Pegzilarginase for treating arginase-1 deficiency [ID4029]

For public – confidential information redacted

Highly Specialised Technology Appraisal Committee [15th August 2024]

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Pegzilarginase for treating arginase-1 deficiency

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

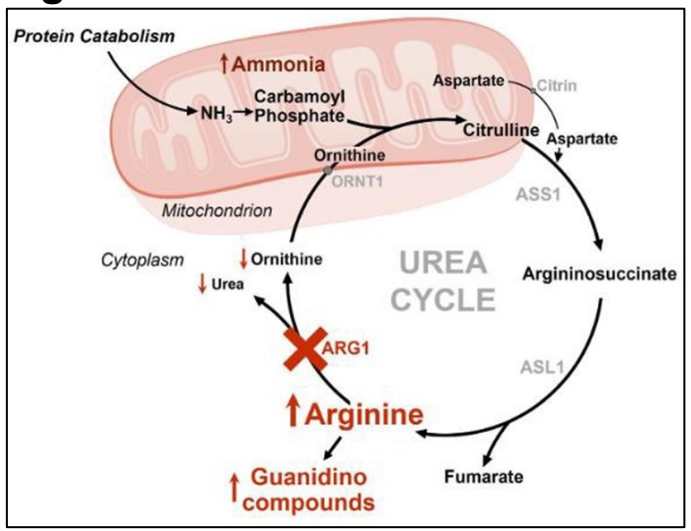
Background on arginase-1 deficiency (ARG1-D)

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 hyperarginemia

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

Patient and carer perspectives

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

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 hyperarginaemia, 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

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

Are there any relevant equality issues?

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

Key issues

Issue	ICER impact
Starting distribution of patients across GMFCS states	Large
Assuming patients remain in same GMFCS state after 3 years with pegzilarginase	Large
Uncertainty around transition probabilities for IDM	Small/moderate
Assumption that almost all patients die by 35 years of age	Large
Life expectancy for patients receiving pegzilarginase treatment	Large
Distribution of peak ammonia levels during a HAC	Moderate
Cognitive improvement associated with pegzilarginase treatment	Large
Utility gain associated with an improved diet	Moderate
Disutility for carers	Moderate
Pegzilarginase drug wastage/dosing	Large/moderate
Discontinuation rate	Large
QALY losses attributed to carers when calculating the weights for QALYs	Moderate

GMFCS: Gross Motor Function Classification System; HAC: Hyperammonaemic crises; IDM: Individualised disease management; QALY: Quality-adjusted life years

Decision problem

EAG does not have any concerns with company's deviations from final NICE scope

	Final NICE scope	EAG and tech team comments
Population	People with ARG1-D aged 2 years and older	As per NICE scope
Intervention	Pegzilarginase	As per NICE scope but with individualised disease management
Comparators	• Established clinical management without pegzilarginase (including dietary protein restrictions, essential amino acid supplementation and/or the use of ammonia scavengers)	Uses the term 'individualised disease management' as opposed to 'established clinical management without pegzilarginase' ➔ Better aligns with published literature, UK clinical practice and PEACE trial
Outcomes	The outcome measures to be considered include: • Plasma arginine concentration • Level of ornithine and guanidino compounds • Mobility • Adaptive behaviour • Neurocognitive function • Adverse effects of treatment • Health-related quality of life	As per NICE scope

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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

See appendix slides: 'PEACE study design' and 'Study101A/102A design'

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 ≥250 µM (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 ≥100 µM 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	

NICE

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

See appendix slide: 'Other baseline characteristics: PEACE study'

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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

See appendix slide: 'Other baseline characteristics: Study 101A/102A'

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

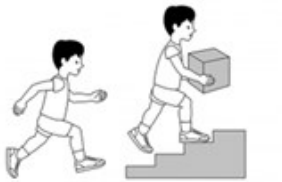
Clinical expert submission

- 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

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

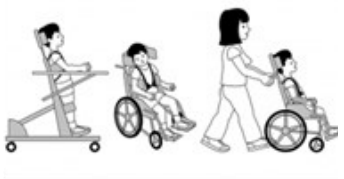
- Has the ability to walk indoors and outdoors and climb stairs with a railing
- Has difficulty with uneven surfaces, inclines and crowds
- Has only minimal ability to run or jump

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

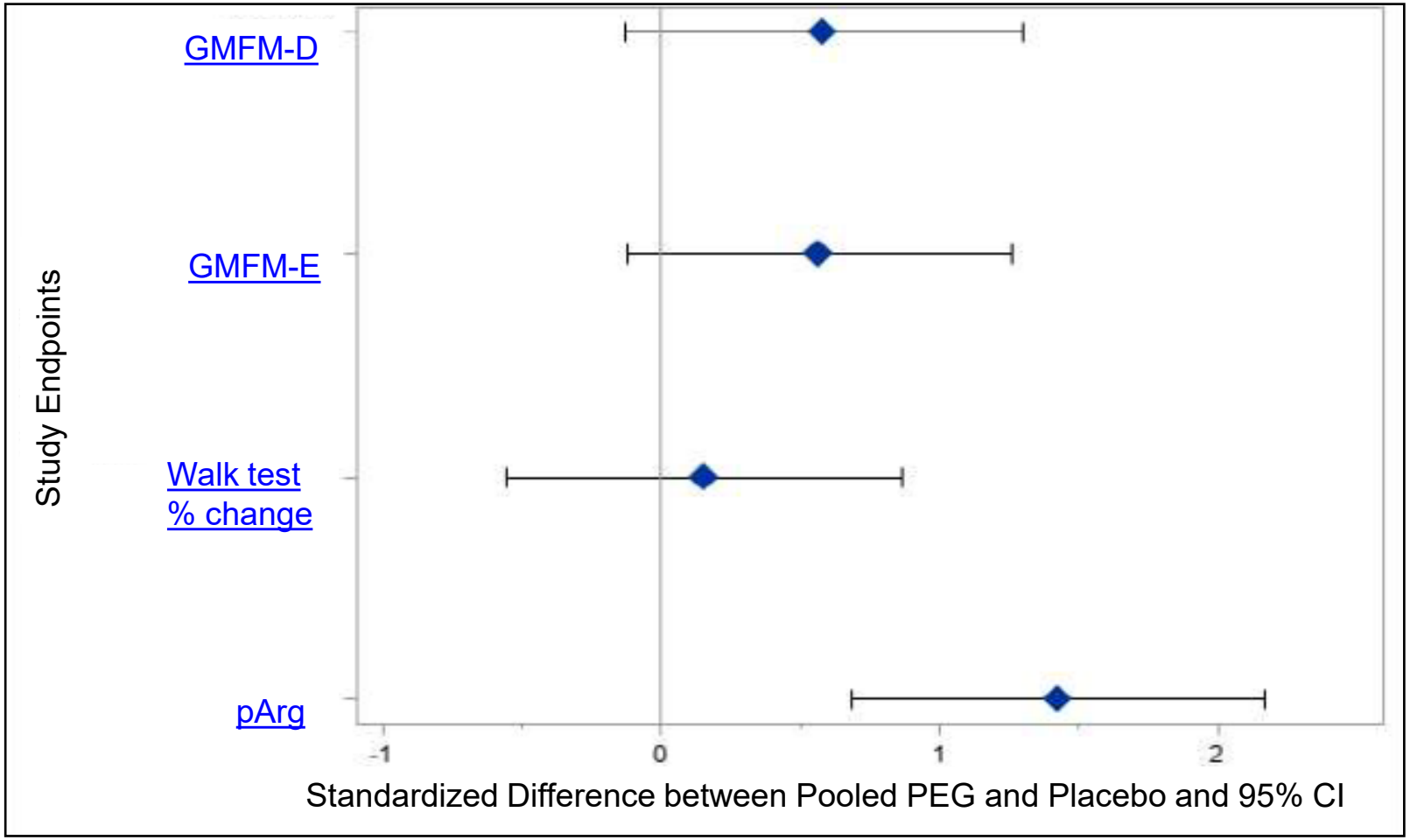
Source: EAR, Figure 2

GMFCS: Gross Motor Function Classification System

PEACE and Study 102A results

Pooled analysis of biomechanical and motor outcomes

Figure: Pooled analysis of PEACE and Study 102A



Source: EAR, Figure 7

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

For other outcome results, see appendix slide: 'PEACE results: Effect of pegzilarginase on ornithine and GC levels'

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

PEACE results
Neurocognitive outcomes

Table: Clinical efficacy results for neurocognitive outcomes from PEACE

Trial arm		Baseline	Week 24	LTE24	LTE96	EOS
VABS-II						
Pegzilarginase	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	[redacted]
Placebo-pegzilarginase	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	[redacted]
Between group	Change from baseline	(LS mean difference: [redacted] 95% CI: [redacted] *p* [redacted]		-	-	-
Wechsler						
Pegzilarginase	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	[redacted]
Placebo-pegzilarginase	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	[redacted]
Between group	Change from baseline	NR		-	-	-

Source: EAR, Table 10

CI: Confidence interval; EOS: End of study; LS: Least square; LTE: Long term extension; MCFB: Mean change from baseline; NR: Not reported; SD: Standard deviation; VABS-II: Vinelands Adaptive Behaviour Scale, Second Edition

EAG critique of clinical effectiveness evidence

Results for pArg levels are promising. Other outcome results uncertain and underpowered due to small patient numbers

EAG comments:

- Pegzilarginase appears to have a robust effect on pArg levels within first 24 weeks
  - pArg levels do not have a consistent relationship with disease severity. But it is a marker of disease used to monitor patients ➔ Also closely linked to hyperammonaemic crises (HACs)
- Effect on clinical outcomes (motor, neurocognitive and QoL) in short-term less certain ➔ Results were not both clinically and statistically significant or were not tested for statistical significance
- Uncertainty around generalisability of MCIDs used for ARG1-D and underpowering may have affected outcomes ➔ Some risk of bias from imbalances in baseline characteristics between arms in PEACE study
- Long-term pArg levels and motor outcomes uncertain ➔ Lack of comparator arm and small patient numbers
- Long term effects on neurocognition and QoL were mixed and uncertain
- Results for HACs favoured pegzilarginase numerically but subject to limitations for analyses performed
- Plausible ceiling effect for mobility and spasticity outcomes ➔ Small improvements in GMFCS-I state was expected as little room for improvement when baseline measurements are high

2MWT: 2-minute walk test; GMFM-D: Global Motor Function Measure, Part D; GMFM-E: Global Motor Function Measure, Part E; HACs: Hyperammonaemic crisis; MCIDs: Minimal clinically important differences; pArg: Plasma arginase; QoL: Quality of life

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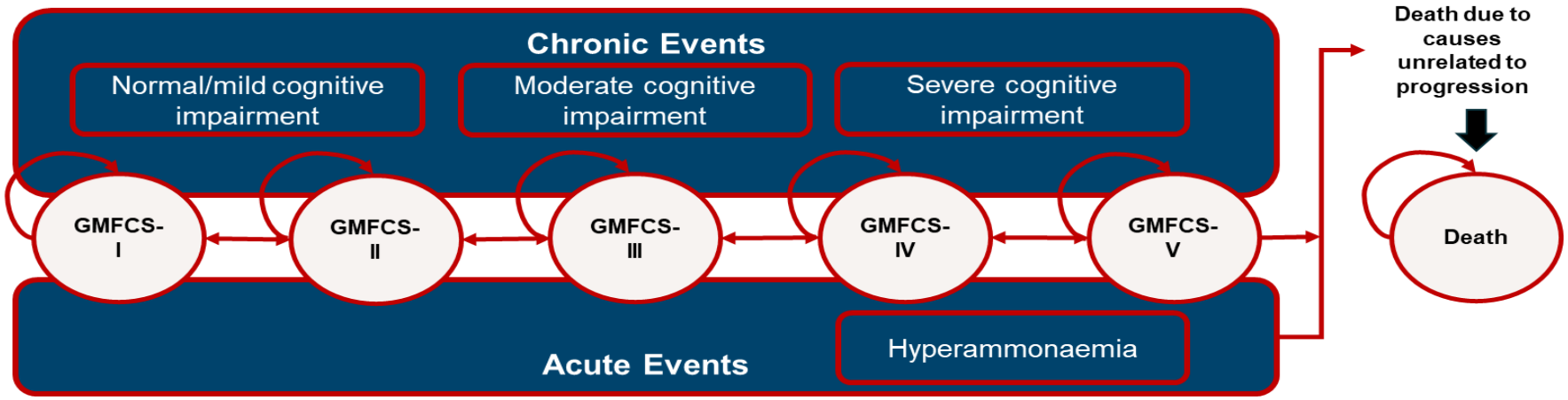
Company's model overview

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

Assumptions with large impact on cost effectiveness results

- **Pegzilarginase stops disease deterioration after 3 years**
- Starting distribution of patients across GMFCS states
- Assumption that almost all patients die by 35 years of age
- Life expectancy for patients receiving pegzilarginase treatment
- Cognitive improvement associated with pegzilarginase treatment
- Disutility for carers
- Pegzilarginase drug wastage
- Treatment discontinuation assumptions for pegzilarginase

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

Summary of evidence used in the company's base case (1)

Parameter group		Source
Patient characteristics (Age, gender, distribution across GMFCS states)		Pooled data from PEACE, Study 101A/102A, and European BOI survey – [redacted] years
Weight ratio vs general population		Ratio of pooled weight in PEACE and Study 101A/102A compared with the expected weight given same age and sex distribution: [redacted] for paediatric, [redacted] for adult
Initial transition probabilities		Calculated using data from the PEACE study
Longer-term transition probabilities		Pegzilarginase: Assumed no change in GMFCS state IDM: Decline in GMFM DE score per year used to derive transition probabilities
HAC	Frequency (IDM)	Frequency: pooled data from Urea Cycle Disorders Consortium Registry and placebo arm in PEACE
	Rate ratio (pegzilarginase compared with IDM)	PEACE

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; HAC: Hyperammonaemic crisis; IDM: Individualised disease management

Summary of evidence used in the company's base case (2)

Parameter group		Source
Mortality	General population	UK life tables
	SMR for IDM	Model calibration assuming 'nearly all' patients die by 35 years of age
	SMR for Pegzilarginase	HST 18
	HAC	Published data for urea cycle disorders conditional on age and peak ammonia levels
	Distribution of peak ammonia level in HACs	PEACE study dependent on treatment arm
Utilities	GMFC-II to -V	European BOI survey mapped to EQ-5D-3L
	GMFC-1	Midway between the European BOI survey mapped to EQ-5D-3L values and the general population value matched for age and sex
	Cognitive disutility	HST18
	Utility gain from improved diet	Calculated from data in HST13, a vignette study, and general population data
Source of costs		European BOI survey, with HST18 used as supplementary evidence

HST13: Volanesorsen for treating familial chylomicronaemia syndrome
HST18: Atidarsagene autotemcel for treating metachromatic leukodystrophy

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; HAC: Hyperammonaemic crisis; HST: Highly specialised technology; IDM: Individualised disease management; SMR: Standardised mortality ratio

Large impact

Key issue: Starting distribution by GMFCS states

Company

- Uses pooled data from PEACE, Study101A/102A and BOI survey to inform starting distribution across GMFCS states in base case

EAG comments

- Clinical advice suggests distribution of patients across GMFCS states may be more representative in the European BOI survey than in clinical studies where more severe patients may be underrepresented
- Presented scenario analyses setting the initial distribution equal to that observed in the BOI survey (SA5)

NICE technical team

- Issue has large impact on ICER – clinical expert input could be informative for NHS England population

Table: Alternative starting distribution between GMFCS states

	Distribution of GMFCS at model entry					Source
	I	II	III	IV	V	
Company's 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=64)
EAG scenario analysis (SA5)	50.00%	31.25%	0.00%	12.50%	6.25%	BOI survey (n=16)

Source: EAR, Table 29

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

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; SA5: Scenario analysis 5

Large impact

Key issue: Assuming patients on pegzilarginase remain in same GMFCS state after 3 years

Company

- Model assumes people receiving pegzilarginase treatment remain in same state after 3 years of treatment
  - In trials, some patients' GMFM D&E scores were still improving up to 4 years post treatment initiation
  - Controlled pArg results in controlled underlying disease pathogenesis ➔ No reason for progression
  - Patients can't become resistant to pegzilarginase

EAG comments

- Whilst clinical experts consulted by EAG believe that this is plausible, PEACE study only reported data on mobility outcomes for a short period ➔ Assumption hinges on expert opinion
- Presented four scenario analyses (SA1):
  1) After 3 years of treatment, the risk of transition to the next worse GMFCS state is 10% (SA1a) and 20% (SA1b) of that associated with IDM
  2) People remain in the same GMFCS state after 2 years (SA1c) or 4 years (SA1d) of treatment with pegzilarginase

What should be assumed for long term outcomes with pegzilarginase and at what time point should this be applied in the model?

GMFCS: Gross Motor Function Classification System; SA1: Scenario analysis 1

Transition probabilities: disease progression

Initial disease progression:

- Transition probabilities between health states estimated using GMFCS changes between visits in PEACE study for duration of follow-up
- For pegzilarginase, a time-invariant transition matrix was estimated based on 96 weeks of data, which is assumed to apply for 3 years (157 weeks)
- For IDM, a time-invariant transition matrix was estimated based on 24 weeks of data, which the company assumed to be generalisable for half a year (26 weeks)

Long term disease progression:

- For pegzilarginase, company assumed no disease progression after 3 years ➔ All patients remain in GMFCS state that they were in at 3 years if receiving pegzilarginase
- For IDM, company estimated transition probabilities in multiple steps
  - Estimated relationship between GMFM DE score and GMFCS state ➔ Assumed thresholds for change between GMFCS states were mid-way between lower CI for better health state and upper CI for worse health state
  - Calculated average times taken to move through GMFCS states based upon a linear regression of GMFM DE score and patient age ➔ 1.45 decline in GMFM DE estimated per year
  - Constant transition probabilities generated using inverse of mean time in state, converting from annual to cycle-specific transition probabilities
- **EAG comment:** Inverse of mean time in state should be considered as a rate rather than probability

GMFCS: Gross Motor Function Classification System; IDM: Individualised disease management

Small/moderate impact

Key issue: Uncertainty around long-term transition probabilities for IDM (1)

1) Error in calculating the transition probabilities for IDM

Company: Transition probabilities generated using inverse of time in each health state

EAG: Inverse of time spent in a GMFCS state is a rate which should be converted to a probability (EA1)

2) Starting GMFM DE score for patients in GMFCS-I

Company: Assumes a score of [redacted] for patients in GMFCS-I

EAG: Uses GMFM DE score of [redacted] (mean of PEACE and Study 101A/102A) for patients in GMFCS-I (EA2)

3) Decrease in GMFM DE score as patients age

Company: Assumed that patients' GMFM DE score declines by 1.45 per year

EAG: Uses upper limit of 95% CI (2.66) for decline in GMFM DE scope per year (EA3)

- EAG also provided scenario analysis (SA7) where transition probabilities between GMFCS states for patients receiving IDM, were changed from the EAG base case to those associated with the time in a GMFCS state calculated using the midpoint GMFM DE score values for each GMFCS state

See appendix slides: 'Error in calculating the transition probabilities for IDM', 'Starting GMFM DE score for patients in GMFCS-I' and 'Decrease in GMFM DE score as patients age'. Back to slides: 'Key issues' and 'Questions for committee'

GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management

Small/moderate impact

Key issue: Uncertainty around long-term transition probabilities for IDM (2)

Table: IDM transition probabilities

Transitioning from	Company's base case	EA1	EA2	EA3	EAG's base-case (EA1+EA2+EA3)*	SA7
GMFCS-I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAR, Table 28

See appendix slides: 'Error in calculating the transition probabilities for IDM', 'Starting GMFM DE score for patients in GMFCS-I' and 'Decrease in GMFM DE score as patients age'. Back to slides: 'Key issues' and 'Questions for committee'

1. Is the EAG's approach to use the upper limit of the 95% CI (2.66) as the decline in GMFM DE score per year appropriate for decision making?
2. For IDM arm, is the EAG's approach to calculate transition probabilities between GMFCS states using inverse of the time spent in a GMFCS state appropriate for decision making?
3. Is the EAG's approach to use the mean GMFM DE score from PEACE and STUDY101A/102A for patients starting in GMFCS-I appropriate for decision making?
4. Is the EAG's approach for calculating transition probabilities for IDM in SA7 appropriate for decision making?

GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management

Mortality

- Little literature evidence was found for mortality associated with ARG1-D
- Company not aware of many patients >40 years in any centres throughout Europe ➔ Only one patient aged 49 in BOI survey
- To estimate long-term survival, company calibrated the model such that “nearly all” patients receiving IDM die by 35 years of age, including deaths associated with HACs
- Assumed that (i) SMRs from MLD compared to an age- and sex-matched population captured the impact of neuro-disability on mortality and were generalisable for people with ARG1-D treated with pegzilarginase, having removed the toxicity associated with the MLD treatment (atidarsagene autotemcel) and (ii) that a multiplier would be applied to pegzilarginase SMRs to obtain SMRs for patients treated with IDM

ARG1-D: Arginine-1 deficiency; BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; HACs: Hyperammonaemic crisis; IDM: individualised disease management; MLD: Metachromatic leukodystrophy; SMR: Standardised mortality ratio

Large impact

Key issue: Assumption that almost all patients die by 35 years of age

Company

- Model assume that "nearly all" patients receiving IDM die by 35 years of age, including deaths associated with HACs

EAG comments

- Clinical advice suggests it is unlikely that nearly all patients would die by 35 years of age
- Notes that one patient was aged 49 years in the BOI survey
- Presented following scenario analyses (SA6):
  - **1) SA6a:** Age at which nearly all people were dead was 50 years
  - **2) SA6b:** Calibrated the model using the assumed starting age of patients in the model ([redacted] years) rather than assuming patients were aged 4 years

Is it appropriate to assume that nearly all patients receiving IDM die by 35 years of age?

BOI: Burden of illness; HACs: Hyperammonaemic crisis; IDM: individualised disease management; SA6: Scenario analyses 6

Large impact

Key issue: Life expectancy for patients receiving pegzilarginase

Company

- Model assumes data from an age- and sex-matched population with metachromatic leukodystrophy, with impact of toxicity removed, were generalisable to patients with ARG1-D receiving pegzilarginase
- Multiplier applied to pegzilarginase SMRs to obtain SMRs for IDM - company estimated an SMR for IDM 800 times greater than SMR for pegzilarginase. With this, proportion of alive is 0.0008% at 35 years

EAG comment

- Presented scenario assuming SMR for pegzilarginase arm is twice the company's base case (SA11)

Clinical expert submission

- Not possible to comment if technology will impact on length of life based on currently available data

Table: Alternative SMRs applied in the model by the EAG

Health State	SMR (company and EAG's base case)		SMR (SA7)	
	Pegzilarginase	IDM	Pegzilarginase	IDM
GMFCS-I	1.16	928.0	2.32	1160.00
GMFCS-II	1.32	1056.0	2.64	1320.00
GMFCS-III	1.80	1440.0	3.60	1800.00
GMFCS-IV	1.80	1440.0	3.60	1800.00
GMFCS-V	8.14	6508.8	16.27	8136.00

Source: EAR, Table 19 and 32

NICE technical team

- Query company's modelled estimates of similar life years gained (LYGs) for pegzilarginase across health states

Back to slides: 'Key issues' and 'Questions for committee'

Is EAG's scenario assuming the SMR associated with pegzilarginase arm is twice that in the company's base case more appropriate for decision making?

ARG1-D: Arginine-1 deficiency; GMFCS: Gross Motor Function Classification System; ICER: Incremental cost-effectiveness ratio; IDM: individualised disease management; MLD: Metachromatic leukodystrophy; SA11: Scenario analysis 11; SMR: Standardised mortality ratio

Moderate impact

Key issue: Distribution of peak ammonia levels during a HAC

Company

- A proportion of HACs are assumed to result in death ➔ Risk of death due to a HAC estimated, using data from UCDC registry, conditional on age and four peak ammonia categories

EAG comments

- Peak ammonia levels during a HAC on pegzilarginase treatment informed by only [redacted] data points and [redacted]
- Presented a scenario analysis by applying a continuity correction, operationalised by splitting one additional data point across all four peak ammonia categories for both treatment arms (SA8)

Table: Peak ammonia levels during HACs conditional on treatment

Peak ammonia level	Distribution of peak ammonia level in HACs			
	Company base case		EAG scenario (SA8)	
	Pegzilarginase	IDM	Pegzilarginase	IDM
≤200 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
>200-500 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
>500-1000 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
>1000 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAR, Table 30

Back to slides: 'Key issues' and 'Questions for committee'

Is the distribution of peak ammonia levels from company's base case or EAG scenario SA8 more appropriate for decision making?

NICE

HAC: Hyperammonaemic crisis; IDM: individualised disease management; ICER: Incremental cost effectiveness ratio; SA8: Scenario analysis 8; UCDC: Urea cycle disorders consortium

Utility Values

- Health state utility values are mainly taken from European BOI survey - includes EQ-5D-5L responses from **2 patients and 14 carers** ➔ EQ-5D-5L responses mapped to EQ-5D-3L
- For GMFCS-I, company stated EQ-5D-3L value substantially lower than in similar health states in cerebral palsy and metachromatic leukodystrophy. Instead, company used mean of utility value of the GMFCS-I state in BOI survey and general population utility at 13 years old
- For GMFCS-III, average of GMFCS-II and GMFCS-IV was used
- Additionally, disutility is applied for cognitive disability, HACs (0.067) and caregiver disutility
- Utility values for GMFCS-V with severe cognitive impairment are capped at -0.250
- Utility gain of 0.01 is applied associated with an improved diet due to pegzilarginase treatment

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; HACs: Hyperammonaemic crisis; IDM: individualised disease management

Disutility: Cognitive disability

- Model includes disutility associated with cognitive disability persisting indefinitely in each health state
- Disutility values estimated by GMFCS state, using values for MLD presented in a report for the Institute for Clinical and Economic Review
  - Disutility was calculated by subtracting utility values for moderate and severe cognitive function health states from that for mild/normal cognitive function health state in early juvenile patients with MLD
- Company assumed no loss of utility in no impairment and mild impairment states

Table: Cognitive deficit by GMFCS health state

Health State	Disutility Associated with		Source
	Moderate impairment	Severe impairment	
GMFCS-I	0.24	0.53	Calculated from an Institute for Clinical and Economic Review report on MLD
GMFCS-II	0.28	0.57	
GMFCS-III	0.28	0.49	
GMFCS-IV	0.16	0.17[2]	
GMFCS-V	0.12[1]	0.12[3]	

[1] Original value 0.17; 0.12 used as the company assumes utility cannot be below -0.250
[2] Original value 0.33; 0.17 used as the company assumes utility cannot be below -0.250
[3] Original value 0.33; 0.12 used as the company assumes utility cannot be below -0.250

Source: EAR addendum, Table 2

GMFCS: Gross Motor Function Classification System; MLD: Metachromatic leukodystrophy

Large impact

Key issue: Cognitive improvement associated with pegzilarginase

Company

- Model assume random improvements in cognitive ability associated with pegzilarginase treatment over IDM for patients in same GMFCS state for GMFCS-I to GMFCS-III

EAG comments

- Whilst clinical experts consulted by the EAG believe that this is plausible, there is also a large degree of uncertainty related to this benefit provided by pegzilarginase
- Presented a scenario analysis (SA2) which assumes cognitive impairment by GMFCS state is independent of treatment (i.e. distributions of cognitive impairment for pegzilarginase = IDM)

See appendix slide: 'Distributions across cognitive impairment bands'
Back to slides: 'Key issues' and 'Questions for committee'

How should improvement in cognitive ability associated with pegzilarginase treatment be modelled?

NICE

GMFCS: Gross Motor Function Classification System; ICER: Incremental cost effectiveness ratio; IDM: individualised disease management; SA5: Scenario analysis 5

Moderate impact

Key issue: Utility gain associated with an improved diet

Company

- Presented data showing >25% of people in LTE receiving pegzilarginase had increased protein consumption of >15% relative to baseline
- Attributed a benefit of less strict dietary protein restriction estimated using a utility decrement reported in HST13 informed by a vignette study ➔ Assumed an improved diet associated with utility gain of 0.039
- Applied to 24.7% of patients (difference in % of patients in PEACE that increased protein consumption by >15% in pegzilarginase arm (42.9%) compared with IDM arm (18.2%)
- Resulted in average increase in utility of 0.01, due to benefits in improvements in dietary restrictions which was applied indefinitely

EAG comments

- EAG clinical experts supported increase in utility for patients eating more protein
- Associated gain in utility value is uncertain
- EAG provided a scenario assuming a utility gain of zero (SA3)

Back to slides: 'Key issues' and 'Questions for committee'

Is it appropriate to apply a utility gain of 0.01 associated with an improved diet due to pegzilarginase treatment?

HST13: Highly Specialised Technology 13; IDM: Individualised disease management; LTE: Long term extension; SA3: Scenario analysis 3

Utility values: summary

Table: Starting utility values for patients used in company's base case excluding decrements due to HACs and including utility gain associated with an improved diet due to pegzilarginase treatment

	GMFCS-I	GMFCS-II	GMFCS-III	GMFCS-IV	GMFCS-V
IDM					
Mild/no cognitive impairment	0.855	0.604	0.263	-0.077	-0.126
Moderate cognitive impairment	0.615	0.324	-0.017	-0.237	-0.250
Severe cognitive impairment	0.325	0.034	-0.227	-0.250	-0.250
Pegzilarginase + IDM*					
Mild/no cognitive impairment	0.865	0.613	0.273	-0.067	-0.117
Moderate cognitive impairment	0.624	0.333	-0.007	-0.227	-0.240
Severe cognitive impairment	0.334	0.043	-0.217	-0.240	-0.240
* Utility gain of 0.01 associated with an improved diet due to pegzilarginase treatment					

Source: EAR, Table 21

GMFCS: Gross Motor Function Classification System; HACs: Hyperammonaemic crisis; IDM: individualised disease management

Key issue: Disutility for carers

Company

- Base case model applies caregiver disutilities from HST18 ➔ GMFC-MLD health states are collapsed into GMFCS health states according to clinical expert feedback
- Model assumes 2 carers up to 16 years of patients age, followed by 1 carer after 16 years of age

EAG comments:

- Provided scenario analyses (SA10):
  1) SA10a: Carer disutility = 0.062 based on difference between caregivers and population norm in UK reported (Sevin et al.) but only applied to carers of patients in GMFCS-III and above
  2) SA10b: Carer disutility values from BOI survey pooled for GMFCS-IV and GMFCS-V

Table: Company base case and EAG's alternative carer disutility values

Health State	Company and EAG base case	EAG alternative assumption 1	EAG alternative assumption 2
GMFCS-I	0.01	0	0.018
GMFCS-II	0.03	0	0.149
GMFCS-III	0.07	0.062	0.106
GMFCS-IV	0.11	0.062	0.063
GMFCS-V	0.16	0.062	0.063

Source: EAR, Table 31

Back to slides: '<u>Key issues</u>' and '<u>Questions for committee</u>'

Are the caregiver disutilities used in the company and EAG base case model appropriate?

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; GMFC-MLD; Gross Motor Function Classification in Metachromatic Leukodystrophy; HST18: Highly Specialised Technology 18; SA10: Scenario analyses 10

Large/moderate impact

Key issue: Pegzilarginase drug wastage/dosing

Company

- Assumes a 10% margin when estimating the number of vials required for patients
- Assumes a single value for weight at each age that was assumed to be applicable for all patients
- Method of using a weight distribution used in sensitivity analyses assuming full or no drug wastage

EAG comments

- Clinical experts to EAG indicated:
  - i. Company's approach of 10% margin most appropriate, although uncertainty around true level of drug wastage
  - ii. There would be a concerted effort to reduce drug wastage which could include having an additional vial every two weeks should the optimal dose indicate half a vial a week
- Provided following scenario analyses (SA4):
  1) SA4a: Assuming full drug wastage (10% margin removed) **2) SA4b:** Assuming no drug wastage

NICE technical team

- Weight-based drug costs: company assume same lower weight ratios from trials for patients throughout model – clinical expert input useful to state whether patients would gain weight with diet improvement etc on pegzilarginase. Provide scenarios with heavier weights assumed (including general population weights)

Back to slides: 'Key issues' and 'Questions for committee'

What proportion of drug wastage is appropriate to assume in the economic model?
Is it appropriate to assume same lower weight ratios for lifetime of the model?

NICE

Large impact

Key issue: Discontinuation rate

Back to slides: 'Key issues' and 'Questions for committee'

Company

- Model does not include a stopping rule based on pArg levels ➔ Lack of consensus from clinical experts
- Although one patient (4.8%) discontinued pegzilarginase in the trial, model assumes a low (1%) annual discontinuation rate ➔ Patient in the trial discontinued treatment early when receiving pegzilarginase by infusion in hospital. In practice patients can receive subcutaneous injections from treatment initiation

EAG comments

- Clinical experts to EAG agreed that it's unlikely patients would discontinue pegzilarginase treatment where it was positively impacting on pArg levels ➔ Presented scenario (SA9) assuming 0% discontinuation
- Company's model does not appear to have the functionality to incorporate responders and non-responders to pegzilarginase treatment ➔ Unable to generate ICERs incorporating responders and non-responders ➔ Cost-effectiveness likely improve if only patients that benefit most remaining on treatment

Clinical expert submission

- It would be useful to have stop and start rules ➔ Should be agreed with all the specialist centres

NICE technical team

- Issue has large impact on weighted ICER – assuming a higher discontinuation rate substantially reduces number of undiscounted QALYs – provide scenarios with 2% and 4.8% (trial based) discontinuation rates

Should pegzilarginase treatment discontinuation be included in the economic model? If so,

- What proportion of treatment discontinuation should be included in the model?
- Should responders and non-responders be modelled separately?

ICERs: Incremental cost effectiveness ratios; pArg: Plasma arginine; SA9: Scenario analysis 9

Moderate impact

Key issue: QALY losses attributed to carers when calculating the weights for QALYs

Company

- In company's base case the undiscounted incremental QALY gain associated with pegzilarginase treatment was 28.69 ➔ Applied a weight of 2.87 to QALYs in line with NICE HST methods

EAG comments

- Unclear whether calculation of incremental QALYs should include carer QALYs to estimate HST QALY weighting ➔ QALY loss associated with carers for patients receiving pegzilarginase was 1.056 and 0.262 for patients receiving IDM
- Removing QALY losses for carers results in undiscounted incremental QALYs of 29.763 and a QALY weighting of 2.976
- Provided scenario analysis where QALYs associated with carers are removed from QALY weighting (SA12)

NICE technical team

- QALY losses associated with carer disutility should not be included in calculation of QALY weights

Back to slides: 'Key issues' and 'Questions for committee'

Should QALY losses attributed to carers be included in the QALY weighting calculation?

HST: Highly Specialised Technology; ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management; QALY: Quality-adjusted life year; SA12: Scenario analysis 12

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Base case assumptions and cost-effectiveness results**
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company's base case results

See appendix slide: 'Difference between company and EAG base case assumptions'

Deterministic incremental base case results

	Total			Incremental			ICER (£/QALY)	
Technology	Costs (£)	QALYs	LYGs[1]	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted*
Pegzilarginase	[redacted]	[redacted]	48.14	[redacted]	[redacted]	43.54	581,036	202,511
IDM	[redacted]	[redacted]	4.59	-	-	-	-	-

* QALY weight of 2.87 is applied to the unweighted ICER
[1] Undiscounted

Probabilistic incremental base case results**

	Total			Incremental			ICER (£/QALY)	
Technology	Costs (£)	QALYs	LYGs[1]	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted*
Pegzilarginase	[redacted]	[redacted]	NR	[redacted]	[redacted]	NR	568,635	202,647
IDM	[redacted]	[redacted]	NR	-	-	-	-	-

* QALY weight is applied to the unweighted ICER as follows: From 1000 iterations, mean: 2.77, min: 1.77, max: 3.00
** EAG corrected an error in relation to the starting distribution used in the company's probabilistic analyses
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management; LYGs: Life years gained; QALYs: Quality-adjusted life years

See appendix slide: 'Difference between company and EAG base case assumptions'

EAG's base case results

Deterministic incremental base case results

	Total			Incremental			ICER (£/QALY)	
Technology	Costs (£)	QALYs	LYGs[1]	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted
Pegzilarginase	[redacted]	[redacted]	48.12	[redacted]	[redacted]	43.66	570,050	196,782
IDM	[redacted]	[redacted]	4.46	-	-	-	-	-

* QALY weight of 2.90 is applied to the unweighted ICER
[1] Undiscounted

Probabilistic incremental base case results

	Total			Incremental			ICER (£/QALY)	
Technology	Costs (£)	QALYs	LYGs[1]	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted
Pegzilarginase	[redacted]	[redacted]	48.41	[redacted]	[redacted]	42.64	558,411	197,659
IDM	[redacted]	[redacted]	5.77	-	-	-	-	-

* QALY weight of is applied to the unweighted ICER as follows: From 1000 iterations, mean: 2.77, min: 1.77, max: 3.00
[1] Undiscounted

EAG comment: EAG's sensitivity analyses should be deliberated by the Appraisal Committee and a preferred set of assumptions defined, for which the EAG can produce an Appraisal Committee ICER

Results include confidential commercial discount for pegzilarginase

ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management; LYGs: Life years gained; QALYs: Quality-adjusted life years

EAG exploratory analysis

Exploratory analysis[#]	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
Company base case	[redacted]	[redacted]	**43.54**	**581,036**	**202,511**	**2.87**
EA1: Correction of error in IDM transition probabilities	[redacted]	[redacted]	43.54	581,541	202,777	2.87
EA2: Assumed starting GMFM DE score for patients in GMFCS-I	[redacted]	[redacted]	43.56	578,715	201,293	2.87
EA3: Using lower 95% CI for decrease in GMFM DE score when ageing one year	[redacted]	[redacted]	43.66	571,449	197,503	2.89
EAG deterministic base case (EA1+EA2+EA3)	[redacted]	[redacted]	**43.66**	**570,050**	**196,782**	**2.90**
EAG probabilistic base case (EA1+EA2+EA3)	[redacted]	[redacted]	**42.64**	**558,411**	**197,659**	**2.79**

[#] Exploratory analysis are applied to company base case
* QALY weight of is applied to the unweighted ICER
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management; LYGs: Life years gained; QALYs: Quality-adjusted life years

EAG deterministic scenarios analyses (1)

Scenario analysis#	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG deterministic base case (EA1+EA2+EA3)	[redacted]	[redacted]	**43.66**	**570,050**	**196,782**	**2.90**
SA1a: Risk of transition to the next worse GMFCS state is 10% of that associated with IDM	[redacted]	[redacted]	42.93	660,361	290,084	2.28
SA1b: Risk of transition to the next worse GMFCS state is 20% of that associated with IDM	[redacted]	[redacted]	42.16	756,108	413,825	1.83
SA1c: Remain in same health state after 2 years of pegzilarginase treatment	[redacted]	[redacted]	43.55	607,880	223,560	2.72
SA1d: Remain in same health state after 4 years of pegzilarginase treatment	[redacted]	[redacted]	43.76	544,422	181,474	3.00
SA2: Distribution of cognitive impairment independent of treatment	[redacted]	[redacted]	43.66	595,814	214,499	2.78
SA3: No utility gain from improved diet	[redacted]	[redacted]	43.66	579,193	203,093	2.85
SA4a: Full pegzilarginase wastage	[redacted]	[redacted]	43.66	604,664	208,731	2.90
SA4b: No pegzilarginase wastage	[redacted]	[redacted]	43.66	551,443	190,359	2.90

Scenario analysis are applied to EAG's deterministic base case
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

GMFCS: Gross Motor Function Classification System; Incremental cost effectiveness ratio; IDM: Individualised disease management; LYGs: Life years gained; QALYs: Quality-adjusted life years

EAG deterministic scenarios analyses (2)

Scenario analysis#	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG deterministic base case (EA1+EA2+EA3)	[redacted]	[redacted]	**43.66**	**570,050**	**196,782**	**2.90**
SA5: Starting distribution aligned with the European BOI study	[redacted]	[redacted]	43.48	604,747	219,465	2.76
SA6a: Assuming nearly all patients died before 50 years of age for the calibration	[redacted]	[redacted]	39.52	590,812	209,138	2.82
SA6b: Assuming a starting age of [redacted] years for the calibration	[redacted]	[redacted]	43.92	567,728	195,504	2.90
SA7: Using time in GMFCS health state based on midpoint GMFM DE scores	[redacted]	[redacted]	43.68	580,493	202,208	2.87
SA8: Adding a continuity correction to the peak ammonia levels data for HAC	[redacted]	[redacted]	42.60	570,730	201,596	2.83
SA9: Assuming no discontinuation (0%) of pegzilarginase treatment	[redacted]	[redacted]	61.10	570,668	190,223	3.00

Scenario analysis are applied to EAG's deterministic base case
** NICE technical team scenarios validated by EAG
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; HAC: Hyperammonaemic crisis; ICER: Incremental cost effectiveness ratio; LYGs: Life years gained; QALYs: Quality-adjusted life years

EAG deterministic scenarios analyses (3)

Scenario analysis#	Incremental			ICER (£/QALY)		
	Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG deterministic base case (EA1+EA2+EA3)	[redacted]	[redacted]	**43.66**	**570,050**	**196,782**	**2.90**
SA10a: Assuming a carer disutility of 0.062 for patients in GMFCS-III and above	[redacted]	[redacted]	43.66	559,359	189,134	2.96
SA10b: Assuming carer disutility from the BOI survey pooling GMFCS-IV and GMFCS-V	[redacted]	[redacted]	43.66	592,828	213,717	2.77
SA11: Assuming double the SMR associated with pegzilarginase treatment	[redacted]	[redacted]	40.38	564,433	208,685	2.70
SA12: Removing QALY losses for carers when calculating the QALY weight	[redacted]	[redacted]	43.66	570,050	191,530	2.98
SA13: Using a starting age of 18 years	[redacted]	[redacted]	42.64	557,132	201,354	2.77
SA14: Utility from Ryan et al. (in cerebral palsy and using EQ-5D-Y)	[redacted]	[redacted]	43.66	566,727	193,127	2.93

Scenario analysis are applied to EAG's deterministic base case
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; ICER: Incremental cost effectiveness ratio; LYGs: Life years gained; QALYs: Quality-adjusted life year; SMR; Standardised mortality ratio

NICE technical team analyses (1)

Scenario analysis#		Incremental			ICER (£/QALY)		
		Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG deterministic base case (EA1+EA2+EA3)		[redacted]	[redacted]	**43.66**	**570,050**	**196,782**	**2.90**
Weight: [redacted] patients under 16 years of age and 0.95 patients aged 16 years or over relative to general pop (age matched)**		[redacted]	[redacted]	43.66	664,455	229,371	2.90
Weight: patients assumed to have general population weight (age matched)**		[redacted]	[redacted]	43.66	674,136	232,712	2.90
GMFCS** subgroups	GMFCS 1	[redacted]	[redacted]	43.66	483,222	161,074	3.00
	GMFCS 2	[redacted]	[redacted]	43.93	532,778	77,593	3.00
	GMFCS 3	[redacted]	[redacted]	43.78	747,564	359,730	2.08
	GMFCS 4	[redacted]	[redacted]	43.39	1,637,042	1,637,042	1.00
	GMFCS 5	[redacted]	[redacted]	39.91	dominated	dominated	1.00

Scenario analysis are applied to EAG's deterministic base case
** NICE technical team scenarios validated by EAG [1] Undiscounted

Results include confidential commercial discount for pegzilarginase

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; HAC: Hyperammonaemic crisis; ICER: Incremental cost effectiveness ratio; LYGs: Life years gained; QALYs: Quality-adjusted life years

NICE technical team analyses (2)

Scenario analysis#		Incremental			ICER (£/QALY)		
		Costs (£)	QALYs	LYGs[1]	Unweighted	Weighted	Weight
EAG deterministic base case (EA1+EA2+EA3)*		[redacted]	[redacted]	**43.66**	**570,050**	**196,782**	**2.90**
Pegzilarginase discontinuation	0% (assumption) EAG SA9	[redacted]	[redacted]	61.10	570,668	190,223	3.00
	2% annually (assumption)**	[redacted]	[redacted]	32.40	569,773	259,761	2.19
	4.8% annually (trial based)**	[redacted]	[redacted]	16.74	569,916	478,657	1.19

Scenario analysis are applied to EAG's deterministic base case
* EAG base case uses 1% pegzilarginase discontinuation annually
** NICE technical team scenarios validated by EAG
[1] Undiscounted

Results include confidential commercial discount for pegzilarginase

BOI: Burden of illness; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; HAC: Hyperammonaemic crisis; ICER: Incremental cost effectiveness ratio; LYGs: Life years gained; QALYs: Quality-adjusted life years

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Base case assumptions and cost-effectiveness results
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Potential for managed access

- Managed access not proposed by the company

Pegzilarginase for treating arginase-1 deficiency

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ✓ **Summary**

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Key issues and questions for committee (1)

Cost-effectiveness issues

Starting distribution of patients across GMFCS states

- Is the starting distribution of patients across GMFCS states informed by BOI survey more appropriate than pooled data from the PEACE study, study 101A/102A, and BOI survey?

Assuming patients on pegzilarginase treatment remain in the same GMFCS state after 3 years

- What should be assumed for long term outcomes with pegzilarginase and at what time point should this be applied in the model?

Uncertainty around transition probabilities for IDM

1. Is the EAG's approach to use the upper limit of the 95% CI (2.66) as the decline in GMFM DE score per year appropriate for decision making?
2. For IDM arm, is the EAG's approach to calculate transition probabilities between GMFCS states using inverse of the time spent in a GMFCS state appropriate for decision making?
3. Is the EAG's approach to use the mean GMFM DE score from PEACE and STUDY101A/102A for patients starting in GMFCS-I appropriate for decision making?
4. Is the EAG's approach for calculating transition probabilities for IDM in SA7 appropriate for decision making?

Assumption that almost all patients die by 35 years of age

- Is it appropriate to assume that nearly all patients receiving IDM die by 35 years of age?

Life expectancy for patients receiving pegzilarginase treatment

- Is EAG's scenario assuming the SMR associated with pegzilarginase arm is twice that in the company's base case more appropriate for decision making?

Key issues and questions for committee (2)

Cost-effectiveness issues
Distribution of peak ammonia levels during a HAC • Is the distribution of peak ammonia levels from company's base case or EAG scenario SA8 more appropriate for decision making?
Cognitive improvement associated with pegzilarginase treatment • How should improvement in cognitive ability associated with pegzilarginase treatment be modelled?
Utility gain associated with an improved diet due to pegzilarginase treatment • Is it appropriate to apply a utility gain of 0.01 associated with an improved diet due to pegzilarginase treatment?
Disutility for carers • Are the caregiver disutilities used in the company and EAG base case model appropriate
Pegzilarginase drug wastage/dosing • What proportion of drug wastage is appropriate to assume in the economic model? • Is the company's weight assumptions appropriate throughout the economic model?

Discontinuation rate
• Should pegzilarginase treatment discontinuation be included in the economic model? If so,
  ○ What proportion of treatment discontinuation should be included in the model?
  ○ Should responders and non-responders be modelled separately?

QALY losses attributed to carers when calculating the weights for QALYs • Should QALY losses attributed to carers be included in the QALY weighting calculation?

Pegzilarginase for treating arginase-1 deficiency

Supplementary appendix

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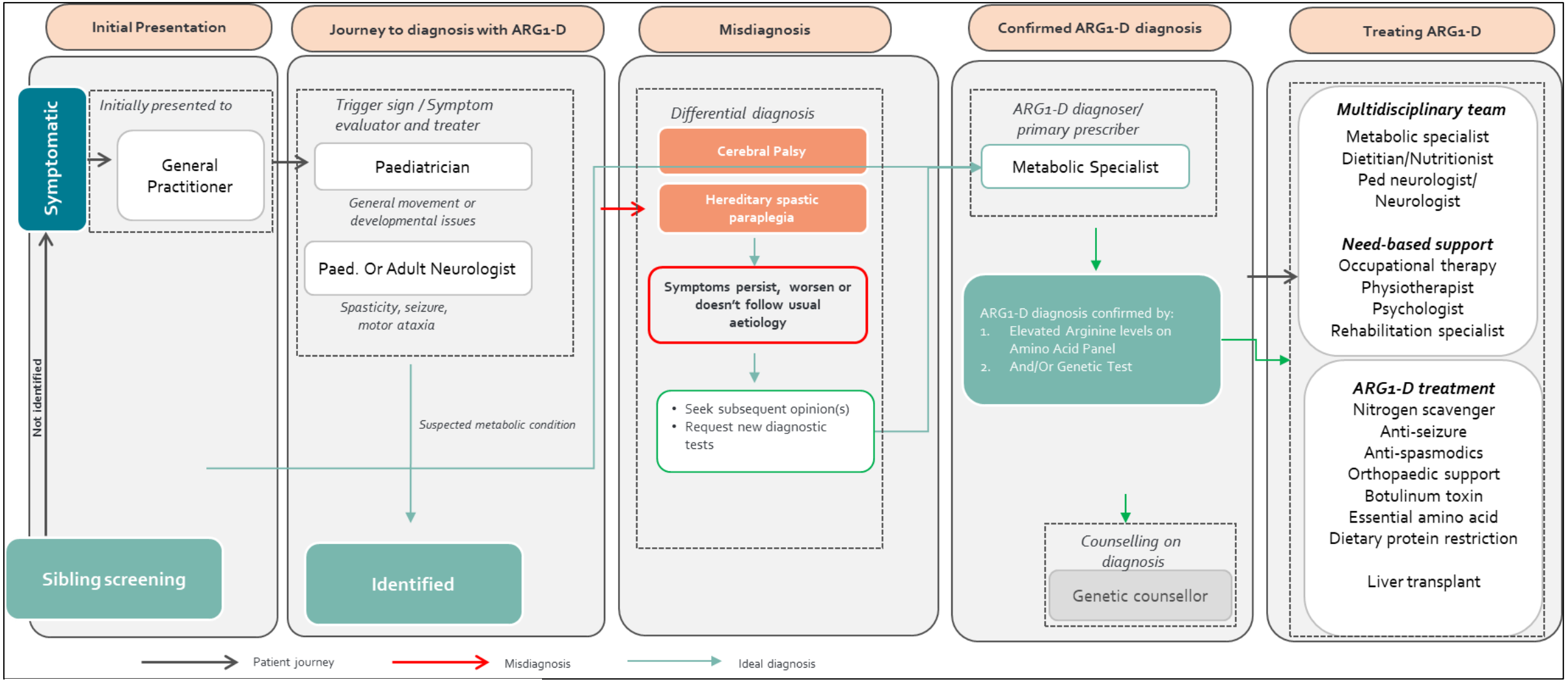
Treatment pathway

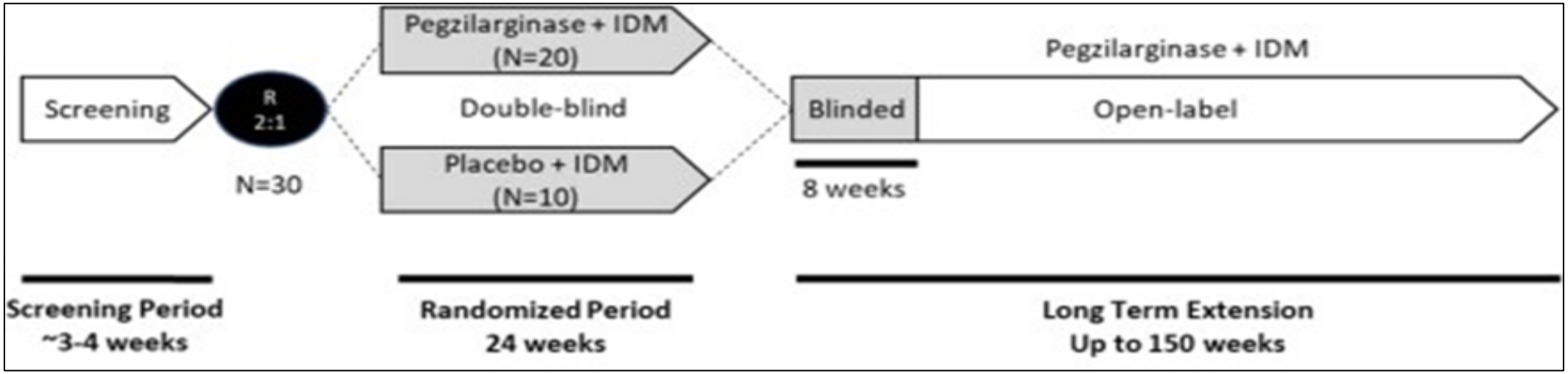
Figure: Current clinical care pathway for ARG1-D patients in England



Source: Company submission, Figure 10

Clinical effectiveness evidence: PEACE study design

Figure: PEACE study design



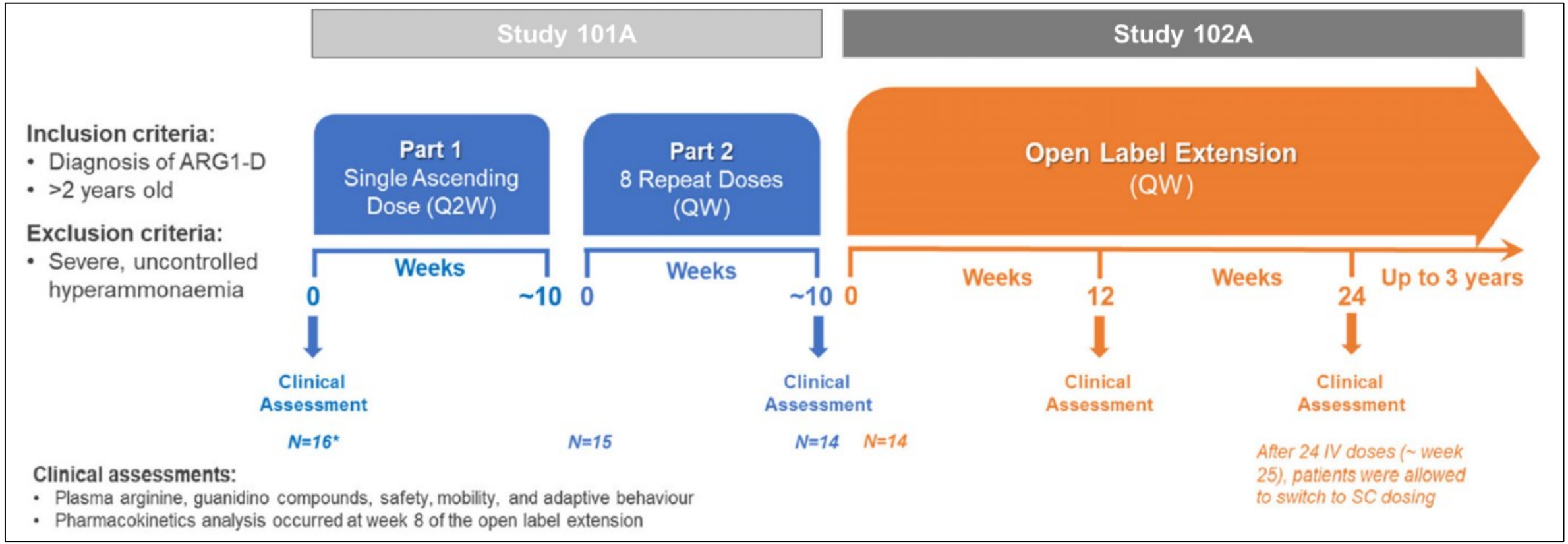
Source: Company submission, Figure 12

Back to slide: ‘Clinical effectiveness evidence: Overview’

IDM: Individualised disease management

Clinical effectiveness evidence: Study 101A/102A design

Figure: Study 101A and Study 102A study design



Source: Company Submission, Figure 13

Back to slide: '[Clinical effectiveness evidence: Overview]'

ARG1-D: Arginase-1 deficiency; QW: Every week; Q2W: Every two weeks

Other baseline characteristics: PEACE study

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

		Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Level of spasticity, n (%)	Any	13 (61.9)	8 (72.7)	21 (65.5)
	Lower-limb	13 (61.9)	8 (72.7)	21 (65.6)
	Upper-limb	1 (4.8)	3 (27.3)	4 (12.5)
	Moderate to severe	6 (28.6)	6 (54.5)	12 (37.5)
History of seizures, n (%)	Yes	7 (33.3)	4 (36.4)	11 (34.4)
	No	14 (66.7)	7 (63.6)	21 (65.6)
History of hyperammonaemia, n (%)	Yes	12 (57.1)	6 (54.5)	18 (56.3)
	No	9 (42.9)	5 (45.5)	14 (43.8)
GMFCS level at baseline, n (%)[b]	I	9 (42.9)	5 (45.5)	14 (43.8)
	II	4 (36.4)	4.2 (3.1)	13 (40.6)
	III	0	0	0
	IV	3 (14.3)	2 (18.2)	5 (15.6)
	V	0	0	0
Baseline GMFM-E score, points[c]	Mean (SD)	48.3 (19.93)	46.5 (24.56)	47.7 (21.25)
Baseline 2MWT, metres[d]	N	20	11	31
	Mean (SD)	109.0 (55.76)	99.9 (49.00)	105.8 (52.82)
Baseline GMFM-D score, points[e]	Mean (SD)	28.0 (9.6)	29.5 (12.4)	28.5 (10.4)

[b] No patients at GMFCS Level V were enrolled due to inability to complete functional mobility assessments
[c] One patient was not assessed at baseline because of severe disability and wheelchair dependence
[d] Baseline 2MWT was assessed in 20 of 21 patients in the pegzilarginase group; one patient was not assessed at baseline due to young age
[e] Excludes one patient (placebo) with missing baseline value

Source: Company submission, Table 11

Back to slide: 'Baseline characteristics: PEACE study'

2MWT: 2-minute walk test; GMFCS: Gross Motor Function Classification System; GMFM-D: Global Motor Function Measure, Part D; GMFM-E: Global Motor Function Measure, Part E; SD: Standard deviation

Other baseline characteristics: Study 101A/102A

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

		Study 101A (n=16)	Study 102A (n=14)
Level of spasticity, n (%)	None	4 (25.0)	[redacted]
	Mild	3 (18.8)	[redacted]
	Moderate	5 (31.3)	[redacted]
	Severe	4 (25.0)	[redacted]
History of seizures, n (%)	Yes	7 (43.8)	[redacted]
	No	9 (56.2)	[redacted]
History of hyperammonaemia, n (%)	Yes	7 (43.8)	6 (42.9)
	No	9 (56.2)	8 (57.1)
GMFCS level at baseline, n (%)[b]	I	9 (56.3)	7 (50.0)
	II	4 (25.0)	4 (28.6)
	III	2 (12.5)	2 (14.3)
	IV	1 (6.3)	1 (7.1)
	V	0	0
Baseline GMFM-E score, points	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Baseline 6MWT, metres	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Baseline GMFM-D score, points	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

[b] The GMFCS is a 5-level scale that assesses current motor function and what mobility aids a subject may need in the future.

Source: Company submission, Table 15

Back to slide: '[Baseline characteristics: Study 101A/102A]'

6MWT: 6-minute walk test; GMFCS: Gross Motor Function Classification System; GMFM-D: Global Motor Function Measure, Part D; GMFM-E: Global Motor Function Measure, Part E; SD: Standard deviation

PEACE and Study 102A results
Biomechanical outcomes (pArg)

Table: Plasma arginine: Results from PEACE and Study 102A

Trial arm		Baseline	Week 24	LTE24 or week 48	LTE96 or week 120	LTE120 or week 144 or last reported week
PEACE trial results						
Pegzilarginase	N	21	21	[redacted]	[redacted]	NR
	Mean (SD)	365.4 (93.7)	[redacted]	[redacted]	[redacted]	-
	MCFB	-	[redacted]	[redacted]	[redacted]	-
Placebo-pegzilarginase	N	11	11	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	-
Between group	Change from baseline	−76.7% (95% CI: −67.1%, −83.5%, p<0.0001)		-	-	-
Study 102A results						
Pegzilarginase	N	-	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	309.2 (97.60)	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAR, Table 8

Back to slide: ‘PEACE and Study 102A results’

LTE: Long term extension; CI: Confidence interval; MCFB: Mean change from baseline; pArg: Plasma arginine; SD: Standard deviation

PEACE and Study 102A results
Motor outcomes (2MWT and 6MWT)

Table: Clinical efficacy results for key motor outcomes from PEACE and Study 102A – 2MWT and 6MWT

Trial arm		Baseline	Week 24	LTE24 or week 48	LTE48 or week 96	LTE96 or week 120	LTE120 or week 144	EOS
PEACE trial results (2MWT)								
Pegzilarginase	N	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	109.0 (55.7)	115.9 ± 51.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	7.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo-pegzilarginase	N			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	99.0 (49.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between group	Change from baseline	LS mean difference: 5.5 metres; (95% CI: -15.6%, 26.7[redacted]		-	-	-	-	-
Study 102A results (6MWT)								
Pegzilarginase	N	[redacted]	-	-	-			
	Mean (SD)	304.8 (139.2)	322.6 (161.4)	346.2 (177.3)	-			
	MCFB	-	[redacted]	[redacted]	Through to week 144: [redacted]			

Source: EAR, Table 9

Back to slide: ‘PEACE and Study 102A results’

2MWT: 2-minute walk test; 6MWT: 6-minute walk test; CI: Confidence interval; LS: Least square; LTE: Long term extension; MCFB: Mean change from baseline; SD: Standard deviation

PEACE and Study 102A results
Motor outcomes (GMFM-E)

Table: Clinical efficacy results for key motor outcomes from PEACE and Study 102A – GMFM-E

Trial arm		Baseline	Week 24	LTE24 or week 48*	LTE48 or week 96*	LTE96 or week 120 *	LTE120 or week 144*	EOS
PEACE trial results								
Pegzilarginase	N	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	48.3 (19.9)	52.0 (21.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	4.2 (7.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo-pegzilarginase	N			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	46.5 (24.6)	46.1 (25.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	-0.4 (6.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between group	Change from baseline	LS mean difference: 4.6 (95% CI: -1.1, 10.2; p[redacted]		-	-	-	-	-
Study 102A results								
Pegzilarginase	N	[redacted]	[redacted]	[redacted]	[redacted] (week 144)			
	Mean (SD)	[redacted]	48.9 (24.6)	53.6 (20.7)	[redacted]			
	MCFB	-	[redacted]	[redacted]	[redacted]			

Source: EAR, Table 9

Back to slide: ‘PEACE and Study 102A results’

CI: Confidence interval; EOS: End of study; GMFM-E: Global Motor Function Measure, Part E; LS: Least square; LTE: Long term extension; MCFB: Mean change from baseline; SD: Standard deviation

PEACE and Study 102A results
Motor outcomes (GMFM-D)

Table: Clinical efficacy results for key motor outcomes from PEACE and Study 102A – GMFM-D

Trial arm		Baseline	Week 24	LTE24 or week 48*	LTE48 or week 96*	LTE96 or week 120 *	LTE120 or week 144*	EOS
PEACE trial results								
Pegzilarginase	N	21	20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	28.0 (9.6)	30.5 (10.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	2.7 (3.88)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo-pegzilarginase	N	11	11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	28.2 (13.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MCFB	-	0.4 (1.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between group	Change from baseline	LS mean difference: 2.3 (95% CI 0.4, 4.2) MMRM *p*-value: 0.02 WRS *p*-value: [redacted]		-	-	-	-	-
Study 102A results								
Pegzilarginase	N	[redacted]	[redacted]	[redacted]	[redacted] (week 144)			
	Mean (SD)	[redacted]	29.1 (11.0)	31.8 (8.4)	[redacted]			
	MCFB	-	[redacted]	[redacted]	[redacted]			

Source: EAR, Table 9

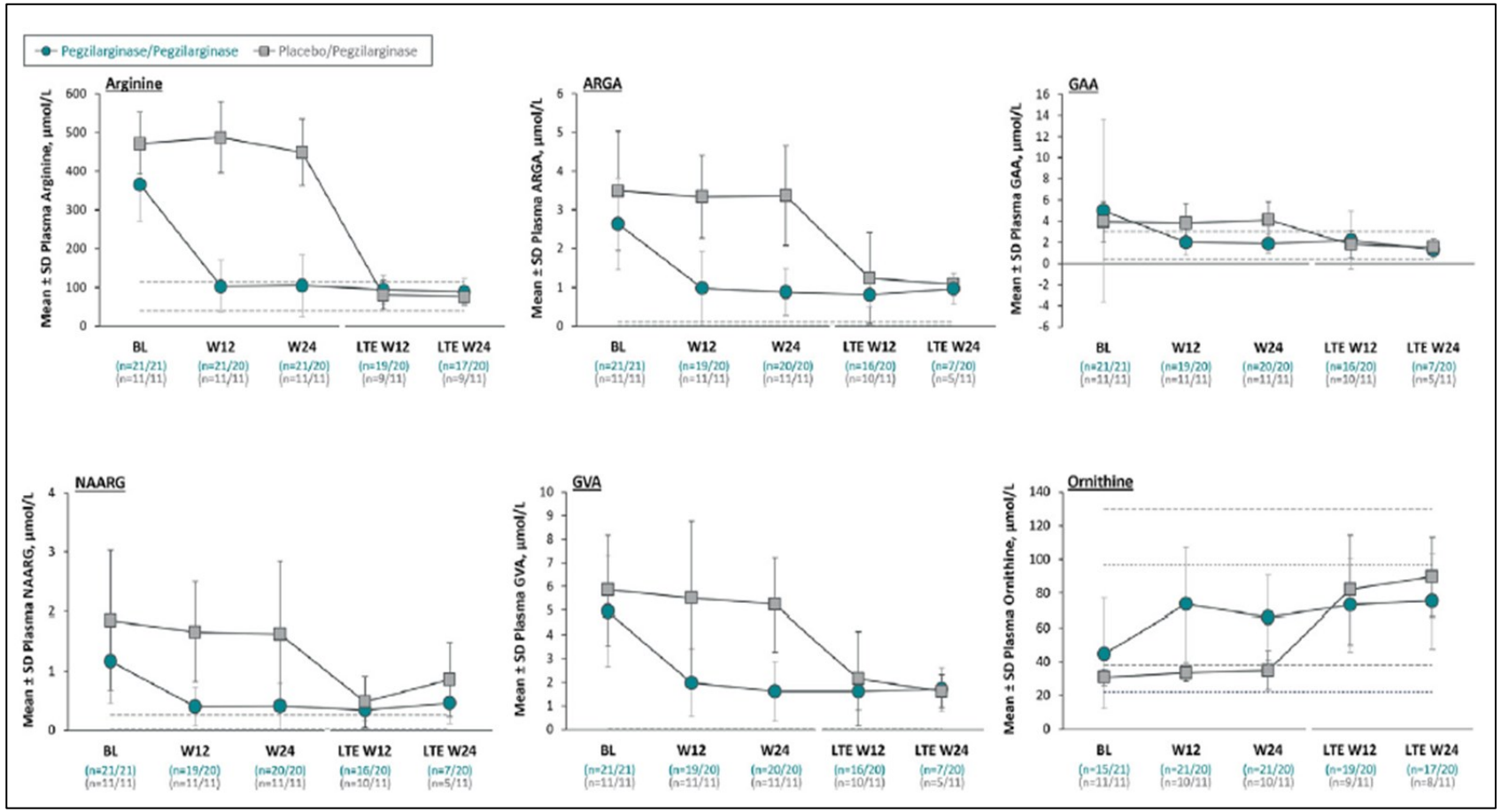
Back to slide: 'PEACE and Study 102A results'

CI: Confidence interval; EOS: End of study; GMFM-D: Global Motor Function Measure, Part D; LS: Least square; LTE: Long term extension; MCFB: Mean change from baseline; MMRM: Mixed model repeated measures; SD: Standard deviation; WRS: Wilcox robust statistics

PEACE results

Effect of pegzilarginase on ornithine and GC levels

Figure: Effect of pegzilarginase on ornithine and GC levels (μM) over time during the double-blind period and LTE through Week 24 (PEACE; Final analysis set)



Source: Company submission, Figure 17

Back to slide: '[PEACE and Study 102A results]'

GC: Guanidino compound; LTE: Long term extension

Small impact

Key issue: Error in calculating the transition probabilities for IDM

Company

- For IDM arm, estimated time spent in a GMFCS state by calculating time to move from one GMFM DE threshold value to next threshold value ➔ Transition probabilities generated using inverse of time in each state

EAG comments

- Believe that inverse of time spent in a GMFCS state is a rate which needs to be converted to a probability
- Calculated transition probabilities between GMFCS states using corrected formulae, given company's assumptions (EA1) ➔ Used in EAG's base case analysis

Back to slides: 'Key issues', 'Uncertainty around transition probabilities for IDM' and 'Questions for committee'

For IDM arm, is the EAG's approach to calculate transition probabilities between GMFCS states using inverse of time spent in a GMFCS state appropriate for decision making?

EA1: Exploratory analysis 1; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; ICER: Incremental cost effectiveness ratio; IDM: Individualised disease management

Small impact

Key issue: Starting GMFM DE score for patients in GMFCS-I

Company

- Assumed that patients in GMFCS-I would have a combined GMFM DE score of [redacted] when calculating the transition probabilities for progressing from GMFCS-I to GMFCS-II

EAG comments

- Based on PEACE and Study 101A/102A, the 95% CI around the GMFM DE score was [redacted]
- Company's assumption suggesting that patients can be identified as having ARG1-D without deterioration on the GMFM DE score is unlikely
- Uses a GMFM DE score of [redacted] (mean of the PEACE and Study 101A/102A) for patients starting in GMFCS-I in its base case analysis (EA2)

Back to slides: 'Key issues', 'Uncertainty around transition probabilities for IDM' and 'Questions for committee'

Is the EAG's approach to use the mean GMFM DE score from PEACE and STUDY101A/102A for patients starting in GMFCS-I appropriate for decision making?

NICE

ARG1-D: Arginine-1 deficiency; CI: Confidence interval; EA2: Exploratory analysis 2; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; ICER: Incremental cost effectiveness ratio

Moderate impact

Key issue: Decrease in GMFM DE score as patients age

Company

- For transition probabilities, assumed that patients' GMFM DE score declines by 1.45 per year

EAG comments

- Uncertainty around decline in GMFM DE score as 95% CI is 0.23 to 2.66
- GMFM DE score decline by 1.45 results in time estimated to move from GMFCS-I to GMFCS-V of approximately [redacted] years ➔ Significantly higher than that predicted by clinicians (5-6 years to decades)
- Uses upper limit of 95% CI (2.66) in base case analysis - reduces estimated mean time of moving from GMFCS-I to GMFCS-V to approximately [redacted] years (likely higher than clinician estimates, but more aligned to these estimates) (EA3)

Back to slides: 'Key issues', 'Uncertainty around transition probabilities for IDM' and 'Questions for committee'

Is the EAG's approach to use the upper limit of the 95% CI (2.66) as the decline in GMFM DE score per year appropriate for decision making?

NICE

CI: Confidence interval; EA3: Exploratory analysis 3; GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; ICER: Incremental cost effectiveness ratio

Distributions across cognitive impairment bands

Table: QALY weightings for size of benefit for HSTs

Health State	Normal/Mild	Moderate	Severe	Source
	Cognitive impairment when receiving IDM (Company and EAG base case)			
GMFCS-I	90.00%	5.00%	5.00%	Assumption
GMFCS-II	53.00%	38.00%	9.00%	HST18 (MLD)
GMFCS-III	33.00%	42.00%	25.00%	HST18 (MLD)
	Cognitive impairment when receiving pegzilarginase (after 52 weeks) (Company and EAG base case)			
GMFCS-I	100.00%	0.00%	0.00%	Assumption
GMFCS-II	70.00%	25.00%	5.00%	Assumption
GMFCS-III	43.00%	32.00%	25.00%	Assumption
	Cognitive impairment independent of treatment (EAG SA2)			
GMFCS-IV	17.00%	28.00%	55.00%	HST18 (MLD)
GMFCS-V	4.00%	17.50%	78.50%	HST18 (MLD)

Back to slide: ‘Cognitive improvement associated with pegzilarginase treatment’

GMFCS: Gross Motor Function Classification System; ICER: Incremental cost effectiveness ratio; IDM: individualised disease management; SA5: Scenario analysis 5

Decision modifiers: size of benefit for HST

- There needs to be compelling evidence that the treatment offers significant QALY gains
- Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator, the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained (section 6.2.23 to 6.2.25 of NICE health technology evaluations: the manual [PMG36])

Table: QALY weightings for size of benefit for HSTs

Inc QALYs gained (per patient using lifetime horizon)	Weight
≤ 10	1
11 to 29	Between 1 & 3 (using equal increments)
≥ 30	3

Table: QALY weightings and thresholds for size of benefit for HSTs

Number of additional QALYs (X)	Weight	Threshold
≤ 10	1	£100, 000
10 < X< 30	W = X/10	W * £100, 000
≥ 30	3	£300, 000

Example: A QALY gain of 16.7 would result in/be assigned a weighting of 1.67, leading to a threshold of £167,000

Back to slides: 'QALY losses attributed to carers when calculating the weights for QALYs'

HSTs: Highly Specialised Technologies; QALY: Quality-adjusted life year

Differences between company and EAG base case assumptions

Assumption	Company base case	EAG base case
IDM transition probabilities	Inverse of the time in each state	Inverse of the time spent in a GMFCS state converted to a probability
Starting GMFM DE score for patients in GMFCS-I	GMFM DE score of [redacted]	GMFM DE score of [redacted] (mean of the PEACE and Study 101A/102A)
Decrease in GMFM DE score as patients age	GMFM DE score declines by 1.45 per year	GMFM DE score declines by 2.66 per year

Back to slides: 'Company's base case results' and 'EAG's base case results'

GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; IDM: Individualised disease management