental cost-effectiveness ratio; IDM: individualised disease management; SMR: Standardised mortality ratio, HAC: Hyperammonaemic crisis

Large impact

Key issue: Life expectancy (3/3)

Stakeholder comments (Clinical experts, Metabolic UK)

- Clinician survey:
  - 8 clinicians responded to a question about whether they expect life expectancy to be positively affected by pegzilarginase – 7/8 (87.5%) responded "yes".
    - Of those who expected positive impact on life expectancy, 5 commented on duration of impact and indicated that they thought this could extend from "many years" to "normal life".
- No disease could exactly mimic Arginase 1 deficiency. MLD is a close comparator for mobility and cognitive impact, but it does not cover risks of hyperammonaemia.

Table: SMRs in company's revised base case and EAG C1 analysis

Health State	SMR (company)		EAG-preferred analysis	
	IDM	Peg	IDM	Peg
GMFCS-I	67.42	1.16	88.89	1.16
GMFCS-II	83.71	1.32	101.15	1.32
GMFCS-III	193.22	96.61	137.94	68.97
GMFCS-IV	1414.46	707.23	137.94	68.97
GMFCS-V	118.12	59.06	623.47	311.74

Which SMRs are appropriate to use in the economic model?

EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: Incremental cost-effectiveness ratio; IDM: individualised disease management; SMR: Standardised mortality ratio, MLD: Metachromatic leukodystrophy

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Key issues – transitions/effectiveness
- ✓ **Key issues – utilities**
- ❑ Key issues – drug usage
- ❑ Other Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Utility values – summary of key issues

There are several issues which impact on estimation of benefits of pegzilarginase

Health utility issues
Changed methodology on health state utilities (including how cognitive impact is modelled)
Cognitive disutilities
Changed methodology on caregiver dis-utility (with more than 1 child with condition)
Proportion of people assumed to have a diet improvement utility benefit

NICE technical team:

- These issues can interact with each other and make the impact of each of these on the cost-effectiveness results larger.
- Health utility in the model is impacted by several inputs.
- It is noteworthy that both company base case and EAG C1 analyses estimates negative total utilities for the comparator arm in the model. May call into question the face validity of these results.

Large impact

Key issue: Changed methodology on utilities

Recap (DG 3.13):

- Company original base case: predefined proportion of patients with normal/mild, moderate and severe cognitive impairment within each GMFCS health state; more severe health states were associated with more severe cognitive impact.
- Committee conclusion: treatment-specific cognitive disutility applied to GMFCS I-III is uncertain, but supported by clinical experts and may be conservative; concluded that the application is appropriate.

Company (response to DG)

- Changed model so that cognitive progression is modelled independently to motor function deterioration:
  - Cognitive health state categories were changed to None, Mild, and Moderate/Severe
  - IDM transitions were derived from regression analysis of BOI study data, and for pegzilarginase 'nominal' improvements were assumed for first 36 months, then patients were assumed to remain in the same state.
- Utility values for cognitive impairment revised to reflect the updated cognitive health states (see later slide)

EAG comments

- Unclear whether company had individual patient data to retain original state grouping.
- Limitations with company's revised methodology and potential lack of face validity in the utility value for no cognitive impairment in GMFCS-I; prefer to use EAG's original base case.

BOI: Burden of illness; EAG; evidence assessment group; GMFCS: Gross Motor Function Classification System; IDM: individualised disease management

Large impact

Key issue: Changed methodology on utilities – transition probabilities

Table: Annual transitions between cognitive health states

	Transition from	Transition to None	Transition to Mild	Transition to Moderate / Severe	Source
For patients receiving IDM (in all time periods)	None	[redacted]	[redacted]	[redacted]	Regression analysis from the European BOI study
	Mild	[redacted]	[redacted]	[redacted]	
	Moderate/Severe	[redacted]	[redacted]	[redacted]	
For patients receiving pegzilarginase (first 36 months only)	None	100%	-	-	Assumed
	Mild	2%	98%	-	
	Moderate/Severe	-	1%	99%	
For patients receiving pegzilarginase (after 36 months)	None	100%	-	-	Assumed
	Mild	-	100%	-	
	Moderate/Severe	-		100%	

BOI: Burden of illness; IDM: individualised disease management

Large impact

Key issue: Changed methodology on utilities – regression analysis

Figure: Regression analyses using baseline data for cognition in BOI study

EAG comments

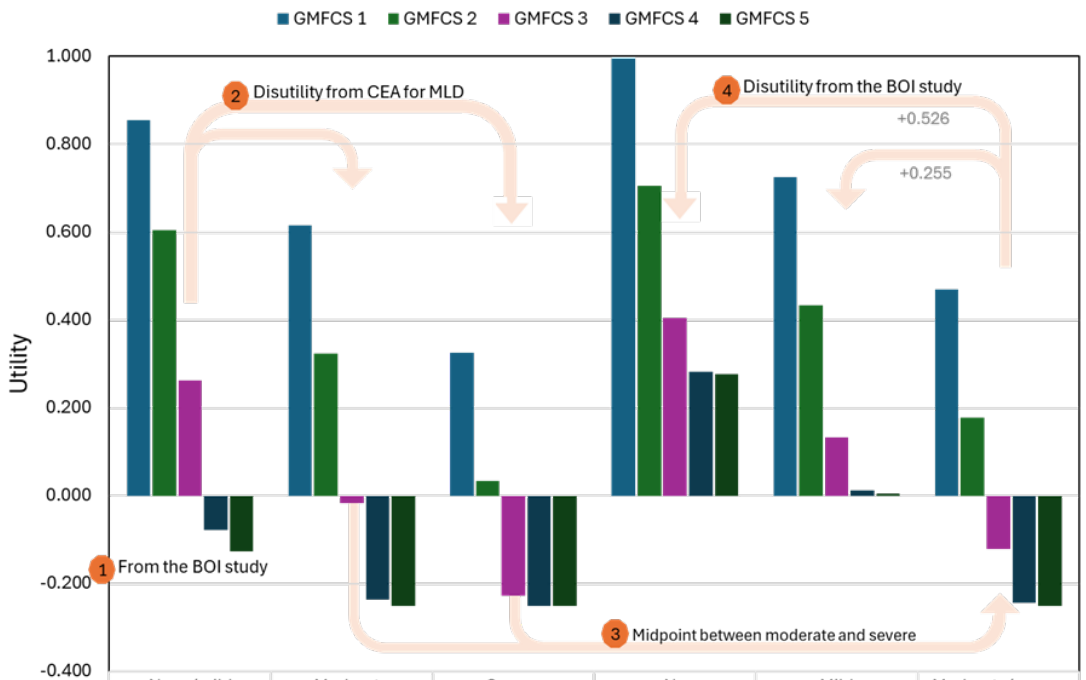
- Company states that "Regression analyses from the European BOI study indicated that with time, cognitive score declines with IDM."
- No additional details were provided regarding regression model used or covariates included; IDM transitions therefore lack transparency and cannot be validated.
- Coefficient for age is [redacted] ([redacted], 95% CI [redacted]) and based on small sample size (n=17); therefore, relationship between cognition score and age is highly uncertain.

BOI: Burden of illness; CI: confidence interval; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; IDM: individualised disease management

Large impact

Key issue: Changed methodology on utilities – change in disutility values

Figure: The utility values used in the previous base case and the revised base case



	None/mild	Moderate	Severe	No	Mild	Moderate/severe
		Original			New	
GMFCS 1	0.855	0.615	0.325	0.996	0.725	0.470
GMFCS 2	0.604	0.324	0.034	0.705	0.434	0.179
GMFCS 3	0.263	-0.017	-0.227	0.404	0.133	-0.122
GMFCS 4	-0.077	-0.237	-0.250	0.282	0.011	-0.244
GMFCS 5	-0.126	-0.250	-0.250	0.276	0.005	-0.250

<u>Moderate/severe:</u>

- Average of previously used values for moderate and severe states.

<u>Mild:</u>

- Combines utility of moderate/severe impairment with utility gain of mild compared with moderate/severe in BOI.

<u>No cognitive impairment:</u>

- Combines utility of moderate/severe impairment with utility gain of no impairment compared with moderate/severe in BOI.

EAG comments

- Different approaches to utilities introduces an inconsistency; company did not state why BOI study was not used to inform moderate/severe impairments.
- This overestimates utility in no impairment state.
- Utility for GMFCS-I with no cognitive impairment indicates quality of life close to full health (0.996); if patients also had utility from improved diet (later slides), utility would exceed 1.

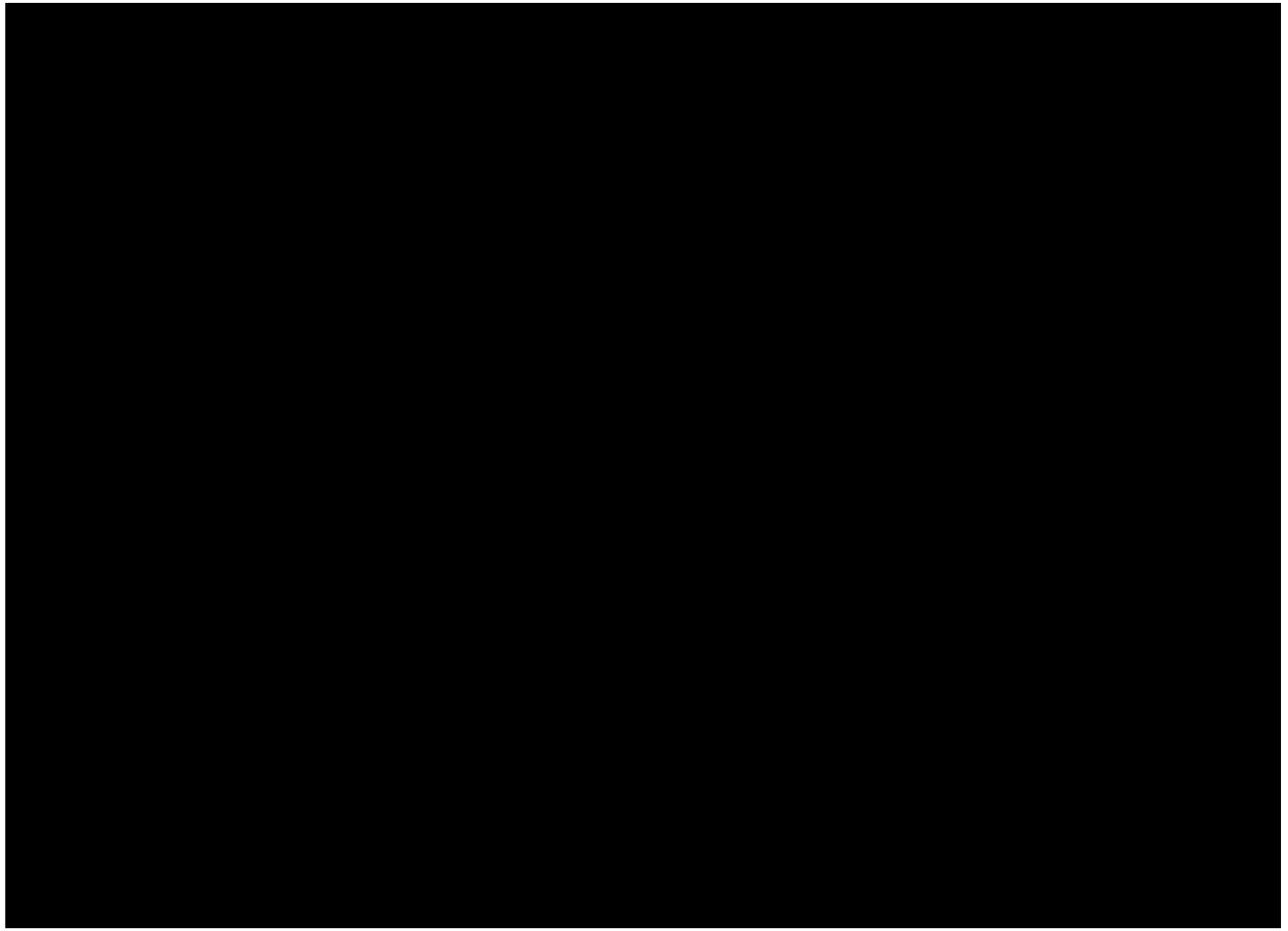
NICE

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

Large impact

Key issue: Changed methodology on utilities – change in cognition disutility values

Figure: Relationship between GMFCS health states and cognitive score (from the BOI study report, Figure 4)



EAG comments

- Utility values for the non/mild cognitive impairment by GMFCS health state are underestimated as based on the average from all patients withing a GMFCS state
- E.g. GMFCS-II has patients with score indicating severe cognitive impairment, but their EQ-5D-3L values have been used to generate a value for people with no/mild cognitive impairment.
- Disutilities associated with mild or moderate/severe health states are likely to be confounded by GMFCS health states, which have not been considered or statistically controlled for.

Which approach(es) to model utility is appropriate?

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

Moderate impact

Key issue: Increased proportion of patients receiving improved diet utility

Recap (DG 3.12):

- Company original base case: 24.7% patients have utility gains due to a more liberal diet; based difference between patients who had increased their dietary protein by >15% on IDM vs pegzilarginase.
- Committee conclusion: company's approach appropriate for decision making,

Company (response to DG)

- Increased proportion from 24.7% to 83.3% based on RWE from France

EAG comments

- Percentage of patients with >15% increased protein intake not reported; appears 67% of patients in treatment-naive group increased protein intake by >15%, implying that company's 83.3% is too high.
- RWD not adjusted to consider a placebo response (like in company submission); if placebo response was at least as good as in PEACE (18.2%), then >100% would be receiving a benefit (83.3% + 18.2%)
- Without additional data from RWE, cannot provide a robust estimate of proportion of patients who could increase protein intake by >15%.
- EAG scenario:
  - C1 - % of patients with diet liberalisation is 48.5% (66.7% from RWE study - 18.2% placebo effect).
  - C2 - % is 24.7%, as per company's original base case

Should an additional utility benefit be assumed for improved diet?
If so, to what proportion on pegzilarginase?

BOI: Burden of illness; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; RWD: real-world data; RWE: real world evidence

Moderate impact

Key issue: Additional carer disutility for more than 1 child (1/2)

Recap (DG 3.14):

- Company original base case: assumed caregiver disutilities for MLD were appropriate to apply to ARG1-D; 2 caregivers were needed for patients under 16.
- Committee conclusion: uncertainty in the carer disutility values but acceptable for decision making.

Company (response to DG)

- Used Delphi study to address uncertainty, as well as explore additional utility of carers with more than one child with ARG1-D and the proportion of children with ARG1-D who also had a sibling with ARG1-D.
- Additional disutility for carers with 2 or more children estimated from BOI study (based on difference in utilities for carers of one child and carers of 2 or more)
- Delphi study: 63% of children with ARG1-D in the UK have a sibling with ARG1-D; disutility would be most significant from GMFCS III onwards; consensus on appropriate scaling factor and disutilities for >1 child.

Table: Caregiver disutility values used in the model

Health State	Disutility in initial company submission	Disutility in EAG scenario analysis	Additional caregiver disutility for caregivers with more than 1 child with ARG1-D
GMFCS-I	0.010	None	0.002
GMFCS-II	0.027	None	0.002
GMFCS-III	0.068	0.062	0.135
GMFCS-IV	0.108	0.062	0.152
GMFCS-V	**0.162**	**0.062**	0.169

ARG1-D: Arginine-1 deficiency; BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; MLD: metachromatic leukodystrophy

Moderate impact

Key issue: Additional carer disutility for more than 1 child (2/2)

EAG comments

- While there will be additional disutility associated with caring for more than 1 child with ARG1-D, not confident in company methodology or robustness of data, particularly when there are few data points from BOI study; Company's approach will overestimate burden, but difficult to ascertain how much.
- BOI study EQ-5D-5L values not mapped to EQ-5D-3L.
- Proportion of siblings with ARG1-D who have a sibling with ARG1-D likely to overestimate the number of families with more than 1 child with ARG1-D; likely to have been the case with the Delphi panel wording.
- Programming errors in applying carer disutility in the model for >1 child; corrected in EAG version.
- 63% used by the company was increased from the [redacted] mean value from round 2 of the Delphi panel, EAG preference to use this value, which lies between value from the BOI study and 63% (C1 analysis).
- Additional scenarios explored in C2:
  - Additional caregiver burden for >1 child with ARG1-D is a quarter, a half or three-quarters of company's estimate, revert to previous EAG scenario for families with a single child with ARG1-D

NICE Technical Team:

- Believe company are double counting as economic model already applies carer disutility per child (not clear how 1 family with 2 children with ARG1-D would incur more disutility than 2 families with 1 child with ARG1-D combined) – believe no additional carer disutility should be applied as method not robust.

Should any additional carer disutility be applied for families with more than 1 child with ARG1-D? If so, which proportion of families with 2 or more children with ARG1-D is most reflective of the UK population? What is the appropriate disutility to apply when caring for more than 1 child with ARG1-D?

NICE

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

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Key issues – transitions/effectiveness
- ❑ Key issues – utilities
- ✓ **Key issues – drug costs**
- ❑ Other Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Pegzilarginase drug costs – summary of key issues

There are several issues which impact on estimation of pegzilarginase costs

Pegzilarginase drug cost estimation issues
Dosing amount of pegzilarginase per kg of weight
Thresholds for use of an additional vial (wastage)
Weight of people on treatment with pegzilarginase over their lifetime
How weight is modelled (average weight versus distribution of weight)
Proportion of males/females with the condition assumed
Compliance with pegzilarginase dosing
Treatment discontinuation rate

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: Pegzilarginase dosing per kg

Recap (DG 3.15):

- Company base case: average pegzilarginase dose of 0.14 mg/kg per week for the first 24 weeks, increasing to 0.16 mg/kg afterwards based on PEACE data.

Company (DG response)

- Updated long-term dose based on pooled PEACE and Study 102A: mean dose 0.14mg/kg throughout (previously 0.14mg/kg for 24 weeks, then 0.16mg/kg).
- RWE from France (n=14) suggests dose of 0.14mg/kg maintains reductions in plasma arginine.
- Once initial doses of pegzilarginase clear elevated plasma arginine, reduced dose may be sufficient for maintenance.

EAG comments

- Uncertainty around 0.14mg/kg dose not presented (notes French RWE study reports a range of [redacted] to [redacted] mg/kg).
- RWE study is based on 14 patients only.
- Explore alternative where previous fixed dose of 0.16 mg/kg is assumed (C2 analysis).

Which dosing is acceptable for decision making?

NICE

DG: draft guidance; EAG: external assessment group; RWE: real world evidence

Large impact

Key issue: Thresholds for use of additional vials (wastage)

Recap (DG 3.15):

- Company assumed 10% weight margin = that 10% weight above the threshold for an additional vial or less would not need an additional vial.
- Clinical advice to EAG: 10% appropriate, but uncertainty around the true level of drug wastage; EAG provided scenario analyses removing the 10% margin, and assuming not wastage.
- Committee conclusion: level of drug wastage, including the 10% margin, is uncertain.

Company (DG response)

- Maintains 10% weight margin; considers it conservative and more aligned with UK clinical practice and supported by Delphi Panel.

EAG comments

- Preferred approach would use a distribution for weight + 10% margin, altering the average number of vials needed; not possible within company's model so scenarios assuming a weight distribution (without 10% margin) at full drug wastage and no drug wastage.
- Includes scenarios to address uncertainties in drug wastage and weight-based dosing (see next slides).

Should a 10% weight margin be applied in the model for vial usage/drug wastage? If not, what should be assumed?

DG: draft guidance; EAG: external assessment group

Large impact

Key issue: Weight of people on pegzilarginase over lifetime (1/2)

Recap (DG 3.15):

- NICE tech team: model assumes same lower weight ratios from trial to apply throughout the model: treatment effects of pegzilarginase may enable weight gain closer to population norms due to improved diet.
- Committee: Adults weighing 95% of general population (NICE tech team scenario) most plausible; company approach not appropriate. Requested further input on impact of pegzilarginase on weight over lifetime.

Company (DG response)

- Post-hoc analysis of PEACE data shows: **≥13 years,** no trend for increasing weight compared to the general population treated with pegzilarginase but there is a trend for reducing weight after initial rise following treatment initiation; **<13 years,** weight tends to slowly approach general population; but as model baseline age is 13 years, patients will not start treatment early enough to benefit.
- Base case: average weight ratio based on ratio ≥13 years across all observation across time (0.782)

NICE Technical Team:

- Company's position on patient weight while on pegzilarginase is inconsistent with other model assumptions:
  - Relatively high utility values in least severe states but assuming significantly underweight population
  - Assume utility gains for pegzilarginase for diet liberalisation but no weight gain assumed
  - State that patients >13 years will not benefit from improved growth and model starts at 13 years of age:
    - Mean = 13 years, substantial % would be <13 years of age + would benefit from improved growth
  - If patients do not benefit from growth and a healthier weight, high utility utilities value lack face validity

DG: draft guidance

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

Large impact

EAG comments

- Assuming patients on pegzilarginase will weigh 90% of population norms is realistic for sensitivity analyses (Delphi agreed average patient with pegzilarginase would remain below 90% of population norms) .
- If pegzilarginase is recommended and future treatment starts at a young age, the future weight ratio could be similar to <13 years.
- EAG scenarios include (inclusive of other pegzilarginase drug costing issues):
  - increase costs of pegzilarginase by 10%, no drug wastage + weight distribution, weight ratio of 0.9 for dosing, using alternative weight data from ONS
  - increase costs of pegzilarginase by 20%, full drug wastage + weight distribution.

Stakeholder comments (Metabolic UK, Clinical experts and Patient expert)

- Pegzilarginase has resulted in improved appetite and weight in people on the treatment.
- In a clinician survey:
  - few paediatric patients were underweight prior to pegzilarginase treatment (3/15); 2 gained weight on pegzilarginase (the other patient discontinued – not treatment related).
  - none of the adult patients (n=4) were underweight prior to pegzilarginase. 3 gained weight while on treatment; diet liberalisation was reported despite patients being advised to maintain diet.

How should weight be applied in the model? (fixed versus distribution?, most appropriate ratio to general population to use?).

NICE

EAG: external assessment group; ONS: Office for National Statistics

Large impact

Key issue: How weight is modelled

NICE technical team believe number of vials of pegzilarginase is underestimated in company model

Background:

- NICE technical team consider that using an average weight in the model to estimate number of vials is incorrect and underestimates costs. Also believe that proportion of Male/females in model should be 50/50

NICE Technical Team:

- Average weight approach highly likely to underestimate pegzilarginase costs:
  - Threshold for 5 vials is 63.8kg (dose of 0.14mg/kg + 10% margin); company mean weight modelled for ages 25 to 74 is between 61.25kg to 63.67kg – almost at threshold, meaning nobody uses 5 vials.
  - If modelled by distribution around average weight, a sizable proportion would be over the threshold.
  - Other dosing issues (weight ratios vs general population, % female, dosing per kg of pegzilarginase, drug wastage) also impact on this issue.
- Literature suggests that there is not expected to be a difference in prevalence of condition by male/female.

EAG comments

- Model does not allow for a distribution around average weight; provides scenarios with 10% and 20% increase in costs due to additional vials needed.
- 50% Proportion of male/female based on Bin Sawad et al. systematic review is more appropriate.

Should increased costs be assumed due to average weight use?
What proportion of males and females should be assumed in the model?

NICE

EAG: external assessment group

Key issue: Compliance with pegzilarginase

Large impact

Background:

- Company original base case: all patients received full dose of pegzilarginase (100%); compliance not included at ECM1; not discussed in DG.
- Model updated to included compliance data from PEACE and LTE (Study 101A/102A excluded as data insufficient). Updated company base case: 94.1% of dose taken in PEACE double-blind period; [redacted] in long term extension.

Company (response to DG)

- Compliance is important to correctly capture costs of pegzilarginase.

EAG comments

- No changes to company base case made, but note that reverting back to 100% compliance would increase company's base case ICER.
- No reason given for the reduced compliance; favourable to pegzilarginase if related to not allowing drug wastage (see previous slide).
- Aligning costs (reduced dosage compliance) with observed benefits usually appropriate, but many benefits applied are disconnected as they are from the Delphi panel, not the PEACE study; therefore adjusting dose is more questionable.
- No change made from company base case; notes that reverting to 100% compliance would increase company's ICER.

Is the approach to align dosage compliance to PEACE study appropriate?

DG: draft guidance; GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio; LTE: long-term extension

Large impact

Key issue: Treatment discontinuation rate (1/2)

Recap (DG 3.16):

- Company original base case: 1% discontinuation each year with pegzilarginase.
- Committee conclusion: 2% is appropriate, based on clinical expert input at ECM1, but uncertain.

Company (response to DG)

- Fitted distribution rates to discontinuation data from PEACE and Study 101A/102A
- Gompertz fit most appropriate (~92% discontinued at year 1, no discontinuation following) as aligns closely to study data; clinical input agreed Gompertz most clinically plausible
- Delphi panel consensus: unlikely that patients will discontinue after 1 year of initiating pegzilarginase.
- Scenarios with log-logistic and Weibull reduced the ICER; therefore Gompertz conservative.

EAG comments

- Applies committee preferred 2% discontinuation rate in a sensitivity, but notes that it does not fit initial years of the Kaplan-Meier curve well.
- Unlikely for there to be no discontinuations after year 1; EAG preference is for the log-logistic distribution (continued discontinuation after year 1, ~20% at 30 years)

NICE Technical Team:

- Notes that a 2% annual discontinuation is relatively low and results in 50% of people still on treatment at 35 years post starting (48 years of age) and ~20% of still on treatment at 80 years post start (93 years of age)
- Very limited data to inform discontinuation. Issue impacts on QALY weighting, costs and outcomes
- Stakeholder comments appear to suggest a non-small % of people do discontinue pegzilarginase

BOI: Burden of illness; DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Large impact

Key issue: Treatment discontinuation rate (2/2)

Stakeholder comments (Clinical experts, Metabolic UK)

Clinician survey:

- 3 out of 15 paediatric patients (all English patients) stopped pegzilarginase treatment for personal reasons.
- Clinicians suggested potential treatment stopping rules based on several events:
  - worsening of disease
  - severe adverse events
  - no response
  - poor compliance
  - exploring response to treatment after 1 to 3 years

Figure: Distributions considered by the company plus the 2% discontinuation rate per year mentioned in the DG (committee preferred)

Which discontinuation assumption is most appropriate? (2%, Gompertz, Log-logistic, other?)
Is there appropriate stopping rules for pegzilarginase?

BOI: Burden of illness; DG: draft guidance; EAG: external assessment group; GMFCS: Gross Motor Function Classification System

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Key issues – transitions/effectiveness
- ❑ Key issues – utilities
- ❑ Key issues – drug costs
- ✓ **Other Key issues**
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

High impact

Key issue: QALY weighting

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*"
- At ECM1, committee concluded *"The committee concluded that it could not apply a QALY weighting at this stage because of the high uncertainty around key – It requested further input on these from consultation with stakeholders*."

NICE Technical Team:

- Many scenarios show substantial undiscounted QALY gains (company base case = >40)
- Riles on several model inputs/assumptions:
  - Long life expectancy on pegzilarginase treatment
  - High utility while on pegzilarginase treatment
  - Low QALYs in standard of care arm
  - Long time on treatment and very low treatment discontinuation

Should a QALY weight be applied?

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

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Key issues - transitions
- ❑ Key issues – utilities
- ❑ Key issues – drug usage
- ❑ Other Key issues
- ✓ **Base case assumptions and cost-effectiveness results**
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company base case

Issue	Company base case
Starting distribution of GMFCS states	Pooled data from PEACE, Study101A/102A and BOI survey
SMR calibration	IDM: Individual multipliers 10% alive at 32; 1% alive at 50 Pegzilarginase: GMFCS I-II same as ECM1 (1.16 and 1.32) GMFCS III+ half of IDM SMR
Dosing, wastage and weight	Fixed average weight 10% margin for wastage 0.782 weight ratio to general population
Approach to discontinuation	Gompertz
Proportion of families with 2 or more children with ARG1-D	63% - apply additional caregiver dis-utility
Cognitive impairment utilities	Independent from GMFCS state Updated utility values
Proportion of patients with improved diet	83.3%
Proportion of female patients	56%
QALY weighting	Includes QALY losses for carers

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 – C1

Analyses in **bold** have the biggest impact on cost-effectiveness estimates

C1-1. Removing QALY losses for carers when calculating the QALY weight used to calculate the weighted ICER

C1-2. Correction of a programming error associated with QALY losses for caregivers

C1-3. Using the distribution for starting GMFCS state from the BOI study

C1-4. Assuming 50% of patients are female

C1-5. Applying a log-logistic model for the distribution of treatment discontinuation

C1-6. Assuming [redacted] of families have more than one child with ARG1-D

C1-7. Reverting to the company's original method for estimating disutility from cognitive impairment

C1-8. Updating the proportion of patients with utility gains from improved diet to [redacted]

C1-9. Using transition probabilities derived from the difference in average ages in each GMFCS health

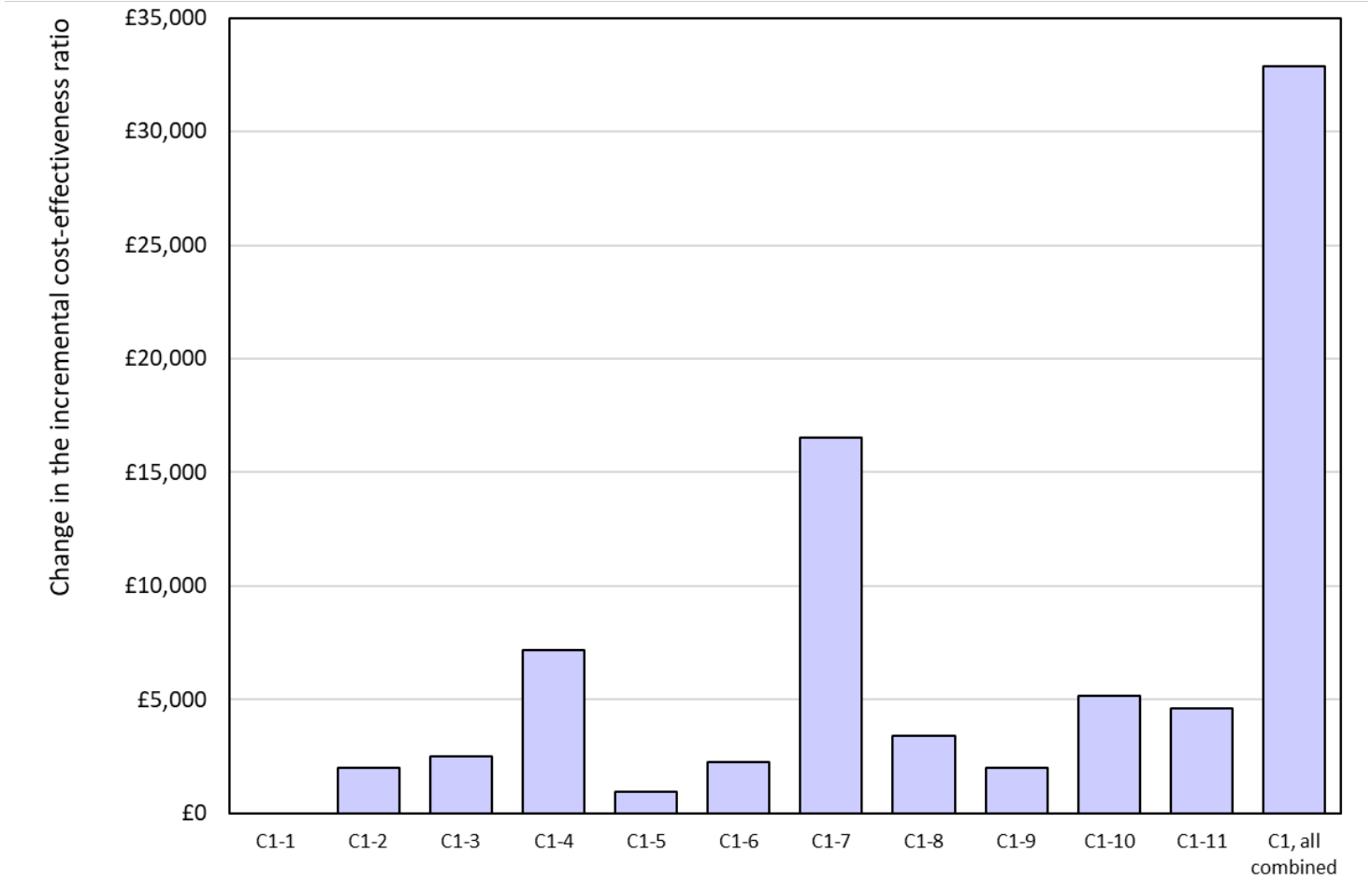
C1-10. Transitions from GMFCS-II/III to GMFCS-V stopped after age 16; applied relative risk for transitions to GMFCS-V for pegzilarginase-treated patients.

C1-11. Applying recalibrated SMRs using the original method, assuming 10% of patients diagnosed at age 5.1 in GMFCS-I remain alive at 32 years of age

BOI: burden of illness; EAG: external assessment group; 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 – C1 results

Figure: The change in ICER associated with each C1 change



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

Overview of EAG analyses – C2

Analyses in **bold** have the biggest impact on cost-effectiveness estimates

C2-1. Assuming the proportion of patients with utility gains from improved diet to be 24.7%

C2-2. Applying caregiver burden for families with multiple children at 25% of the company's estimate

C2-3. Applying caregiver burden for families with multiple children at 50% of the company's estimate

C2-4. Applying caregiver burden for families with multiple children at 75% of the company's estimate

C2-5. Reverting to EAG scenario for families with a single child with ARG1-D

C2-6. Assuming a fixed dose of 0.16 mg/kg per person

C2-7. Assuming no drug wastage and applying a weight distribution for patients

C2-8. Reverting to the transition probabilities between GMFCS states in the previous EAG base case

C2-9. Applying SMRs for pegzilarginase-treated patients equal to half of those used for IDM

C2-10. Assuming a weight ratio of 0.900 for dosing calculations

C2-11. Assuming a 10% increase in pegzilarginase cost to explore higher drug costs due to uncertainties in the distribution of weight

C2-12. Assuming the risk of transition to the next worse GMFCS state is 10% of that associated with IDM

C2-13. Assuming the risk of transition to the next worse GMFCS state is 20% of that associated with IDM

C2-14. Assuming that after month 3, that 20% of subcutaneous administrations occur in a hospital setting

C2-15. Using the weight data from the ONS provided by the NICE technical team

ARG1-D: Arginine-1 deficiency; EAG: external assessment group; GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; SMR: Standardised mortality ratio

Overview of EAG analyses – C3

Analyses in **bold** have the biggest impact on cost-effectiveness estimates

C3-1. Assuming an exponential distribution for treatment discontinuation at 2% annually (see Section 2.2)

C3-2. Assuming full drug wastage; applying a weight distribution for patients

C3-3. Applying the SMRs assuming that 10% of patients diagnosed at age of 13 years with the distribution of GMFCS health states remain alive at age 32

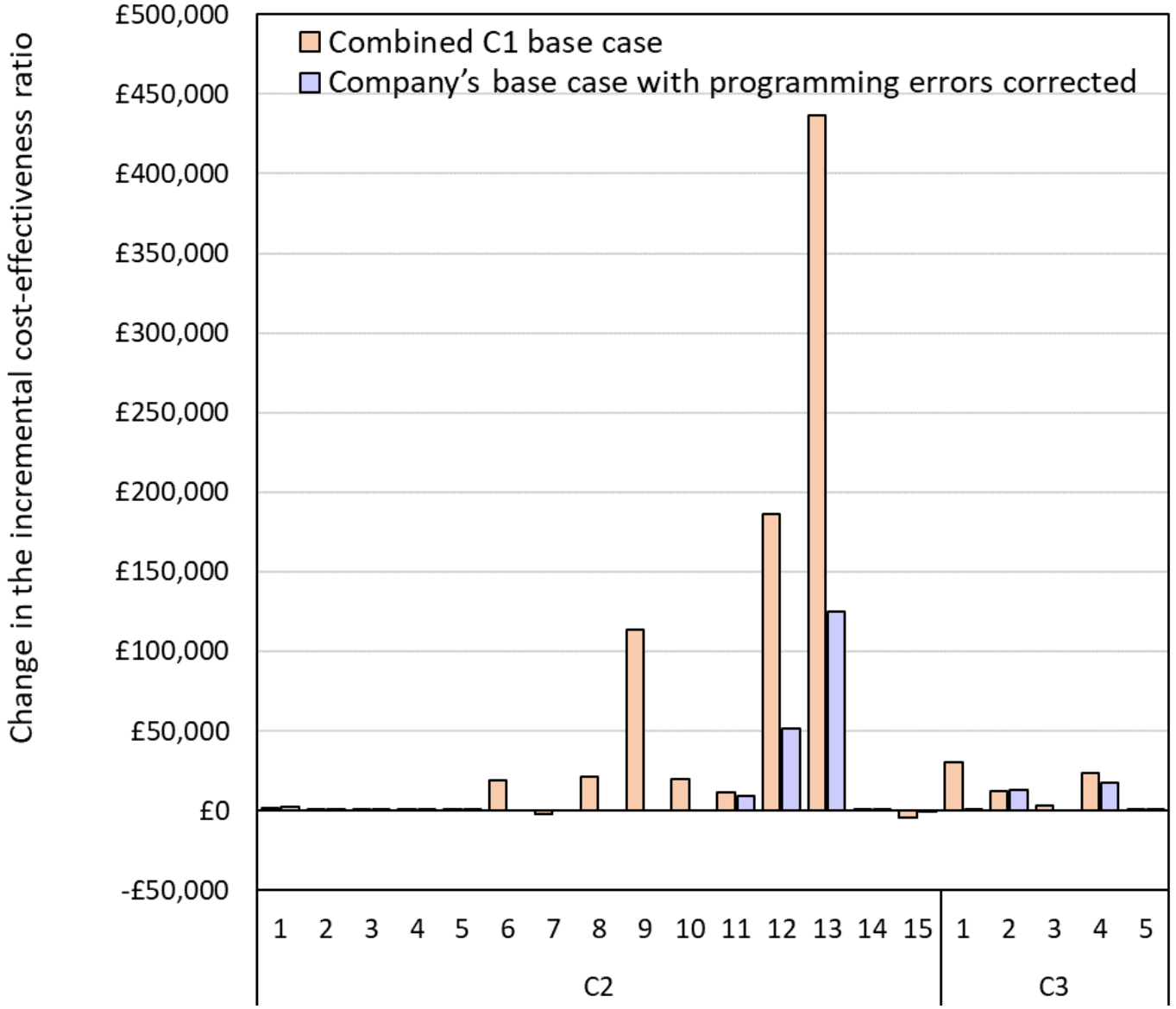
C3-4. Assuming a 20% increase in pegzilarginase cost to explore higher drug costs due to uncertainties in the distribution of weight

C3-5. Assuming that after month 3, that 10% of doses are intravenous and that 30% of subcutaneous administrations occur in a hospital setting

EAG: external assessment group; GMFCS: Gross Motor Function Classification System; SMR: Standardised mortality ratio

Overview of EAG analyses – C2 and C3 results

Figure: The change in ICER associated with each C2 and C3 change



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

EAG exploratory analysis results - Deterministic

Table: Deterministic results

	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight[2]
Company base case	[redacted]	[redacted]	**44.66**	[redacted]	£88,595	[redacted]
EAG C1, combined	[redacted]	[redacted]	37.74	[redacted]	£121,465	[redacted]

Table: Probabilistic results

	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight, mean (range) [2]
Company base case	[redacted]	[redacted]	**44.30**	[redacted]	£93,063	[redacted]
EAG C1, combined	[redacted]	[redacted]	37.48	[redacted]	£124,327	[redacted]

Results include confidential commercial discount for pegzilarginase

[1]Undiscounted

[2]Calculated using undiscounted QALY gains

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

EAG C2 analyses with the biggest impact - Deterministic

Scenario analysis#	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG C1 combined	[redacted]	[redacted]	37.74	[redacted]	£121,465	[redacted]
C2-6: Assuming a fixed dose of 16 mg/kg per person	[redacted]	[redacted]	37.74	[redacted]	£140,596	[redacted]
C2-8: Reverting to the transition probabilities between GMFCS states in the previous EAG base case	[redacted]	[redacted]	36.27	[redacted]	£142,647	[redacted]
C2-9: Assuming a weight ratio of 0.900 for dosing calculations	[redacted]	[redacted]	37.74	[redacted]	£141,287	[redacted]
C2-10: Applying SMRs for pegzilarginase-treated patients equal to half of those used for IDM	[redacted]	[redacted]	11.74	[redacted]	£234,953	[redacted]
C2-12: Assuming the risk of transition to the next worse GMFCS state is 10% of that associated with IDM	[redacted]	[redacted]	23.87	[redacted]	£308,095	[redacted]
C2-13: Assuming the risk of transition to the next worse GMFCS state is 20% of that associated with IDM	[redacted]	[redacted]	16.99	[redacted]	£558,402	[redacted]

Scenario analysis are applied to EAG C1 combined.
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: incremental cost effectiveness ratio; IDM: individualised disease management; LYGs: Life years gained; QALYs: quality-adjusted life-year.

EAG C3 analyses with the biggest impact - Deterministic

Scenario analysis#	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG C1 combined	[redacted]	[redacted]	37.74	[redacted]	£121,465	[redacted]
C3-1: Assuming an exponential distribution for treatment discontinuation at 2% annually	[redacted]	[redacted]	24.81	[redacted]	£151,934	[redacted]
C3-2: Assuming full drug wastage; applying a weight distribution for patients	[redacted]	[redacted]	37.74	[redacted]	£133,527	[redacted]
C3-4: Assuming a 20% increase in pegzilarginase cost to explore higher drug costs due to uncertainties in the distribution of weight	[redacted]	[redacted]	37.74	[redacted]	£145,185	[redacted]

Scenario analysis are applied to EAG C1 combined.
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

EAG: external assessment group; GMFCS: Gross Motor Function Classification System; ICER: incremental cost effectiveness ratio; IDM: individualised disease management; LYGs: life years gained; QALYs: quality-adjusted life-year.

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Key issues - transitions
- ❑ Key issues – utilities
- ❑ Key issues – drug usage
- ❑ Other Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Other considerations

Potential for managed access

- Managed access not proposed by the company

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Key issues - transitions
- ❑ Key issues – utilities
- ❑ Key issues – drug usage
- ❑ Other Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issues	
Transitions	**Impact**
Starting distribution by GMFCS state	LARGE
Company's modelling approach to starting age	MODERATE
Time spent in GMFCS states for patients on IDM	LARGE
5% patients move from GMFCS-II and II to IV	MODERATE
Disease progression with pegzilarginase	LARGE
Life expectancy	LARGE
Utilities	
Changed methodology on utilities for cognitive impairment	LARGE
Increased proportion of patients receiving improved diet utility	MODERATE
Additional carer disutility for more than 1 child	MODERATE
Cost of pegzilarginase	
Pegzilarginase dosing per kg	LARGE
Weight thresholds for use of additional vials (wastage)	LARGE
Weight of people on pegzilarginase over lifetime	LARGE
How weight is modelled	LARGE
Compliance with pegzilarginase	LARGE
Treatment discontinuation rate	LARGE
Other issues	
QALY weighting	LARGE

GMFCS: Gross Motor Function Classification System; ICER: incremental cost-effectiveness ratio; IDM; individualised disease management; PSA; probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

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

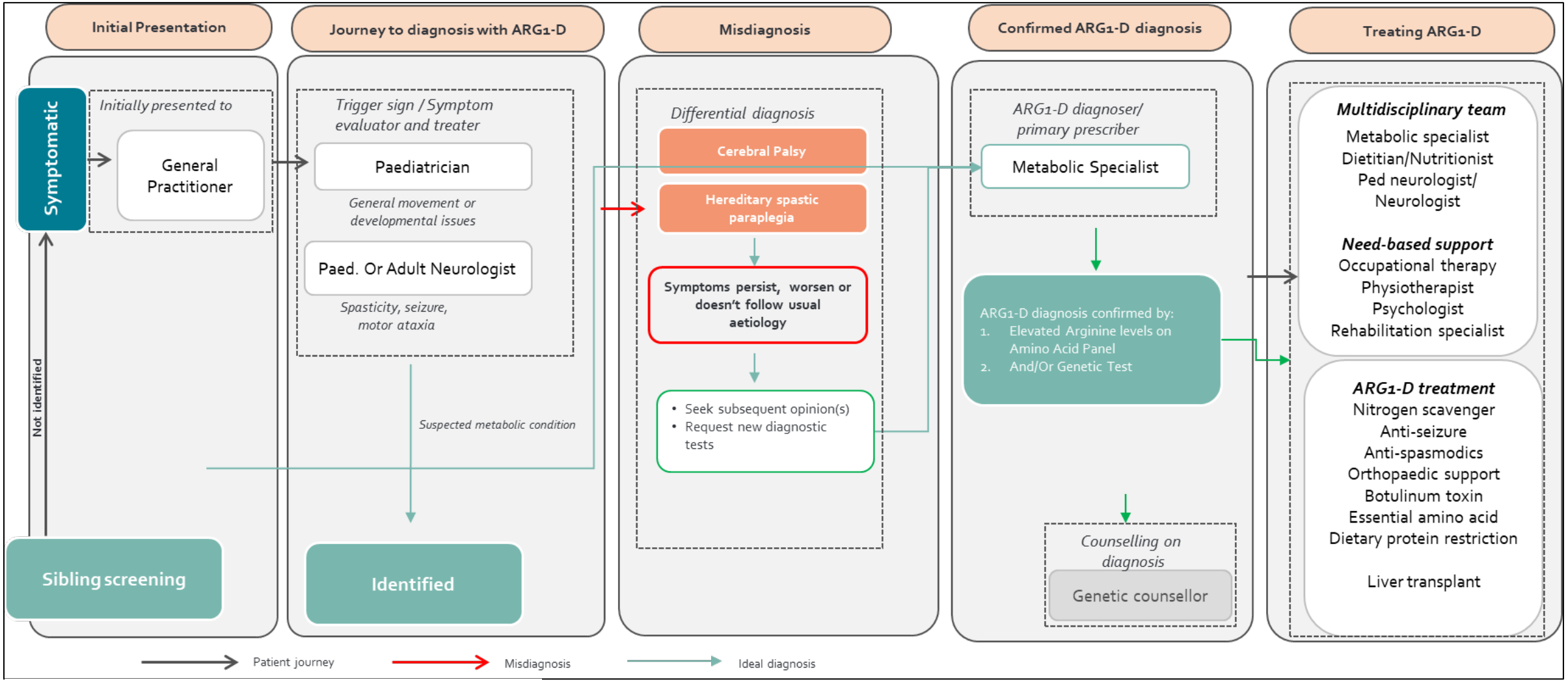
Clinical expert perspectives

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

*Back to main presentation

ARG1-D: Arginase-1 deficiency

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

PEACE and Study 101/102A eligibility criteria

Table: PEACE and Study 101A/102A inclusion and exclusion criteria

	PEACE	Study 101A	Study 102A
Inclusion criteria	• Documented ARG1-D diagnosis (through elevated plasma arginine [pArg], pathogenic variants in ARG1, and/or erythrocyte ARG1 activity) • pArg ≥250μM (mean of all screening values) • Male and female patients aged ≥2 years of age on the date of informed consent/assent • Impairment on any secondary functional mobility assessment	• Patient ≥2 years old with baseline plasma arginine (pArg) levels >200 μM. • Diagnosis confirmed by the presence of pathogenic variants in the *ARG1* gene or deficiency in red blood cell enzyme activity	As per Study 101A but patients were also required to complete Study 101A without experiencing any clinically significant adverse event or other unmanageable drug toxicity that would preclude continued dosing
Exclusion criteria	• Symptomatic hyperammonaemia (ammonia ≥100μM requiring acute care or hospitalisation) • Extreme mobility deficit (i.e., unable to complete mobility assessments) • Other medical conditions or comorbidities that would preclude study compliance • Patients with ongoing or planned initiation of treatment with botulinum toxin • Participation in previous pegzilarginase study • Prior liver or haemopoietic transplant procedure	• Recent hyperammonaemic episode requiring hospitalisation or active infection requiring treatment • History of hypersensitivity to polyethylene glycol	

ARG1-D: Arginase-1 deficiency; pArg: Plasma arginine;

Baseline characteristics: PEACE study

Table: Patient demographics and baseline characteristics (full analysis set)

		Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Age at enrollment (years)	Mean (SD)	9.6 (6.16)	12.9 (6.77)	10.7 (6.47)
Age categories (years), n (%)	2 - <6	5 (23.8)	1 (9.1)	6 (18.8)
	6 - <12	8 (38.1)	4 (36.4)	12 (37.5)
	12 - <18	7 (33.3)	4 (36.4)	11 (34.4)
	≥18	1 (4.8)	2 (18.2)	3 (9.4)
Sex, n (%)	Female	9 (42.9)	4 (36.4)	13 (40.6)
	Male	12 (57.1)	7 (63.6)	19 (59.4)
Age at onset of manifestations, years	N	11	10	21
	Mean (SD)	1.6 (2.5)	2.5 (2.0)	1.9 (2.4)
Age at diagnosis, years	N	17	9	26
	Mean (SD)	2.8 (4.1)	4.2 (3.1)	3.3 (3.8)
Baseline pArg, μM[a]	N	19	11	30
	Mean (SD)	365.4 (93.7)	471.7 (79.9)	402.0 (101.8)

[a] One patient had pArg <250 μM (screening, 242 μM; baseline, 202 μM) but was considered eligible for the study based on documented historical pArg levels.

Source: Company submission, Table 11

pArg: Plasma arginine; SD: Standard deviation

Baseline characteristics: Study 101A/102A

Table: Patient demographics and baseline characteristics (full analysis set)

		Study 101A (n=16)	Study 102A (n=14)
Age at enrollment (years)	Mean (SD)	15.1 (8.47)	[redacted]
Age categories (years), n (%)	2 - <6	2 (12.5)	[redacted]
	6 - <12	4 (25.0)	[redacted]
	12 - <18	5 (31.3)	3 (21.4)
	≥18	5 (31.3)	5 (35.7)
Sex, n (%)	Female	11 (68.8)	[redacted]
	Male	5 (31.3)	[redacted]
Age at initial symptoms, years[a]	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Baseline pArg, µM[a]	Mean (SD)	373.4 (91.31)	309.2 (97.60)

[a] One patient was diagnosed via newborn screening and did not present with initial symptoms

Source: Company submission, Table 15

pArg: Plasma arginine; SD: Standard deviation

EAG critique of PEACE and Study 101A/102A study design

PEACE:

- 24 weeks randomised double blind period is a short timescale ➔ Longer period preferable to demonstrate clinical benefit in outcomes such as changes in walk tests and neurocognitive outcomes
- LTE had no comparator arm and no comparison to disease natural history was attempted
- Primary outcome was a surrogate (pArg) ➔ Clinical advice to EAG noted pArg levels do not have a consistent relationship with severity of disease but is closely linked to hyperammonaemic crises (HACs)
- Agree stratification at baseline according to prior history of HACs may balance disease severity across groups at baseline, but unclear if other patient characteristics may be equally or more important ➔ No justification provided by company in selecting factors
- Lower mean age and mean age at diagnosis in pegzilarginase arm compared with placebo arm may advantage pegzilarginase arm ➔ Clinical advice to EAG noted that outcomes get worse with age. People in placebo arm likely to have worse prognosis as they are older

Study 101A/102A:

- 102A had a higher mean age and lower pArg levels compared to PEACE

Clinical expert submission

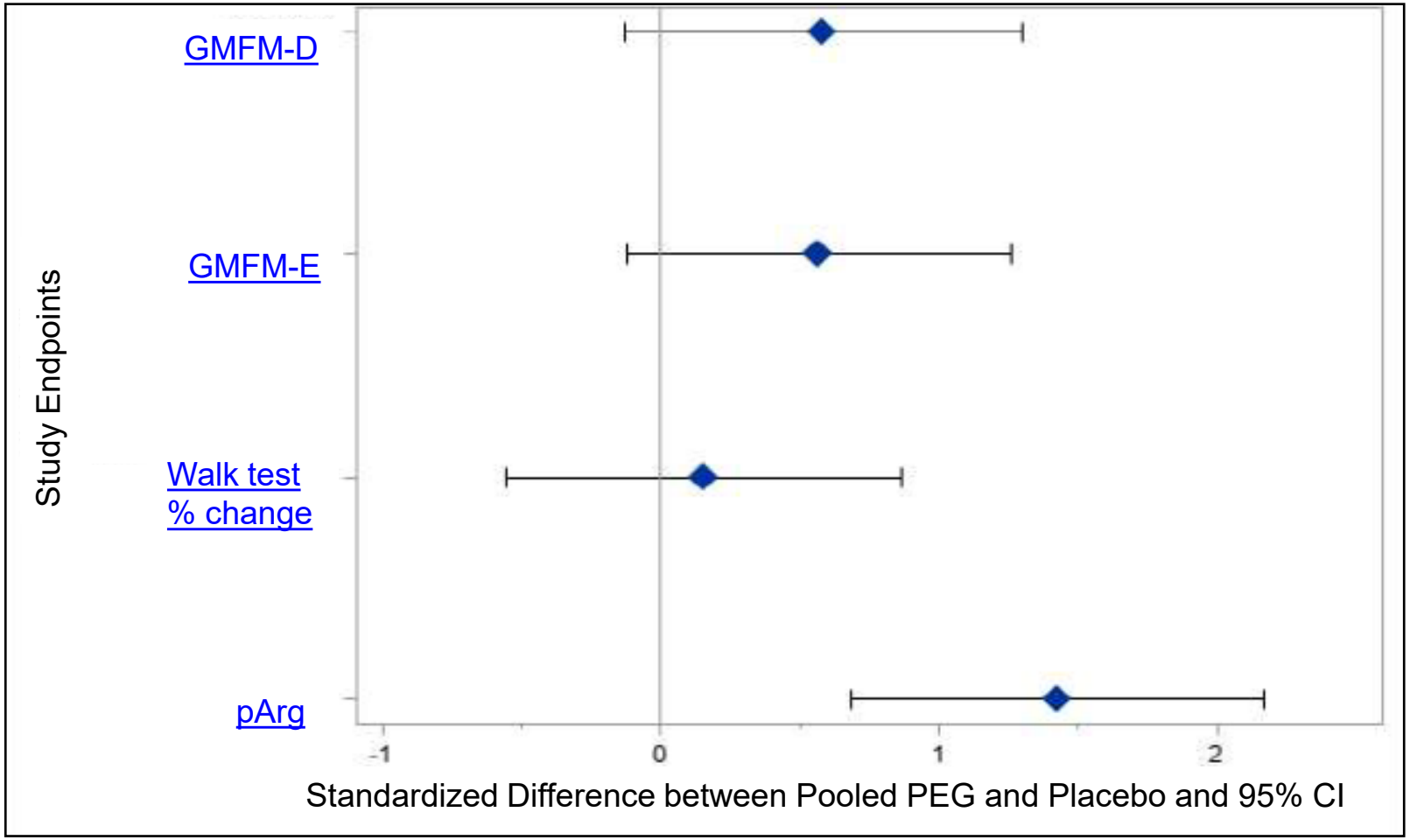
- Plasma arginine as a surrogate marker is reasonable given the implication of hyperargininaemia in the pathogenesis of neurological disease in arginase deficiency

pArg: Plasma arginine

PEACE and Study 102A results

Pooled analysis of biomechanical and motor outcomes

Figure: Pooled analysis of PEACE and Study 102A



EAG comment:

- Pooled analysis of pArg is consistent with PEACE: Pooled (PEACE and Study 102A) mean change from baseline compared to placebo was -77.9%, consistent with -76.7% in PEACE

Source: EAR, Figure 7

CI: Confidence interval; GMFM-D: Global Motor Function Measure, Part D; GMFM-E: Global Motor Function Measure, Part E; pArg: Plasma arginine; PEG: Pegzilarginase

Delphi study: Dosing

Round 1 question: Based on your experience, to what extent do you agree/disagree that dose adjustments will be made to eliminate drug wastage with pegzilarginase in clinical practice (i.e., clinical advice to the EAG included using an additional vial every 2 weeks should the optimal dose indicate using half a vial a week)?

Round 2 question: N/A

Consensus meeting: N/A

Likert response	Round 1
Strongly disagree	0
Disagree	0
Somewhat disagree	0
Neutral	1
Somewhat agree	1
Agree	0
Strongly agree	6

Report conclusion:

- Consensus achieved; 87.5% of participants agreed in round 1.
- Final consensus statement: Dose adjustments will be made to eliminate drug wastage with pegzilarginase in clinical practice.

Source: Company Data on File. Delphi Panel Report. March 2025.

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System

Delphi study: Starting distribution by GMFCS states

Round 1 question: To what extent do you agree/disagree that the pooled data from PEACE, Study 101A, Study 102A and European BOI survey reflects the distribution of patients with ARG1-D by GMFCS health states in UK clinical practice?

Round 2 question: To what extent do you agree/disagree that the pooled data from PEACE, Study 101A, Study 102A and European BOI survey reflects the distribution of patients that would be initiated on pegzilarginase treatment in UK clinical practice?

Consensus meeting: N/A

Likert response	Round 1	Round 2
Strongly disagree	0	0
Disagree	0	0
Somewhat disagree	**6**	0
Neutral	0	**2**
Somewhat agree	**2**	**3**
Agree	**1**	**3**
Strongly agree	0	0

Report conclusion:

- Consensus achieved; 75% of participants agreed in round 2.
- Final consensus statement: The pooled data from PEACE, Study 101A, Study 102A and the European burden of illness survey reflects the distribution of patients by GMFCS health state for those who would be initiated on pegzilarginase treatment in the UK.

Source: Company Data on File. Delphi Panel Report. March 2025.

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System

Delphi study: Starting age by GMFCS states (1/2)

Round 1 question: a) To what extent do you agree/disagree that the average age of patients by GMFCS across the clinical trials reflects the current patient pool in the UK? Note that the age for GMFCS III is based on study 102A only, as there are no data available from the PEACE trial for this health state. As a result, the mean age within this health state is likely to be skewed. The average age for GMFCS V is N/A.

b) In general, what is the average age in years of patients in the UK occupying GMFCS III?

c) In general, what is the average age in years of patients in the UK occupying GMFCS V?

Round 2 question: a) Please refer to your response to the mean age of patients in GMFCS III from the round one questionnaire. If you wish to change your response, please answer the following: in general, what is the average age in years of patients in the UK occupying GMFCS III?

b) Please refer to your response to the mean age of patients in GMFCS V from the round one questionnaire. If you wish to change your response from round one, please answer the following: in general, what is the average age in years of patients in the UK occupying GMFCS V?

Consensus meeting: a) To what extent do you agree/disagree that the average age of patients in GMFCS III is 16 years.

b) To what extent do you agree/disagree that the average age of patients in GMFCS IV is 25 years.

c) To what extent do you agree/disagree that the average age of patients in GMFCS V is 15 years.

Delphi study: Starting age by GMFCS states (2/2)

	Round 1 (n=8)	Round 2 (n = 8)	Consensus (n=7)
a)	Somewhat disagree: **1** Somewhat agree: **1** Agree: **5** Strongly agree: **1**	Mean age for GMFCS-III was **17 years**	GMFCS-III is **16** years Neutral: **1** Agree: **6**
b)	Mean age for GMFCS-III was **17 years**	Mean age for GMFCS-V is **24 years**	GMFCS-IV is **25** years Agree: **6** Strongly agree: **1**
c)	Mean age for GMFCS-V is **23 years**	0	GMFCS-V is **15** years Somewhat agree: **3** Agree: **4**

Source: Company Data on File. Delphi Panel Report. March 2025.

Report conclusion:

- Final consensus statement: The average age within each GMFCS health state is as follows: GMFCS I is 11 years; GMFCS II is 12 years; GMFCS III is 16 years; GMFCS IV is 25 years; GMFCS V is 15 years.

Delphi study: Age of diagnosis

Round 1 question: Based on your knowledge and experience, what is the average age of patients at diagnosis of ARG1-D in the UK? **Mean response (n=8) 6.3 years**

Round Two question: Based on your knowledge and experience, what is the average age of patients at diagnosis of ARG1-D in the UK? Please consider all patients, including patients with siblings who are diagnosed at birth due to known family history of ARG1-D. **Mean response (n=8) 5.1 years**

Consensus meeting question: To what extent do you agree/disagree that the average age of patients at diagnosis of ARG1-D in the UK is 5.1 years.

Likert response	Consensus result (n=7)
Strongly disagree	0
Disagree	0
Somewhat disagree	0
Neutral	**1**
Somewhat agree	**2**
Agree	**4**
Strongly agree	0

Report conclusion:

- Consensus achieved; 85.7% agreed with the consensus statement in the meeting.
- Final consensus statement: The average age of patients at diagnosis of ARG1-D in the UK is 5.1 years.

Source: Company Data on File. Delphi Panel Report. March 2025.

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System

Delphi study: Survival of patients with ARG1-D (1/2)

Round 1 question: When patients with ARG1-D who are managed with SoC die for reasons other than HAC, what proportion are within each GMFCS health state?

Round 2 question: Please refer to your response from round one. If you wish to change your response from the round one questionnaire, please answer the following: when patients with ARG1-D who are managed with SoC die for reasons other than HAC, what proportion are within each GMFCS health state?

Consensus meeting question: To what extent do you agree/disagree with the means presented?

Round 1 response (mean, n=7)	Round 2 response (mean, n=6)	Consensus response (Likert scale, n=7)
GMFCS I: 6.1% GMFCS II: 6.9% GMFCS III: 15.3% GMFCS IV: 28.6% GMFCS V: 43.6%	GMFCS I: 5.3% GMFCS II: 6.1% GMFCS III: 13.9% GMFCS IV: 32.3% GMFCS V: 42.3%	Somewhat agree: 4 Agree: 3

Source: Company Data on File. Delphi Panel Report. March 2025.

Report conclusion:

- Consensus achieved; 100% agreed with the consensus statement in the meeting.
- Final consensus statement: The proportion of patients within each GMFCS health state who are managed with SoC die for reasons other than HAC are as follows:
  - GMFCS I: 5.3%
  - GMFCS II: 6.1%
  - GMFCS III: 13.9%
  - GMFCS IV: 32.3%
  - GMFCS V: 42.3%

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System

Delphi study: Survival of patients with ARG1-D (2/2)

Round 1 question: Considering the average patient with ARG1-D who is managed with SoC, at what age would you expect the majority (i.e., over 90%) of these patients to have died (excluding death due to HAC)?

Round 2 question: Please refer to your response from round one. If you wish to change your response from the round one questionnaire, please answer the following: considering the average patient with ARG1-D who is managed with SoC, at what age would you expect the majority (i.e., over 90%) of these patients to have died (excluding death due to HAC)? Please provide a single value between 1 and 100.

Consensus meeting question: To what extent do you agree/disagree that the average age at which 90% of ARG1-D patients die (excluding death due to HAC) is 32 years.

Round 1 response (mean, n=8)	Round 2 response (mean, n=8)	Consensus response (Likert scale, n=7)
31 years	32 years	Somewhat agree: 6 Agree: 1

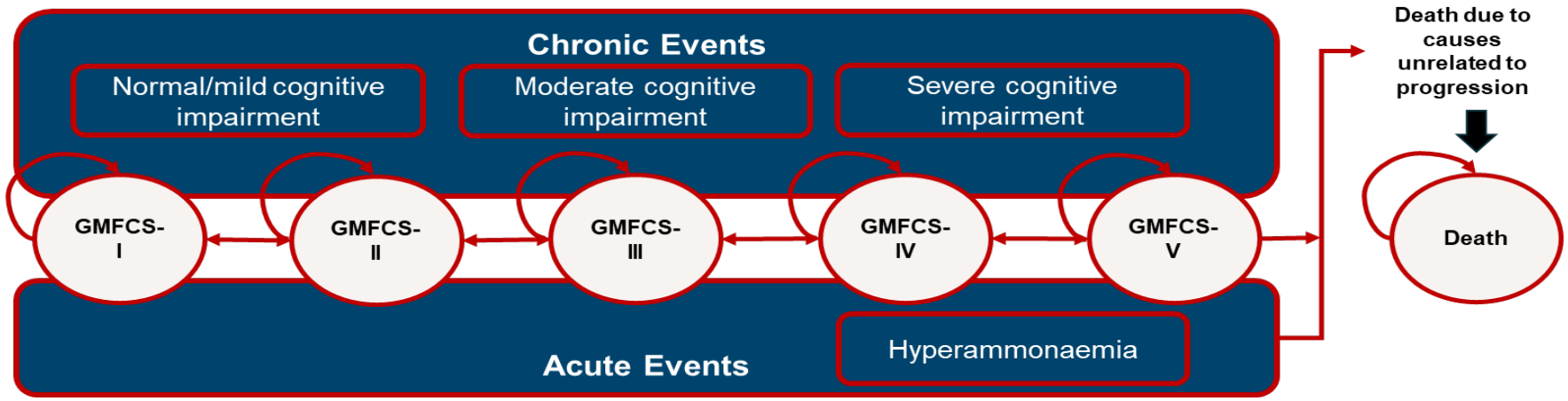
Source: Company Data on File. Delphi Panel Report. March 2025.

Report conclusion:

- Consensus achieved; 100% agreed with the consensus statement in the meeting.
- Final consensus statement: 90% of ARG1-D patients are dead by 32 years (excluding death due to HAC).

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.

NICE

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