NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Comments on the Draft Guidance from** Immedica
   a. Appendix

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Metabolic Support UK

3. **Comments on the Draft Guidance Document from experts:**
   a. Dr Arunabha Ghosh and Dr Reena Sharma – Clinical Experts, nominated by Metabolic Support UK and Dr Spyros Batzios – clinical expert nominated by Immedica

   There were no comments on the Draft Guidance received through the NICE website

4. **External Assessment Group critique of company response to the DG**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025.** Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Immedica Pharma

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Immedica Pharma has no past or current links to, or funding from, the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	Comments
1	**1. Company base case and scenario analyses** The Company is committed to the NICE process to enable eligible patients living with arginase 1 deficiency (ARG1-D) to be treated with pegzilarginase in England and Wales. The Company welcomes the opportunity to comment on the draft guidance, provide additional clarifications, and respectfully ask the Committee to reconsider not recommending pegzilarginase, as published in the draft guidance, to ensure that patients in England and Wales can access this medicine. The Committee's preferred assumptions are listed in Section 3.22 in the draft guidance of June 2025 (NICE, 2025). The Company accepts the following Committee assumptions: **NICE draft guidance excerpt:** • *Distributions in each GMFCS health state informed by the European burden of illness survey, but assuming 50% of people in the GMFCS-2 health state would be in GMFCS-3 instead* • *Everyone in the pegzilarginase arm remaining in the same GMFCS health state after 3 years* • *For transitions between different health states in the standard care arm:* o *Using the mean of PEACE, Study 101A and Study 102A as the starting GMFM-DE score for people in the GMFCS-1 health state* o *A reduction in GMFM-DE score of 2.66 per year*

	○ *Converting inverse of time spent in a GMFCS health state to a probability* • *The EAG's preferred analysis that 5% of people per year transition from the GMFCS-2 and -3 health states to GMFCS-5 after hyperammonaemic crisis in people under 16 years, in both the pegzilarginase and standard care arms* • *Standardised mortality rates for the pegzilarginase arm and standard care used in the EAG's preferred analysis, with the GMFCS-2 health state for pegzilarginase having a standardised mortality ratio equal to 25% of that for standard care* • *GMFCS health-state utility values used in the company's base case* • *Treatment-specific cognitive disutility applied in the GMFCS-1 to GMFCS-3 health states* • *Carer disutility as applied in the Company's base case but not applying additional carer disutility for carers with more than 1 child with the condition* • *The Company's adherence rate, a dosing amount of 0.14 mg/kg and a 10% threshold for drug wastage* • *Using the EAG's log-logistic distribution for pegzilarginase treatment discontinuation.* **Company comment:** For the following Committee assumptions, the Company proposes modifications in line with available evidence: • *Utility gain associated with improved diet with pegzilarginase treatment is applied to 48.5% of people* ○ The Company's preferred assumption is to apply the utility gain to 83.3% of patients as observed in RWD, without any placebo adjustment (see Section 11). • *Adults having pegzilarginase would weigh 90% of the general population weight, and 50% of people with the condition are expected to be female* ○ The Company's preferred assumptions are to use an average weight ratio of 84% (reflecting the mix of children and adults in the

UK) and a female proportion of 76%, based on the European burden of illness study (see Section 12).

- *Applying a QALY weighting equal to 50% of the QALY weighting implied by the economic model using the committee preferences listed above*
    - The Company acknowledges that limitations exist due to the ultra-rare nature of the disease and the duration of the placebo-controlled follow-up period. However, the Company's assumptions used are evidence-based and conservative, supporting the case for applying the full QALY weighting, in line with the NICE health technology evaluations manual (see Section 14).

Company comment:

With the Committee's preferred assumptions, the non-weighted ICER is £431,121 and weighted ICER (full QALY weight) is £147,523 compared with standard of care using the confidential price of [commercial in confidence information removed]. The weighted ICER based on the Company's preferred assumptions, i.e. those listed as accepted above together with the three modified assumptions, is £131,161.

The Company has provided a further reduction in the confidential discount and the new confidential price is [commercial in confidence information removed]

The base case referred to in the document as "Company base case" includes:

- the Committee's preferred assumptions accepted by the Company
- adjusted assumptions for proportion of patients with improved diet
- weight ratio vs general population
- proportion females
- the reduced confidential price
- QALY weight as estimated by the model (full QALY weight).

The weighted ICER based on Company base case is £98,804 – see Table 1 in Appendix.

To aid interpretation, gain further understanding and reduce uncertainty, the Company has conducted several scenario analyses listed below. All analyses are run with the updated confidential price and with the Company base case as baseline. The weighted ICER's are presented below for each scenario. For further information see Table 2 in the Appendix and the discussion in respective section below:

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	• Transition probabilities for pegzilarginase (see Section 7)
	  ○ Pegzilarginase long-term progression (HR 0.005): ICER £110,291
	• Source of utility values (see Section 10)
	  ○ Cognitive dis-utilities reduced by 50%: ICER £100,493
	  ○ Cognitive dis-utilities excluded (set to 0): ICER £106,008
	  ○ Updated utility matrix: ICER £100,648
	• Utility gain associated with improved diet (see Section 11)
	  ○ Proportion of patients with improved diet 48.5%: ICER £101,903
	  ○ Proportion of patients with improved diet 66.7%: ICER £99,959
	• Pegzilarginase weight-based dosing costs (see Section 12)
	  ○ Weight ratio vs general population 0.782: ICER £84,686
	  ○ Weight ratio vs general population 0.9: ICER £99,252
	  ○ Proportion of female patients 50%: ICER 99,693
	• Committee preferred base case
	  ○ Committee preferred base case (NICE, 2025) with full QALY weight applied: ICER £111,272.
	
	In summary, the Company accepts the majority of the Committee preferred assumptions. The Company proposes evidence-based modifications to the assumptions on proportion of patients with improved utility due to improved diet, proportion of female patients and weight ratio vs general population, to be consistent with other assumptions and real-world-data.
	
	The Company also challenge the Committee conclusion that there is not “compelling” evidence to support a full QALY weighting to be applied. In this document, the Company provides additional clarity, scenario analysis, and supporting data to help reduce uncertainty highlighted in the draft guidance.
	
	The Company believes this should support the application of the full QALY weighting, as estimated by the model, in the final appraisal decision

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2	2. **Data sources – available long-term data (Section 3.3 of draft guidance consultation document)** **NICE draft guidance excerpt:** *Study 102A (n=14) was a single-arm, open-label, long-term extension (up to 3 years) of Study 101A (NICE, 2025).* **Company comment:** The Company would like to correct this statement. Study 102A had long-term treatment and follow-up up to 262 weeks, i.e., >5 years (McNutt et al., 2025). This is of importance for the strength of evidence available for the assessment of pegzilarginase long term outcome.
3	3. **Starting distribution by GMFCS health states (Section 3.6 of draft guidance consultation document)** **NICE draft guidance excerpt:** *Clinical advice to the EAG suggested that the starting distributions in the NHS in England may be more like those in the European burden of illness survey. This is because PEACE, Study 101A and Study 102A may have underrepresented people with more severe disease (NICE, 2025).* **Company comment:** The Company would like to clarify that the studies did not only exclude patients with more severe symptoms, but also patients with no or mild neuromotor symptoms. The two relevant inclusion/exclusion criteria are (Immedica, 2024): • Inclusion criterion number 4. The subject must be assessable for clinically meaningful within-subject change (clinical response) on at least 1 component of 1 assessment included in the key secondary/other secondary endpoints. To be considered assessable, the subject must be able to complete the assessment and must have a baseline deficit in at least 1 component as defined in Table 3 in Appendix. • Exclusion criterion number 4. Extreme mobility deficit, defined as either the inability to be assessed on the Gillette Functional Assessment Questionnaire (GFAQ) or a score of 1 on the GFAQ. The rational for excluding patients with no or mild neuromotor symptoms was from a research methodological perspective given the relatively short follow-up period in the clinical trial. Patients with no or mild symptoms would require a

	longer follow-up period to demonstrate no progression. However, from a clinical standpoint, stabilisation or a slowing of disease progression is also to be considered an important therapeutic objective. In the clinical studies though, an improvement in symptoms was demonstrated. Patients with ARG1-D who have elevated arginine levels but do not yet show motor symptoms (or have only cognitive impairment) are likely to avoid motor deterioration and further cognitive decline if treated with pegzilarginase and achieving normal arginine levels. In summary, the GMFCS distribution observed in the clinical trials underrepresents both patients with severe motor impairment and those with no motor function deficit (GMFCS I), largely due to exclusion criteria. While the underrepresentation of severe cases could raise concerns, this is balanced by the concurrent underrepresentation of GMFCS I patients, who are generally more cost-effective to treat.
4	**4. Clinical outcomes (Section 3.4 of draft guidance consultation document) – role of arginine** **NICE draft guidance excerpt:** *But clinical advice to the EAG noted that plasma arginine levels do not have a consistent relationship with disease severity (NICE, 2025).* **Company comment:** The Company would like to clarify that cross-sectional analyses of plasma arginine levels and disease severity are not sufficient to fully inform on the relationship between them. While it is well established how excess plasma arginine is the primary causal component that drives elevations in downstream contributors to disease pathogenesis (Diaz et al., 2023), the relationship between the degree of biomarker accumulation and the functional impairment has previously typically been documented through analyses of arginine assessments at a single or a limited number of points in time, while the lifelong exposure will fluctuate, although elevated to different degrees. Data from an analysis of the Urea Cycle Disorders Consortium (UCDC) Study 5101 (Aeglea, 2020) provides evidence to this matter and support the ultimately strikingly uniform prognosis of ARG1-D, including spasticity, gait disorders, difficulty walking, and developmental and cognitive disability. An association between plasma arginine levels and the extent and rate of progression of clinical manifestations was observed. Higher levels of plasma arginine were associated

	with the development of a wide spectrum of more debilitating symptoms with a faster rate of decline. If the causative agent of the toxicity is removed or decreased, there is clear biological rationale to expect effect on ongoing disease progression. This is well-supported in the literature; substantial body of case reports confirm the clinical benefit of lowering arginine in ARG1-D for halting or slowing disease progression (Brockstedt et al., 1990; Cederbaum et al., 1982; Cederbaum et al., 1979; De Deyn et al., 1997; Lambert et al., 1991; Marescau et al., 1985; Snyderman et al., 1979). Of note, normalisation of arginine level is rarely achieved with dietary intervention (Burrage et al., 2015; Diaz et al., 2023) but is achieved with pegzilarginase. Pegzilarginase demonstrated statistically significant, early, clinically meaningful, consistent, and sustained reduction in plasma arginine to normal levels (McNutt et al., 2025; Russo et al., 2024) – see Figure 1 in Appendix. With the normalisation of plasma arginine concentration, pegzilarginase demonstrated that the lowering of arginine concentrations results in clinically meaningful improvements in functional mobility. Taken together, the evidence supports arginine as the key driver of disease in ARG1-D and lowering of elevated arginine concentrations demonstrate clinical benefit. Sustained arginine control should be interpreted as a key indicator of stabilisation of disease progression.
5	5. **Clinical outcomes (Section 3.4 of draft guidance consultation document) –significance of clinical trial results** **NICE draft guidance excerpt:** *The EAG highlighted that mobility, mental processing and quality-of-life outcomes were uncertain because the results lack clinical and statistical significance.* **Company comment:** The Company would like to highlight that the clinical trial results demonstrate clinically significant results. Pre-defined and literature-based thresholds were applied for minimum clinically important difference (MCID) for the GMFM and timed walk tests. The results show that patients met these thresholds on an individual and population level demonstrating the clinical significance of the results (Immedica, 2024; Russo et al., 2024). Treatment with pegzilarginase demonstrated *improvements* in functional outcomes, not only a slowing of the disease, or even a halting of disease.

	Increases in walking distances and improvements in abilities to stand, walk, run and jump all have significant benefits to the patients and their caregivers and can allow the patients to gain additional independence and improved quality of life. Just enabling patients to move independently within their home is a highly relevant outcome. In summary, clinical trial data show that pegzilarginase leads to meaningful improvements in mobility, exceeding thresholds for clinical significance and highlighting real benefits for patients' independence and quality of life.
6	6. **Clinical outcomes (Section 3.4 of draft guidance consultation document) – clinical trial results** **Company comment:** Company would like to add the following clinical trial results to the list in section 3.4 of the NICE draft guidance document: • Normalisation of plasma arginine concentrations in all patients in the pegzilarginase group. At week 24, normalization was achieved by 90.5% ($p<0.0001$ vs placebo) (Russo et al., 2024). These results include 2 patients (9.5%) that did not have normalised levels at week 24 as explained below. • One pegzilarginase patient withdrew at week 6 (data included via last observation carried forward). • Another patient had an unusual arginine spike at week 23, likely due to a sample mix-up, as a related placebo patient showed opposite anomalies at the same time. Please see the CSR for further details (Immedica, 2024). Hence, not considering those two patients who did not achieve normal arginine levels for reasons unrelated to the drug efficacy, all patients would be considered to achieve normalised plasma arginine concentrations. In the clinical trials, sustained normalisation of plasma arginine was demonstrated up to 262 weeks of follow-up (McNutt et al., 2025) – see Figure 1 in Appendix. In summary, pegzilarginase achieved sustained normalisation of plasma arginine in all treated patients, with minor exceptions explained. This biomarker response underpins its clinical benefit.

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7	**7. Transition probabilities for pegzilarginase (Section 3.7 of draft guidance consultation document)** Clarification: Arginine levels and resistance to drug **NICE draft guidance excerpt:** *The company submission highlighted that the combined GMFM-D and GMFM-E scores (GMFM-DE) were still improving for some people up to 4 years after starting pegzilarginase. It noted that* ***controlled plasma arginine levels result in controlled underlying disease pathogenesis and that people cannot become resistant to pegzilarginase*** *[statement highlighted in bold by Company]. Clinical advice to the EAG thought it plausible that people on pegzilarginase would remain in the same GMFCS health state after 3 years. But the EAG highlighted that this assumption was very uncertain because it solely relied on clinical expert opinion.* **Company comment:** The Company would like to clarify the statement in bold. Please also refer to Section 4 regarding the role of arginine as the key driver of disease progression in ARG1-D. Unlike receptor-targeting therapies, pegzilarginase is a human arginase 1 enzyme therapy acting extracellularly. There is no plausible mechanism to propose resistance to pegzilarginase. This has also been demonstrated in long-term follow-up data in patients treated with pegzilarginase with the assessment of anti-drug antibodies (ADAs). In the clinical trials, ADAs developed early following the initial doses and were transient and resolved during continued treatment. Overall, the presence of ADAs was not associated with long-term clinically relevant changes in pharmacokinetics and pharmacodynamics of pegzilarginase. The majority of patients with anti-pegzilarginase ADAs had antibodies toward the whole molecule and not specific toward the enzymatic component, supporting the hypothesis of low immunogenicity of the pegzilarginase active site and low incidence of potential neutralizing antibodies. Additionally, and theoretically, the active site of arginase 1 is located in a deep cleft, accessible to the small molecule substrate but poorly accessible to the large size of immunoglobulins. PEG groups further obstruct access to the region of the active site. Hence, PEG molecules bound close to the active site prevent access of antibodies to the site and prevent neutralization of pegzilarginase activity.

	Scenario analyses: long-term disease progression for pegzilarginase **Company comment on disease progression:** The Company would like to emphasise a point raised by the clinical experts during the Committee meeting. When discussing disease progression, particularly in patients in more severe health states, it is important to distinguish between deterioration due to comorbidities and progression specifically related to arginase-1 deficiency. Patients may experience a decline in health for reasons unrelated to pegzilarginase, and this should not be mistaken for disease progression caused by the underlying condition. **Analysis from EAG report:** EAG provided two analyses to estimate impact of long-term disease progression for pegzilarginase: • Analysis C-2.12 using HR 0.10 as long-term progression • Analysis C-2.13 using HR 0.20 as long-term progression **Company comment Hazard Ratio (HR):** The Company would like to add some further insights on choice of HR and provide scenario analyses for different assumptions of the HR, as well as implications for long term outcome that different choice of HR will have. In Table 4 in the Appendix, the proportion of patients in respective GMFCS health state is reported: at start of treatment (age 13) and at age 50, for different levels of HR assumed. If a HR of 0.10 is assumed as per EAG scenario for disease progression while on pegzilarginase treatment, the proportion of patients in GMFCS level I declines dramatically from 50% at treatment initiation (age 13) to just 1.64% by age 50, despite ongoing treatment, and 54% of patients are dead vs 23% in the base case (if no progression is assumed). The Company acknowledges the limitation of having only up to five years of long-term data on pegzilarginase treatment from clinical trials. In the absence of longer-term data, scenario analyses are necessary to help shed light on the robustness of the results and the impact of key assumptions. However, based on the evidence presented earlier, the Company considers a HR of 0.1 to represent an unrealistically rapid average rate of disease progression for patients continuing on pegzilarginase. In the Company's view, such a scenario is not

	clinically plausible. Patients with this level of progression are likely non-responders with uncontrolled plasma arginine levels, and would most likely discontinue treatment, see proposed stopping criteria in Section 14. The Company would like to point out that no such non-responders were seen in the clinical trials for pegzilarginase. As a more realistic and clinically plausible scenario analysis on pegzilarginase long-term progression, the Company proposes an alternative scenario using an HR of 0.005 which it believes is more plausible and realistic. Under this assumption, by age 50: • 41% of patients remain in GMFCS-I, and • 26% have died while on treatment. For comparison, in a no-progression scenario, by age 50: • 49% remain in GMFCS-I, and • 23% have died. Using an HR of 0.005 results in a weighted ICER of £110,291. ICERs for other progression scenarios (based on varying HRs) are provided for the Committee's consideration in Table 4 of the Appendix.
8	8. **Life expectancy (Section 3.11 of draft guidance consultation document)** <u>MLD as proxy disease</u> **NICE draft guidance excerpt:** *The company also did not provide further supportive evidence, as requested by the committee, that metachromatic leukodystrophy (HST18) was an appropriate proxy condition.* *The stakeholder responses also stated that no other condition could exactly align with arginase1 deficiency, but that metachromatic leukodystrophy could be a valid proxy. But it did not cover risks of hyperammonaemia. The NICE technical team noted that HST18 evaluated a gene therapy that works differently to pegzilarginase.* **Company comment:** Since some assumptions in the model is from MLD (HST18), the Company would like to add the rationale for why MLD was selected as proxy condition.

	During the model conceptualization phase, clinical experts were asked about diseases to be used as proxy diseases. The feedback was that MLD could be considered an appropriate proxy condition since: • Both are ultra-rare, autosomal recessive metabolic diseases caused by single-enzyme defects • Each lead to progressive accumulation of toxic metabolites that damage the CNS • Both have spasticity, motor decline, loss of developmental milestones, and cognitive impairment • Both associated with high morbidity, shortened survival, and acute crises (demyelination complications vs. hyperammonaemia) • Similar lifelong burden on patients, families, and health services: frequent hospitalisations, multidisciplinary care, and reduced quality of life • Motor function levels are similar: GMFC-MLD and GMFCS used for ARG1-D. Due to those reasons, and the availability of data in the HST18, the Company selected MLD as a relevant proxy disease. <u>Modelling of survival and life expectancy</u> **NICE draft guidance excerpt:** *But it preferred to amend the GMFCS-2 standardised mortality rate to be 25% of the rate seen in the standard care group. This was to reflect the potential impact of an hyperammonaemic crisis.* **Company comment:** The Company would like to clarify that survival has been modelled separately for death due to HAC (hyperammonaemic crisis) and death due to other reasons: • Risk of death due to HAC has been modelled independent of GMFCS health state to capture risk of death due to hyperammonaemia crisis • SMR per GMFCS health state to capture mortality due to functional impairment and immobility. Included in the SMRs are also death due to comorbidities that are related to health state severity. Hence, increases in SMR is not needed to capture deaths due to HAC. Those are modelled separately, and independent of the GMFCS health state.

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9	9. **Ammonia levels (Section 3.12 of draft guidance consultation document)** **NICE draft guidance excerpt:** *The EAG highlighted that there was considerable uncertainty around the peak ammonia levels during a hyperammonaemic crisis when on pegzilarginase.* **Company comment:** The Company would like to comment on the uncertainty around peak ammonia levels during pegzilarginase treatment. Despite the rarity of the event during treatment with pegzilarginase, the available evidence along with clinical expert experience provides useful insights. Hyperammonaemic crises are infrequent during pegzilarginase treatment, but their occurrence still offers valuable information for assessing the treatment's effect on ammonia levels. The placebo-controlled period allows for a direct comparison, strengthening this assessment. The draft guidance comments by the clinical experts ahead of committee meeting 2 states: *"the patient was most commonly admitted for a night for fluids, ammonia would normalise and he'd discharge home. This is in contrast to the very difficult to control hyperammonaemia that he experienced off [pegzilarginase]. Weeks long hospitalisations on/off Ammonul* that had become so troublesome that the family was seriously considering liver transplant…"* The clinical experts conclude that: *"Episodes of high ammonia were reported to occur relatively infrequently in patients on pegzilarginase treatment. Most episodes of high ammonia had a peak ammonia of less than 200 µmol/L, and the severity of hyperammonaemic crises, if they do occur, appears to be less in patients on pegzilarginase. Of note, no patient was reported to have had an ammonia >500 µmol/L while on pegzilarginase."* Across all studies, 15/48 patients (31.3%) had elevated ammonia levels at screening/baseline. In PEACE, mean plasma ammonia levels at baseline were within normal range and similar in both treatment groups. At week 24, mean plasma ammonia levels remained within baseline level and within the normal range in the pegzilarginase group while an increase from baseline outside the normal range was observed in the placebo group. Increases in ammonia levels that were clinically significant but did not meet the protocol-defined criteria for hyperammonaemia were reported as treatment-emergent adverse events (TEAEs). TEAEs of ammonia level increases were reported in a lower proportion of patients in the pegzilarginase group (14.3%) than in the placebo group (27.3%) in the double-blind period of Study 300A.

	Table 5 in the Appendix summarises peak ammonia levels, categorised according to each patient's highest post-baseline value. In collected real-world data (Arnoux et al., 2024), glutamine values were collected. Despite increases in protein intake in these patients (see Section 11), glutamine levels remained stable, indicating stable ammonia levels, given the role of glutamine as a buffer for excess ammonia. These available data provide evidence for an informed assessment in this ultra-rare disease. As shown, untreated patients had higher categories of peak ammonia levels over pegzilarginase-treated patients. In summary, pegzilarginase treatment is associated with fewer ammonia-related adverse events and better ammonia control than placebo.
10	10. **Source of utility values (Section 3.13 of draft guidance consultation document)** **NICE draft guidance excerpt:** *The committee concluded the health-state utility values used in the company's base case were appropriate for decision making but requested further input on this issue (NICE, 2025).* **Company comment:** The Company accepts the Committee preferred assumptions. However, given the Committee request for further input, the Company will in this section provide some clarifications and scenario analyses with the purpose of reducing uncertainty. <u>Negative utility values</u> **Comment from EAG report:** *The EAG explained that the company's utility values meant that some health states were assumed to be worse than death and queried whether this was plausible (NICE, 2025).* **Company comment:** There are indeed some situations when patients can experience their life situation as being worse than death. This was also the case for MLD (see Table 6 in Appendix).

	It can also happen due to what method is used to translate EQ-5D responses to utility values. In the publication of the ARG1-D burden-of-illness study (Olofsson et al., 2024), the van Hout tariff was used (van Hout, 2012). For the purpose of this submission, utilities were re-estimated using the Hernández tariff as per the NICE preferred method (Hernández Alava, 2023). Utility values estimated using respective tariff are reported in Tables 7 and 8 in Appendix. • Using the van Hout tariff, utility for health state "GMFCS I & no/mild cognitive impact" is 0.84 and for "GMFCS IV-V & moderate/severe cognitive impact" is 0.029. • Using the Hernandez tariff, the corresponding utilities are 0.835 and -0.091, respectively. All patients in GMFCS IV and V in the European ARG1-D burden-of-illness study had moderate to severe cognitive impact, and negative utility values when calculated based on the Hernandez tariff. The Company considers it plausible that patients in the most severe stages of the disease - particularly those classified as GMFCS levels IV and V, could experience negative utility values. These patients often face a combination of severe neurological symptoms and multiple comorbidities, resulting in a significantly diminished quality of life. • Patients at GMFCS level IV have severely limited walking ability, even with assistive devices. They rely on a wheelchair for most mobility, may be able to use a powered wheelchair independently, and can sometimes participate in standing transfers. • At GMFCS level V, impairments are even more profound. These patients have severely restricted voluntary movement, cannot maintain head or neck posture against gravity, and experience impairments in all areas of motor function. They are unable to sit, stand, or walk independently even with adaptive equipment, though some may use powered mobility devices. • Patients with severe cognitive impairment have severe problems or cannot communicate; socialize; learn, think and solve problems; or perform activities of daily living. Given this level of disability and dependency, the Company believes it is clinically plausible to expect utility values in these states to be zero or negative.

	Negative total QALYs for IDM **NICE draft guidance excerpt:** *At the second committee meeting, the committee was aware that, in both the company's and EAG's base-case analyses, the total QALYs estimated for standard care were negative. The committee queried the validity of this. (NICE, 2025)* **Company comment:** This is the result of the negative utility values in the more severe health states. Utility values in the Committee preferred base case are reported in Table 9 in Appendix. All utilities in GMFCS health states IV and V are negative (-0.077 and -0.250). Utility values in GMFCS III are also negative in situations of moderate and severe cognitive impairment. Two scenario analyses have been done, to understand the impact of cognitive dis-utilities: reducing the dis-utilities by 50% and to set dis-utilities to 0, respectively. In both analyses, total QALYs estimated for IDM are positive (see Table 2 in Appendix). • If all cognitive dis-utilities are reduced by 50%, then the weighted ICER is £100,493 and the total QALYs in the IDM arm is 0.306 • If all cognitive dis-utilities are set to 0, i.e. dis-utility due to cognitive impairment not considered in the analysis, weighted ICER is £106,008 and total QALYs in the IDM arm 1.302 Underestimation and overestimation of utility values **EAG report excerpt:** *The EAG believes that the utility values assumed for none/mild cognitive impairment by GMFCS health state are underestimated as it is thought to be the average from all patients within a GMFCS health state"* (Stevenson M, 2025). For the revised utility values, not considered by the Committee, EAG notes: *Importantly, the dis-utilities associated with mild or moderate/severe health states used by the company are likely to be confounded because the GMFCS health state of the patients has not be considered.(Stevenson M, 2025)* **Company comment:** The Company acknowledges and accepts the EAG's observation that there is a risk for both under- and overestimation of individual utility values. To understand

	any potential impact of this, a utility matrix based on only utility values from the ARG1-D burden of illness study has been estimated. Then a scenario analysis has been performed based on those utility values. In the Company original submission, utility values for no/mild cognitive impact are from the European ARG1-D burden-of-illness study (with adjusted value for GMFCS I) and dis-utilities for moderate and severe cognitive impairment are from HST18 (MLD). The reason for using dis-utility values from MLD was due to the very few patients reporting utility values for more severe health states in the burden-of-illness study (see Table 11 in Appendix). The Committee's preferred base case utility values are reported in Table 9 in the Appendix. In Table 10 in the Appendix, utility data available from the European burden-of-illness study is presented (and number of patients, patient counts, in Table 11 in the Appendix). For the purpose of this scenario analysis, values were imputed for all empty cells in Table 10 in the Appendix, resulting in a fully populated table shown in Table 12 in the Appendix (method of imputation is described below table 12). In the preferred base cases, both for Committee and Company, utility for the best health state "GMFCS I and no/mild cognitive impairment" is 0.855 and for the worst health state "GMFCS V and severe cognitive impairment" is -0.25 (Table 9 in the Appendix). In the scenario analysis, those utilities are 0.893 and -0.126, respectively (Table 12 in the Appendix). Weighted ICER for the scenario analysis is £100,648 per QALY gained. Total QALYs for the pegzilarginase group is 15.1 and for IDM 2.4. Undiscounted incremental QALYs are 30.97. The utilities used in the preferred base cases might be somewhat underestimated. On the other hand, utilities based only on the ARG1-D burden-of-illness results have limited observations in the more severe health states. In summary, while utility estimates vary by method and source, scenario analyses show that adjustments to the utility values do not materially affect the ICER, and the Company and Committee preferred values remain appropriate for decision-making.
11	11. **Utility gain associated with improved diet (Section 3.14 of draft guidance consultation document)** **NICE draft guidance excerpt:** *The clinical experts agreed and added that food restrictions are one of the most difficult aspects of the condition for people with arginase-1 deficiency. The patient*

	experts also noted that standard care and a restrictive diet prevented children with the condition from living a normal life (NICE, 2025). **Company comment:** The Company would like to comment on the impact of the severely protein-restricted diet, which poses a significant burden on both patients and caregivers, impacting HRQoL. The Company would like to reiterate the input from both clinical and patient experts: Disease management overviews state that at least half of dietary protein should be from natural (complete) sources (Sun et al., 2020). In the real-world evidence data from France, the treatment-naïve patients had a mean daily protein intake of 16.9 g (mean age: 10.9 years) (Arnoux et al., 2024), compared to a recommended amount of 42.1/41.2 g in male/female children 11-14 years (Public Health England, 2016). For reference, one egg contains 7 g of protein, a glass of milk 7 g, a slice of bread 2 g; this constitutes a full day of protein intake for the mean daily protein intake in the French real-world data. Outside the nutritional aspects, the impact on patients and caregivers extends to the time and effort required to prepare special meals including calculating protein intake, weighing foods, and sourcing low-protein options as well as the emotional and mental burden of avoiding dietary mistakes. This daily challenge affects not only home life but also practical aspects such as managing school meals, attending school trips, planning holidays, and ensuring consistent dietary control outside of the home. These burdens are even more significant for families with more than one child affected by the disease, which is the case for many of the families living with ARG1-D in the UK. This was also confirmed by the patient expert and the patient organisation representative during the second Committee meeting. They explained that treatment with pegzilarginase could enable patients to participate more fully in society, including being able to eat foods they previously had to avoid. This potential improvement in diet is a key aspect that patients look forward to when starting treatment, as it has a profound impact on their quality of life. The Delphi panel support even a small improvement in diet liberation makes a big difference to a patient and their family (Immedica, 2025). In the real-world evidence data form France (Arnoux et al., 2024), all but one treatment-naïve patients (83.3% - 5/6 patients) had an increase in dietary protein intake, whereas 66.7% had an increase >15%. Overall, including the previously treated patients, 83.3% (10/12 patients) had an increase in dietary protein intake.

	During the first 12 months of follow-up, the mean dietary protein intake increased by 8.9 g/day for both previously treated patients (in PEACE trial) and treatment-naïve patients. That correlated to a true increase in protein intake also when correcting for the increase in mean weight during the same time. Despite that previously treated patients may already have had an increase in daily protein intake, the increase in 83.3% overall and in the treatment-naïve group indicates the relevance of the proposed proportion. The relevance of the data is to be considered in relation to protein tolerance, i.e. the fact that patients are able to tolerate increased level of protein without a negative effect on biochemical data including ammonia and arginine levels. The Company notes two key concerns regarding the Committee's interpretation of the dietary benefit. • First, the threshold of >15% increase in dietary protein tolerance excludes patients who experienced smaller but still clinically meaningful improvements. In the Company's view, all sustained increases in protein intake are relevant to quality of life. This applies to 83.3% of patients, not just the 66.7% who met the >15% threshold. • Second, the Committee's suggestion that dietary intake would improve in real life without access to pegzilarginase, corresponding to a placebo effect, is not supported by clinical practice. Outside of a controlled trial setting, it is highly unlikely that dietitians would recommend increased protein intake without the biochemical improvements demonstrated with treatment. Doing so would risk rising arginine levels, which are associated with a faster onset and progression of symptoms. In summary, real-world data show that 83.3% of patients experienced improved dietary protein tolerance, not just those meeting the >15% threshold. This is a meaningful and sustained improvement in daily life and should be reflected in the modelled utility gains. Scenario analysis: • Proportion with improved diet 48.5%: weighted ICER £101,903 • Proportion with improved diet 66.7%: weighted ICER £99,959
12	12. **Pegzilarginase weight-based dosing costs (Section 3.18 of draft guidance consultation document)** **NICE draft guidance excerpt:**

	At the second committee meeting, the company stated that a post-hoc analysis of PEACE data showed that, for people 13 years and over, there was no trend for increasing weight on pegzilarginase treatment compared with the general population. But it stated there was a trend for increasing weight in people under 13 years, in which weight tends to slowly approach that of the general population….The NICE technical team noted that the average age in the model was 13 years, but there will be people aged below this age in NHS clinical practice who would have pegzilarginase (NICE, 2025). **Company comment:** Given that the average age at baseline in the model is 13 years, the Company agrees with the Committee that using 0.782 for all patients may underestimate the average weight. However, to use the Committee preferred assumption of 0.9 will overestimate the average weight. The Company suggestion is to use a weight ratio of 0.84 (average of 0.782 and 0.9) for all patients based on the rational that the proportion of patients below vs above 13 years when starting treatment in the model is equal. In Figure 2 in the Appendix, vial use for different average weight ratios is illustrated to highlight the sensitivity of results on dosing assumptions (vial use). For a weight ratio of 0.782, patients move to an average of four vials per injection some years later than if average weight ratio is 0.84 or 0.9. Another difference is that for a weight ratio of 0.782, average number of vials per injection as adult is four vials, whereas for weight ratio 0.9, average number of vials is five between ages 25-75 years. For weight ratio 0.84, five vials are needed between ages 36-64 years. Scenario analyses: • Weight ratio 0.782: weighted ICER £84,686 • Weight ratio 0.9: weighted ICER £99,252 **NICE draft guidance excerpt:** *The EAG provided a scenario in which the weight of people having pegzilarginase was assumed to be 90% of the age-matched general population. It explained that this aligned with the company's clinical expert Delphi panel results (NICE, 2025).* **Company comment:** The Company would like to clarify that the Delphi panel consensus was that the weight of the average patient treated with pegzilarginase and IDM would remain

	below 90% of population norms with continued treatment (Immedica, 2025), i.e. not that all patients would have a weight ratio vs general population of 0.9. Proportion of females **NICE draft guidance excerpt:** *The NICE technical team also noted that the company had modelled a higher percentage of females. The EAG highlighted that a systemic review (Bin Sawad et al., 2022) found that roughly equal percentage of females and males would develop arginase-1 deficiency (NICE, 2025).* **Company comment:** In the Committee preferred base case, starting distribution into GMFCS states are informed by the European ARG1-D burden-of-illness study. To be consistent, the Company preferred base case is to also use the proportion of females from the burden-of-illness study data (76% females). This proportion is also consistent with clinical expert feedback that the majority of patients in the UK are females. In summary, based on model demographics and real-world data, the Company supports using a weight ratio of 0.84 and a female proportion of 76%. This aligns to the demographics of the patient population in the UK and is aligned to using the burden-of-illness data for other key modelling scenarios. Scenario analysis: • Proportion female 50%: weighted ICER £99,693
13	13. **Pegzilarginase treatment discontinuation (Section 3.19 of draft guidance consultation document)** Discontinuation **NICE draft guidance excerpt:** *The NICE technical team highlighted that the assumption around the rate of treatment discontinuation in the pegzilarginase arm had a large impact on the cost-effectiveness estimates. This was because a higher rate of treatment discontinuation than that in the base case substantially reduced the undiscounted QALYs gained in the pegzilarginase arm. This is a factor in deciding whether a QALY weighting should be applied (NICE, 2025).* **Company comment:**

	In the pegzilarginase trials, few patients discontinued treatment: • In the PEACE trial, one patient discontinued early for 'personal reasons'. However, upon commercially available product, the Company have, in interactions with the treating physician, received indications that the patient was later prescribed treatment with pegzilarginase again. • In Study 102A, only one patient withdrew from the study. This caregiver reported being dissatisfied with the medical care they were receiving from the hospital, not reporting any dissatisfaction with the study treatment. In the trial pegzilarginase was delivered IV and patients had to attend multiple study visits and undergo many tests. In real life, the drug can be delivered SC at home, so the Company believes it simplifies administration and follow up significantly. Based on PEACE trial data, Figure 3 in Appendix provides different extrapolation options for long term treatment discontinuation in the model. The Committee preferred assumption is the log-logistic approach (accepted by the Company). With the log-logistic curve, approximately 20% of patients are assumed to have discontinued pegzilarginase treatment at age 50 years. In summary, treatment discontinuation with pegzilarginase is rare, with most patients remaining on therapy long term. The log-logistic assumption is accepted by the Company but likely overstates discontinuation. <u>Stop criteria</u> **NICE draft guidance excerpt:** *The EAG also noted that the company did not incorporate 'responders' and 'non-responders' in its base-case model to reflect pegzilarginase discontinuation. So, the committee questioned the practical application of pegzilarginase start and stop rules in NHS clinical practice (NICE, 2025).* **Company comment:** The Company would like to highlight that preventing or halting disease progression is a clinically relevant treatment goal. Therefore, a reasonable stop criterion, also supported by the clinical experts, could be if the patient does not respond to treatment, i.e., reduction of plasma arginine concentrations is not achieved or kept within target level. It is correct that it is not possible to account for response/no response in the model. However, patients stopping treatment due to "no response" could be

	regarded as captured by the log-logistic curve for discontinuation (see Figure 3 in Appendix), where approximately 20% of patients in the pegzilarginase group is assumed to have discontinued treatment by age 50 years. This is, in the Company perspective, an overestimated rate but could be seen to capture patients discontinuing treatment due to not achieving normalised plasma arginine level. The Company believe discontinuation rates will be very low as discontinuation of pegzilarginase would lead to guaranteed disease progression. In summary, treatment discontinuation with pegzilarginase is rare, with most patients remaining on therapy long term. The log-logistic assumption likely overstates discontinuation and already captures possible non-responders.

14	**14. QALY weighting (section 1 and 3.20 of draft guidance consultation document)** **NICE draft guidance excerpt:** *Clinical trial evidence shows that pegzilarginase plus usual treatment reduces levels of arginine in the blood compared with placebo plus usual treatment. Evidence also suggests improvements in mobility and mental processing, but this is uncertain because the studies were small and short. So, it is unclear how large these benefits are or how long these improvements will last.* *The committee concluded that it could not apply the full QALY weighting as estimated by the economic model. This was primarily because of the very high uncertainty around key model parameters including:* • *life expectancy for people treated with pegzilarginase* • *whether disease progression occurs for some people on pegzilarginase* • *how long people remain on pegzilarginase treatment* • *the high quality-of-life gains for people treated with pegzilarginase compared to standard care* *The committee requested further input on these issues (NICE, 2025).* **Company comment:** Pegzilarginase is the only disease-modifying treatment for ARG1-D, a condition with irreversible and progressive neurological deterioration. Without access, patients face continued loss of function, cognitive decline, and premature death. The clarifications and evidence provided here are not theoretical - they directly affect whether these patients can access life-changing therapy.

	The Company has accepted the majority of the Committee preferred assumptions. For the assumptions not accepted, the Company suggests minor evidence-based adjustments to better align with clinical data and other model parameters. These adjustments have only a modest impact on the ICER. To reduce the Committee uncertainty on key assumptions, the Company have provided clarifications on disease progression and survival, discontinuation and patient utilities, as well as presented targeted scenario analyses where key assumptions are tested. All scenario analyses provide weighted ICER in the range of £100,000. In this document, the Company has provided clarifications and further evidence to support the following key points. Together, these points provide a coherent and consistent case that pegzilarginase delivers sustained clinical benefit aligned with the HST criteria. • arginine is the key driver of disease in ARG1-D; sustained reductions in plasma arginine are associated with disease stabilisation and lowering elevated arginine concentrations has been shown to deliver meaningful clinical benefit. Sustained arginine control should be interpreted as a key indicator of stabilisation of disease progression • results from the pegzilarginase trials show that arginine levels can be reduced to normal level for all patients, and arginine levels will be kept within normal levels over time • the risk of hyperammonaemia is reduced in pegzilarginase-treated patients and less frequent and less severe HAC events are reported • the trials show that the reduced arginine levels, to within normal level, is associated with clinically relevant improvements in motor function with some patients reaching normal level of function • the improvement in symptoms or avoidance of any/further progression is expected to increase survival • very few patients are expected to discontinue pegzilarginase treatment • improved protein tolerance offers meaningful quality of life benefits and may enhance growth in younger patients • patient utility values are strongly correlated with symptom severity, reaching negative values when both motor function and cognition are severely impacted • patients treated with pegzilarginase will experience more years with improved QoL/utilities

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Draft guidance comments form

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	• the updated base case supports cost-effectiveness well within the HST threshold when the full QALY weight is applied. In summary, this response document provides clarification, evidence and scenario analyses addressing the key uncertainties raised by the Committee. The Company believes this should support the application of the full QALY weighting, as estimated by the model, in the final appraisal decision.
15	15. **Managed access (Section 3.23 of draft guidance consultation document)** The Company has no intention to submit managed access proposal.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Appendix

Table 1: Company preferred base case – deterministic results

Technology	Total Costs (£)	Total LYG	Total QALYs	Undiscounted incremental QALYs	ICER (£)	Weighted ICER (£)
Pegzilarginase + IDM	[redacted]	20,505	[redacted]			
IDM	[redacted]	9,925	[redacted]			
Incremental (peg-IDM)	[redacted]	10.580	[redacted]	[redacted]	£296,411	£98,804

Abbreviations: IDM – individual disease management; ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALY- quality-adjusted life year.

Table 2: Scenario analyses. Deterministic results, based on Company preferred base case

Scenario	Techn.	Total Costs (£)	Total LYG	Total QALYs	Undisc increm QALYs	Weighted ICER (£)
HR 0.005	Peg + IDM	[redacted]	20.013	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£110,291
Cogn dis-utility 50%	Peg + IDM	[redacted]	20.505	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£100,493
Cogn dis-utility 0	Peg + IDM	[redacted]	20.505	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£106,008
Updated utility matrix (see Table 12)	Peg + IDM	[redacted]	20.505	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£100,648
Proportion with improved diet 48.5% (83.3%)	Peg + IDM	[redacted]	20.505	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£101,903
Proportion with improved diet 66.7% (83.3%)	Peg + IDM	[redacted]	20.505	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£99,959
Weight ratio 0.782 (0.84)	Peg + IDM	[redacted]	20.505	[redacted]		
	IDM	[redacted]	9.925	[redacted]	[redacted]	£84,686
Weight ratio 0.9 (0.84)	Peg + IDM	[redacted]	20,505	[redacted]		
	IDM	[redacted]	9.925	[redacted]		£99,252

Proportion female 50% (76%)	Peg + IDM	[redacted]	20.164	[redacted]		
	IDM	[redacted]	9.374	[redacted]	[redacted]	£99,693
Committee preferred base case, full QALY weight	Peg + IDM	[redacted]	20.164	[redacted]		
	IDM	[redacted]	9.374	[redacted]	[redacted]	£111,272

Abbreviations: IDM – individual disease management; ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALY- quality-adjusted life year; BoI – European Arg1-D burden of illness study.

Table 3: Definition of baseline deficits for key secondary/other secondary endpoints. Ref: (Immedica, 2024)

Domain	Assessment	Component	Definition of Baseline Deficit
Mobility	Timed Walk Test	2MWD* (meters)	Definition of Baseline deficit for 2MWT varies by age and sex. Age / Female / Male 3-5 / <112.9 / <110.6 6-8 / <155.8 / <154.9 9-11 / <172.0 / <169.9 12-15 / <168.7 / <172.1 16-17 / <167.5 / <173.4 ≥18 / <142.4 / <148.8
	GMFM†	Part D	<35
		Part E	<68

2MWT = 2-Minute Walk Test; 2MWD = 2-Minute Walk Distance; GMFM = Gross Motor Function Measure
* Definition of Baseline deficit is calculated from the NIH Toolbox motor domain dataset (2-minute Walk Endurance Test).
† Definition of Baseline deficit is from Oeffinger 2008.

Figure 1: Pegzilarginase treatment facilitates a sustained reduction in plasma arginine, within the therapeutic range, over the LTE periods Ref: (McNutt et al., 2025)

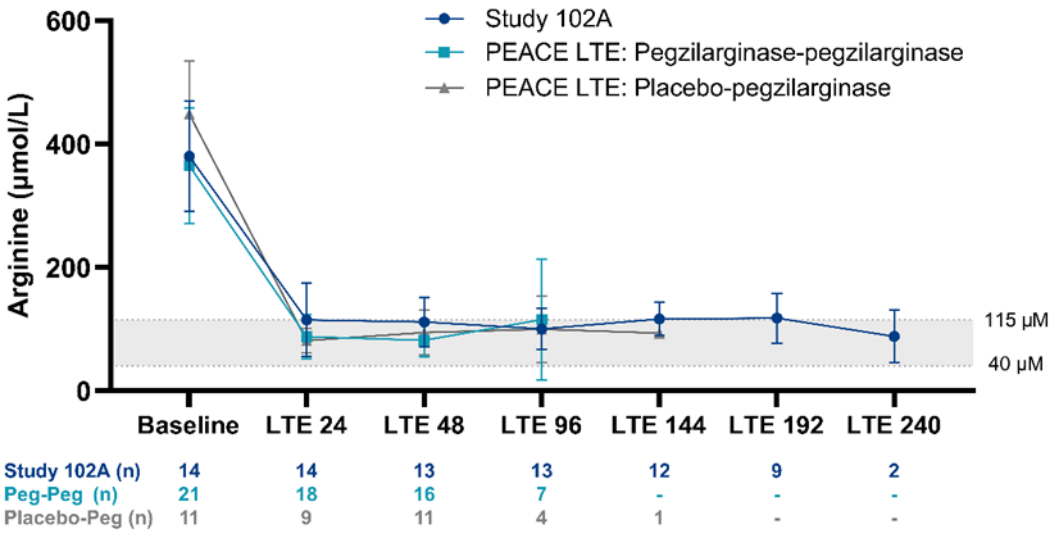


Table 4: Patient distribution in pegzilarginase arm given different assumptions regarding long-term progression (HR). Distribution at start of treatment (patient age 13) and at age 50 yrs (37 yrs after model start).

Progression (HR)	GMFCS 1	GMFCS 2	GMFCS 3	GMFCS 4	GMFCS 5	Dead	Discont. (to IDM)	Weighted ICER
Start (age 13 yrs)	50.00%	15.63%	15.63%	12.50%	6.25%	0.00%	0.00%	
Age 50 yrs								
HR 0 (BC)	49.14%	6.49%	1.13%	0.37%	0.00%	23.10%	19.76%	£98,804
HR 0.0025	45.13%	8.86%	1.20%	0.38%	0.00%	24.70%	19.73%	£104,242
HR 0.005	41.46%	10.97%	1.28%	0.39%	0.00%	26.21%	19.70%	£110,291
HR 0.01	34.98%	14.45%	1.51%	0.40%	0.00%	29.02%	19.63%	£122,437
HR 0.05	8.98%	22.68%	4.28%	0.67%	0.01%	44.15%	19.24%	£213,854
HR 0.10	1.64%	17.48%	6.91%	1.30%	0.04%	53.73%	18.91%	£314,725
HR 0.20	0.05%	7.61%	7.88%	2.66%	0.15%	63.14%	18.50%	£474,635

Note: among discontinued patients, moving to IDM, the majority is dead at age 50 (17.4% of the 19.76%).

Table 5: Overview of peak ammonia values, maximum post-baseline values, double blind period in PEACE trial, data-on-file.

Ammonia (normalized to µM)	Pegzilarginase (N=21)	Placebo (N=11)
Normal, n (%)	[redacted]	[redacted]
ULN to ≤100 µM, n (%)	[redacted]	[redacted]
>100 µM to <250 µM, n (%)	[redacted]	[redacted]
≥250 µM to <500 µM, n (%)	[redacted]	[redacted]
≥500 µM, n (%)	[redacted]	[redacted]

Abbreviations: ULN= upper limit of normal.

Table 6: MLD utilities (available in CE-model, sheet "Data QoL".

MLD Utilities

MLD cognitive sub-state utilities

Rescaled utilties preferred by ICER group in Libmeldy assessment Table 4.3 (2023). Original utilties from Nafees et al. 2020 https://www.valueinhealthjournal.com/article/S1098-3015(20)34123-1/fulltext

		Early Juvenile		
Health State	Late Infantile	Normal Cognitive Function	Moderate Impairment	Severe Impairment
GMFC-0	0,94	0,95	0,75	0,46
GMFC-1	0,71	0,91	0,63	0,34
GMFC-2	0,44	0,84	0,56	0,27
GMFC-3	-0,04	0,38	0,10	-0,11
GMFC-4	-0,13	0,00	-0,16	-0,33
GMFC-5	-0,20	-0,08	-0,25	-0,41
GMFC-6	-0,27	-0,13	-0,29	-0,46

Table 7: Patient utility weights, European ARG1-D Burden-of-Illness study – van Hout Crosswalk tariff.

	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS IV-V (n=3)
0-20=no to mild cognitive impairment*	0.840 SD=0.173 Min=0.548 Max=1.000 (n=7)	0.877 SD=NA (n=1)	0.151 SD=NA (n=1)
21-52=moderate to severe/extreme cognitive impairment	0.381 SD=NA (n=1)	0.528 SD=0.263 Min=0.175 Max=0.735 (n=4)	0.029 SD=0.001 Min=0.028 Max=0.029 (n=2)

SD=Standard Deviation, NA=Not Applicable, n=number of patients. *Three patients reported no cognitive impairment (all in GMFCS 1).

Table 8: Patient utility weights, European ARG1-D Burden-of-Illness study – Hernandez tariff.

	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS IV-V (n=3)
0-20=no to mild cognitive impairment*	0.835 SD=0.176 Min=0.516 Max=0.987 (n=7)	0.925 SD=NA (n=1)	-0.098 SD=NA (n=1)
21-52=moderate to severe/extreme cognitive impairment	0.231 SD=NA (n=1)	0.523 SD=0.215 Min=0.236 Max=0.728 (n=4)	-0.091 SD=0.049 Min=-0.126 Max=-0.056 (n=2)

SD=Standard Deviation, NA=Not Applicable, n=number of patients. *Three patients reported no cognitive impairment (all in GMFCS 1).

Table 9: Utility values used in the Committee preferred base case.

GMFCS	1	2	3	4	5
No/mild	0,855	0,604	0,263	-0,077	-0,126
Moderate	0,615	0,324	-0,017	-0,237	-0,250
Severe	0,325	0,034	-0,227	-0,250	-0,250
Dis-utilities					
Moderate	-0,24	-0,28	-0,28	-0,16	-0,17
Severe	-0,53	-0,57	-0,49	-0,33	-0,33

Table 10: Utility values from the European ARG1-D burden-of illness study. Hernandez tariff.

GMFCS	1	2	3	4	5	
Mean	0,759	0,604		-0,077	-0,126	Mean
No	0,832					0,832
Mild	0,852	0,925		-0,098		0,560
Moderate		0,682		-0,056		0,313
Severe	0,231	0,365			-0,126	0,157
No/mild	0,835	0,925		-0,098		0,554
Mod/Sev	0,231	0,523		-0,056	-0,126	0,143

Definition of cognitive levels: No: 0-10; mild: 11-20; moderate: 21-35; severe: 36-52.

Table 11: Patient counts from the European ARG1-D burden-of illness study.

GMFCS	[redacted]
Count	
No	
Mild	
Moderate	
Severe	

Table 12: Utility values from the European ARG1-D burden-of illness study, Hernandez tariff, with imputations, used for the scenario analyses.

GMFCS	1	2	3	4	5
No/mild	0.893	0.888	0.560	0.231	-0.098
Moderate	0.682	0.682	0.417	0.153	-0.112
Severe	0.298	0.298	0.157	0.015	-0.126
Dis-utilities					
Moderate	-0.211	-0.206	-0.142	-0.078	-0.014
Severe	-0.595	-0.590	-0.403	-0.216	-0.029

GMFCS1/no-mild: average of the general pop aged 13 yrs and 56% female and 0.835 from the burden-of-illness study
GMFCS1/moderate: same as for GMFCS2 (Table 10)
GMFCS1/severe: average for GMFCS1 and 2 (Table 10)
GMFCS2/no-mild: average for mild in GMFCS1 and 2 (Table 10)
GMFCS2/moderate and severe: same as for GMFCS1
GMFCS3: 2/3 of GMFCS2 and 1/3 of GMFCS5
GMFCS4: 1/3 of GMFCS2 and 2/3 of GMFCS5
GMFCS5/no-mild: same as GMFCS4 mild (Table 10)
GMFCS5/moderate: average no/mild and severe
GMFCS5/severe: same as GMFCS5 severe (Table 10)
Disutilities moderate: Difference between utility for no/mild and moderate
Disutilities severe: Difference between utility for no/mild and severe

Figure 2: Average number of vials per injection for different assumptions on weight ratio vs general population. Vertical line to illustrate start of model, i.e age 13 yrs.

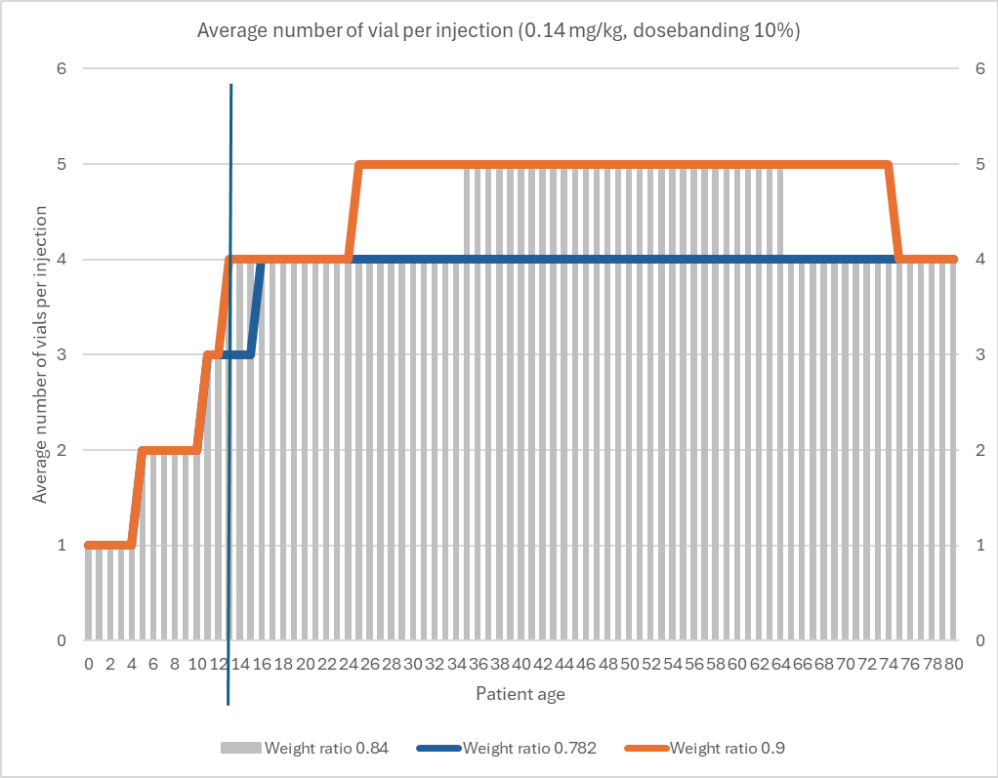
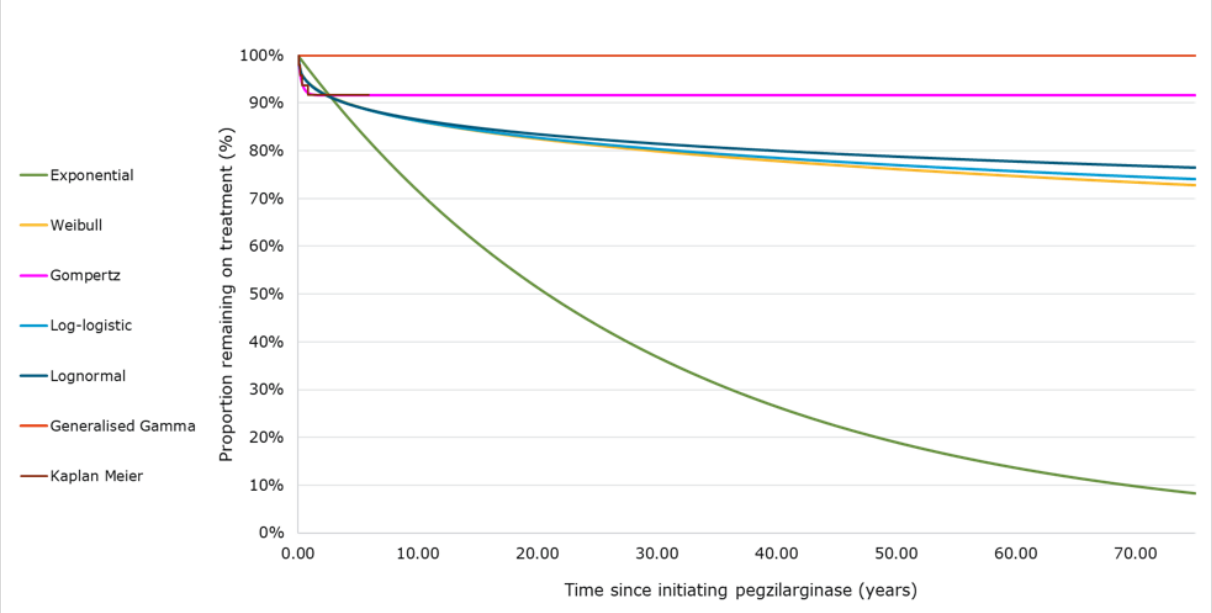


Figure 3: Discontinuation extrapolation. Time to discontinuation of pegzilarginase



References:

Immedica. (2024). *Data on file - CAEB1102-300A - Final Clinical Study Report*.

McNutt, M. C., Rutsch, F., Sanchez Russo, R., Gasperini, S., Batzios, S., Leão Teles, E., Brassier, A., Ganesh, J., Schulze, A., Enns, G. M., & Rudebeck, M. (2025). Long term efficacy and tolerability of pegzilarginase in arginase 1 deficiency: results of two international multicentre open-label extension studies. *JIMD in press*.

NICE National Institute for Health and Care Excellence

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Draft guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Metabolic Support UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to declare

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Pegzilarginase for treating arginase-1 deficiency [ID4029]

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We remain concerned that, in not recommending pegzilarginase for the treatment of arginase 1 deficiency (ARG1d), the Committee has not fully understood and taken into account the high level of unmet need, as well as the high physical and psychological burden ARG1d has on patients and their carers, and how this impacts each of their quality of life. In line with this, we are concerned that the clinically meaningful impact of pegzilarginase on the lives of patients, and their families, as detailed in previously provided evidence by patients, carers, clinical experts and the Company, have not been fully understood and taken into account by the Committee. The address the Committee's concerns as detailed in the Draft Guidance (DG), we have summarised the current evidence in our response below. Alongside this, we would like to highlight that the **long-term uncertainties** raised by the Committee are inherent to all (ultra-)rare disorders. While appropriate consideration should be given to potential uncertainties, it should also be acknowledged and understood that **ultra-rare disorders will not see progression in treatment options, nor innovations**, when evidence requirements set for common disorders are applied to ultra-rare disorders (as also detailed in NICE's HTA manual section 6.2.34). Equally, these requirements **risk England falling behind** other nations across the world; with people living with ARG1d in England remaining destined for a life marked by the disorder's natural progression, while people living with ARG1d in other nations will maintain their mobility and cognitive abilities, enabling them to grow up alongside their unaffected peers.
2	The majority of uncertainties highlighted by the Committee in the DG are similar to those in the previous DG. Below we summarise evidence previously provided, supplemented by clarifications as necessary: - Uncertainty around the **mobility improvements** in people living with ARG1d as a result of pegzilarginase, including how large these benefits are and how long they will last (DG, page 3 and section 3.7)

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	All respondents to the community survey and clinical survey noticed improvements to the mobility of the person with ARG1d when treated with pegzilarginase. In the community survey, community-perceived plateauing of mobility improvements was indicated to occur at 3-6 months; while in the clinical survey no worsening was observed after three years and some HCPs continued to observe mobility improvements after three years. Worsening was only observed after people living with ARG1d were taken off pegzilarginase treatment. Considering the stakeholder evidence previously provided, as well as the clinical data, we disagree with the Committee's statement in the DG that this is associated with "very high levels of uncertainty" (section 3.7). - Uncertainty around **mental processing** in people living with ARG1d as a result of pegzilarginase, including how large these benefits are and how long they will last (DG, page 3 and section 3.7) All respondents to the community survey and clinical survey noticed improvements to the mental processing of the person with ARG1d when treated with pegzilarginase. In the community survey, community-perceived plateauing of mental processing was indicated to occur at 3-6 months; while in the clinical survey, clinician-perceived plateauing occurred after of 6-18 months. Worsening was only observed after people living with ARG1d were taken off pegzilarginase treatment. Considering the stakeholder evidence previously provided, as well as the clinical data, we disagree with the Committee's statement in the DG that this is associated with "very high levels of uncertainty" (section 3.7). - Uncertainty around **worsening** of the condition on pegzilarginase treatment (DG, page 3 and section 3.7) As described above, HCPs only described worsening of people living with ARG1d when they were taken off pegzilarginase treatment. None of the nine HCPs reported that any of the people living with ARG1d under their care experienced worsening while on pegzilarginase. Worsening was also not described by any of the community members in the community survey. Considering the stakeholder evidence previously provided, as well as the clinical data, we disagree with the Committee's statement in the DG that this is associated with "very high levels of uncertainty" (section 3.7) and also refer to section 3 of our comment form in which we discuss that clinical experts widely agree that concentrations of plasma arginine levels below 200 umol/L are the target and stop the disorder's progression (Haberle et al. 2019; Diaz et al. 2022). Note that this target was achieved by 100% of people living with ARG1d on pegzilarginase treatment (McNutt et al. 2023).

- Uncertainty around **life expectancy** for people who have pegzilarginase (DG, page 3 and section 3.4)

Seven out of eight HCPs who responded to our clinical survey indicated that they expected the life expectancy of people living with ARG1d to be positively affected by pegzilarginase. The duration was described as spanning “many years” to “normal lifetime” (n=5). Only one HCP did not expect life expectancy to be impacted.

- Uncertainty around the **duration** over which people receive pegzilarginase (DG, page 3 and section 3.19)

All eight HCPs who responded to this question in our clinical survey indicated that they expected the duration of treatment with pegzilarginase to be lifelong. HCPs suggested stopping rules should be related to worsening (n=5), no response (n=5), severe adverse events (n=3) and poor compliance (n=1). HCPs agreed that stopping should only be considered after at least one year of treatment, with some suggesting at least three years. In line with this, only one person with ARG1d withdrew early for personal reasons. The majority of the PEACE trial participants, both nationally and internationally, have taken up the Company’s offer to re-establish treatment on a compassionate use basis and are doing well.

- Uncertainty around how pegzilarginase affects **body weight** (DG, page 3)

All community respondents to the community survey reported that the weight of the individuals living with ARG1d is impacted by the disorder. The way in which varied over the full spectrum, from being underweight to obese. Limited impact of pegzilarginase on weight was reported. This was also supported by the findings from the clinical survey.

- Uncertainty around how pegzilarginase affects **level of ammonia** in the blood (DG, page 3, and section 3.9, 3.11 and 3.12)

Both community and clinical respondents reported that hyperammonaemia episodes occurred while on pegzilarginase treatment but that **no severe episodes**, i.e. ≥500 µmol/L or “hyperammonaemic crises” (HAC) were reported among people living with ARG1d treated with pegzilarginase.

In relation to this point, and as detailed during the Committee Meeting, we are concerned that our September 2024 stakeholder response to the DG was misinterpreted during the Committee Meeting, which we also flagged as a Factual Error during the Committee Meeting. This Factual Error has been repeated in the DG (section 3.9, page 16) “Stakeholder responses to the draft guidance consultation indicated that some hyperammonaemic crises still occur

	while on pegzilarginase.". The Committee's subsequent conclusion in section 3.9, detailing that the EAG's proposed annual progression of 5% from GMFCS-II or GMFCS-III to GMFCS-V in the pegzilarginase arm is plausible raises concerns as this is not substantiated by any clinical data, nor stakeholder responses. With regards to these uncertainties; while there may indeed be some uncertainties around pegzilarginase, we believe that the clinical data previously provided by the Company, supplemented by the evidence collected by the clinical experts and Metabolic Support UK, showcases a real, meaningful and sustained positive impact of pegzilarginase on those affected by ARG1d; both those living with and caring for. Long-term uncertainties cannot be removed by anything but time and should not come at the expense of the community. *Diaz et al. (2022). The role and control of arginine levels in arginase 1 deficiency. J Inherit Metab Dis;46(1):3–14.* *Haberle et al. (2019). Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis;42(6):1192-1230.* *McNutt et al. (2023). O08: Long-term efficacy and safety of pegzilarginase for arginase 1 deficiency: 2 years of experience in the phase 2 extension study. Genetics in Medicine Open; 1(1): Supplement.*
3	There are two statements in the DG that we would like to comment on: - "Clinical advice to the EAG noted that plasma arginine levels do not have a consistent relationship with disease severity." (section 3.4) We want to ensure that this statement is correctly understood by the Committee, as it may suggest that the phase 3 clinical trial's primary endpoint is not relevant. Any treatment for arginase 1 deficiency, be this the current standard of care, or pegzilarginase, targets the plasma arginine levels of the person with ARG1d, as agreed in international guidelines (Haberle et al. 2019). Arginine and its metabolites are what cause the signs and symptoms of ARG1d. Treatment aims to reduce plasma arginine concentrations below 200 umol/L, where 40-115 umol/L is the normal range for the general population (Haberle et al. 2019; Diaz et al. 2022). Unfortunately, in most people living with ARG1d, despite extremely restrictive diets, plasma arginine levels remain in excess of 300 umol/L (Diaz et al. 2022). This leads to neurotoxicity as the metabolites damage neurons, especially in motor pathways, resulting in cerebral palsy-like symptoms over time and can also cause hyperammonaemia. The only value to be derived from the statement provided in the DG, is that the level of plasma arginine above 200 umol/L does not correlate linearly with disease severity; i.e. someone with consistent plasma arginine levels of 400 umol/L may have less ARG1d symptoms than someone with consistent plasma arginine levels of 300 umol/L (Diaz et al. 2022). Clinical experts widely agree that

	concentrations below 200 umol/L are the target and stop the disorder's progression as a result of increased plasma arginine levels (Haberle et al. 2019; Diaz et al. 2022). The long-term extension study of the open-label phase 1/2 study (101A/102A) demonstrated that at week 96 (n=13), 100% of people living with ARG1d had achieved plasma arginine levels below 200 umol/L, with 77% having plasma arginine levels within the normal range (McNutt et al. 2023). This clearly demonstrates the clinical significance plasma arginine levels has for people living with ARG1d. *Diaz et al. (2022). The role and control of arginine levels in arginase 1 deficiency. J Inherit Metab Dis;46(1):3–14.* *Haberle et al. (2019). Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis;42(6):1192-1230.* *McNutt et al. (2023). O08: Long-term efficacy and safety of pegzilarginase for arginase 1 deficiency: 2 years of experience in the phase 2 extension study. Genetics in Medicine Open; 1(1): Supplement.* - "The EAG highlighted that mobility, mental processing and quality-of-life outcomes were uncertain because the results lack clinical and statistical significance." (section 3.4) This statement suggests that there is no clinically significant result associated with pegzilarginase treatment in relation to mobility, mental processing and quality-of-life for people living with ARG1d. As has been highlighted in the Company submission, the clinical experts' submissions and statements during the Committee Meetings and our submissions and Committee Meetings' comments, the impact of pegzilarginase on mobility, mental processing and quality of life, is very much clinically significant. Each of these stakeholders has described the clinically significant impact pegzilarginase has had on mobility, not just halting progression of mobility limitations, but in numerous cases also improving mobility; with the same applying to mental processing and quality of life. It is therefore inaccurate to suggest that there is a lack of clinical significance for pegzilarginase in relation to these parameters.
4	We would also like to comment on the **starting distribution** (section 3.6). Based on the data collected through the clinical survey and subsequent discussion during the Committee Meeting, the BOI study with a redistributed GMFCS-II percentage across GMFCS-II and GMFCS-III, aligns with the current clinical population in England. This includes considerations shared by clinicians that not all of people living with ARG1d, i.e. some of those in GMFCS-V would be deemed eligible for treatment, patients having both passed away and been newly diagnosed since the clinician survey was conducted in September 2024.

Pegzilarginase for treating arginase-1 deficiency [ID4029]

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	In addition, we would like to highlight that while newborn screening is not available for ARG1d, the current Generation Study provides a new route to screening for people living with ARG1d. With ARG1d included among the 200+ conditions tested for (Generation Study, 2025). Further to this, the NHS 10-year plan details that it aims to improve genetic screening, which will likely mean the extension of the Generation Study in the long run (NHS, 2025). This is likely to have an impact on the starting distributions within the foreseeable future. *Generation Study. (2025). All conditions under A. Retrieved from: https://www.generationstudy.co.uk/conditions-we-test-for/all-conditions (accessed July 2025).* *NHS. (2025). Fit for the Future: 10 Year Health Plan for England. Retrieved from: https://www.gov.uk/government/publications/10-year-health-plan-for-england-fit-for-the-future (accessed July 2025).*
5	Additionally, we want to highlight is that the current economic model will likely **overestimate the cost of treatment** with pegzilarginase as the current assumption in the model is that people living with ARG1d will receive pegzilarginase plus individualised disease management (i.e. ammonia scavengers and a severely protein restricted diet with amino supplementation). Previous discussions around diet liberalisation have focussed on the utility benefit associated with this liberalisation. In line with this, our clinical survey found that all nine HCPs expected to increase protein allowance, with seven (n=6 paediatric, n=1 adult HCP) out of nine HCPs indicating they expected to also reduce the dose of ammonia scavengers. Other reports have also highlighted the relevance and real-life applicability of diet liberalisation, as well as the reduction of ammonia scavengers and amino supplementation (Singh et al. 2024; Arnoux et al. 2024). This would thus suggest that health state costs for people on pegzilarginase would be lower than those for people on IDM alone. In line with this evidence, we believe that the Committee's **assumption that only 48.5% of people will liberalise diet is implausible**. All HCPs responding to the clinical survey indicated that they would expect to liberalise diet and the published literature plus the evidence in the Company Submission are in line with this (Arnoux et al. 2024; Singh et al. 2024). This is further compounded by the **reduction in the requirement for ammonia scavengers for which a utility gain is currently not considered**. As per our original patient organisation submission, when talking about hyperammonaemia, "all of the families said they most feared this symptom" because of the irreversible impact, "resulting in frequent serious admissions to A&E". Considering no severe hyperammonaemia episodes (≥500 µmol/L) have been reported, nor are expected as per clinical feedback, a utility gain should also be attached to this.

Pegzilarginase for treating arginase-1 deficiency [ID4029]

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	Arnoux et al. (2024). PO-613-(20542)-Experience of pegzilarginase for the treatment of arginase 1 deficiency outside clinical trial setting. SSIEM 2024. Singh et al. (2024). EP-120-(20745)-Pegzilarginase treatment in arginase 1 deficiency allows for liberalisation of protein restriction. SSIEM 2024.
6	In this response, we have addressed each of the Committee's areas of uncertainty, including those deemed to be of "very high uncertainty" upon which the Committee has based their **QALY weighting**. It is our hope that taking our comments together with those of the Clinical Experts and Company, as well as any other consultees, will address a substantial part of this uncertainty. In line with this, we would like to highlight that NICE's health technology evaluations manual, section 6.2.34, details that "the committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult because they are: - rare diseases - for use in a population that is predominantly children (under 18 years old) - innovative and complex technologies In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition or technology(s) affects the ability to generate high-quality evidence before applying greater flexibility." We strongly encourage that the Committee takes this, together with all other evidence, into consideration when assessing the appropriate QALY weighting for pegzilarginase in the treatment of people living with ARG1d.
7	We understand that the Company has not submitted a **Managed Access** proposal. If this were the case in the future, Metabolic Support UK would be wholly supportive of supporting any people living with ARG1d enrolling in the Managed Access Agreement, while also acknowledging that the duration over which such an agreement would run is unlikely to address any of the long-term uncertainties raised by the Committee.
8	Finally, we remain concerned about the negative impact the decision to not recommend pegzilarginase has on our community, as well as the extensive duration of the assessment process. This progressive disorder has a marked effect on people living with ARG1d and their families and we have sadly seen disease onset, worsening and lost members of the community while this assessment process has been on-going.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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NICE National Institute for Health and Care Excellence

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025.** Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Clinical experts UK: Dr Arunabha Ghosh, Dr Spyros Batzios, Dr Reena Sharma]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[NO]

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NICE National Institute for Health and Care Excellence

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025.** Please submit via NICE Docs.

Name of commentator person completing form:	[Dr Reena Sharma]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	• We are concerned that Most of the uncertainties in the economic model cannot be addressed by the current state of real-world data. To resolve these uncertainties would need long term follow up (20-30 years) of treated patients. While an international cohort of treated patients exists, waiting to observe the outcomes in that population would mean that we allow patients in England to continue to deteriorate.
2	• There has been some uncertainty expressed regarding the correlation between plasma arginine and clinical symptoms. We would like to clarify as clinical experts that we **do** expect there to be a difference in clinical outcomes between patients who have arginine levels persistently within the target range (though in practice this is rarely, if ever, achieved), versus patients with arginine levels persistently above the target range (who would be expected to deteriorate clinically over time). It is less clear whether there is a correlation between the extent of elevation of plasma arginine and the severity / rate of disease progression.
3	• It is difficult to draw comparisons with other treated inherited metabolic diseases (IMD) as the pathophysiology of arginase I deficiency and its natural history is unique. For example, enzyme replacement therapies (ERTs) used in lysosomal storage disorders work in a different manner with different underlying disease pathology. In those conditions, for example, treatment of neurological manifestations is extremely difficult as it requires targeting of the treatment to the central nervous system, with challenges regarding administration route, distribution, dosing etc. Arginase I deficiency is different in that there is a plausible mechanism by which a treatment delivered to the periphery can have an impact on neurological manifestations.

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4	• The QALY weighting applied in this technology appraisal depends considerably on whether disease progression occurs in patients on treatment. While we as clinical experts feel that that it is very likely that pegzilarginase prevents disease progression, we acknowledge the uncertainties due to the paucity currently of long-term real-world data (see earlier points). However, if the standard required to be achieved is 'no disease progression in patients on treatment' we would argue that this is not comparable with other ERTs and substrate reduction therapies that have been approved, through the NICE HST process, for other IMDs in which a degree of disease progression does occur or is expected despite treatment (examples: elosulfase alfa, cipaglucosidase+miglustat, avalglucosidase alfa, velmanase alfa, pegunigalsidase alfa, migalastat). For example, it is known that ERT-treated patients with infantile Pompe disease will still develop central nervous system disease and have progression of muscle disease in later childhood leading to very high dependency. The most recent publication from one of the UK centres on Fabry does not show any significant improvement in survival. Other comorbidities play an important role in the outcome of these patient. (https://doi.org/10.1016/j.ymgmr.2025.101229). Real-world data on long-term outcomes of adults with Pompe disease on enzyme replacement therapy confirmed the ongoing decline in various parameters. J Neurol 268, 2482–2492 (2021). https://doi.org/10.1007/s00415-021-10409-9. While it is understandable that starting a new approach to existing patients on treatment may not be possible, it could certainly have been considered going forward while considering newer therapies.
5	• The EAG highlighted that mobility, mental processing and quality of life outcomes were uncertain because the results lack clinical and statistical significance. We, as clinical experts disagree and would argue that the results although have not reached statistical significance but are of **clinical significance**.
6	• On the time spent in GMFCS states for patients on IDM, we as clinical experts, agree with the estimates made by the company. EAG may like to revisit their model. • We would also like to reiterate that severe hyperammonaemic crises on pegzilarginase, especially those that will result in worsening to GMFCS-V while on pegzilarginase are highly unlikely.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).

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NICE National Institute for Health and Care Excellence

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025.** Please submit via NICE Docs.

- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
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Pegzilarginase for treating arginase-1 deficiency. [Review of ID4029]

A Highly Specialised Technology evaluation

Report following the company's response to NICE's Draft Guidance Consultation

Produced by	Sheffield Centre of Health and Related Research (SCHARR), The University of Sheffield
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Declared competing interests of the authors

The author has no conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of author

Matt Stevenson critiqued all aspects of the company's response to the Appraisal Consultation Document (ACD), conducted the cost-effectiveness analyses, and authored the report.

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1. Introduction

In August 2024, NICE released a Draft Guidance Consultation (DGD) which did not recommend the use of pegzilarginase within its marketing authorisation for treating arginase-1 deficiency (ARG1-D).[1] This report summarises key aspects of the company's response to the DGD, and a critique of these points undertaken by the External Assessment Group (EAG).

In March 2025, the company submitted new information,[2] which was a 32-page response using NICE's draft guidance comments form, together with a checklist of confidential information (7 pages), a 51-page report (included 3 embedded PowerPoint presentations) describing a Delphi panel undertaken by the company, and a revised economic model. The EAG produced a critique of this new evidence.[3] The NICE committee met in May 2025, with a DGD, again not recommending pegzilarginase, released in June 2025. In this DGD, the committee provided its preferred assumptions (Section 3.22).

In July 2025, the company submitted further information, which included a 28-page word document using NICE's draft guidance comments form, a 9-page appendix, and a revised mathematical model.[4] In addition, there was an increase in the confidential patient access scheme (PAS) discount offered by the company to [redacted] which reduces the list price of a 2mg vial of pegzilarginase from £4690 to [redacted].

The structure of this document is as follows. Section 1 is the introduction, Section 2 describes the changes that the company has made to its base case since the June 2025 DGD, and the EAG's critique of these changes. Section 3 presents the results of the exploratory analyses undertaken by the EAG.

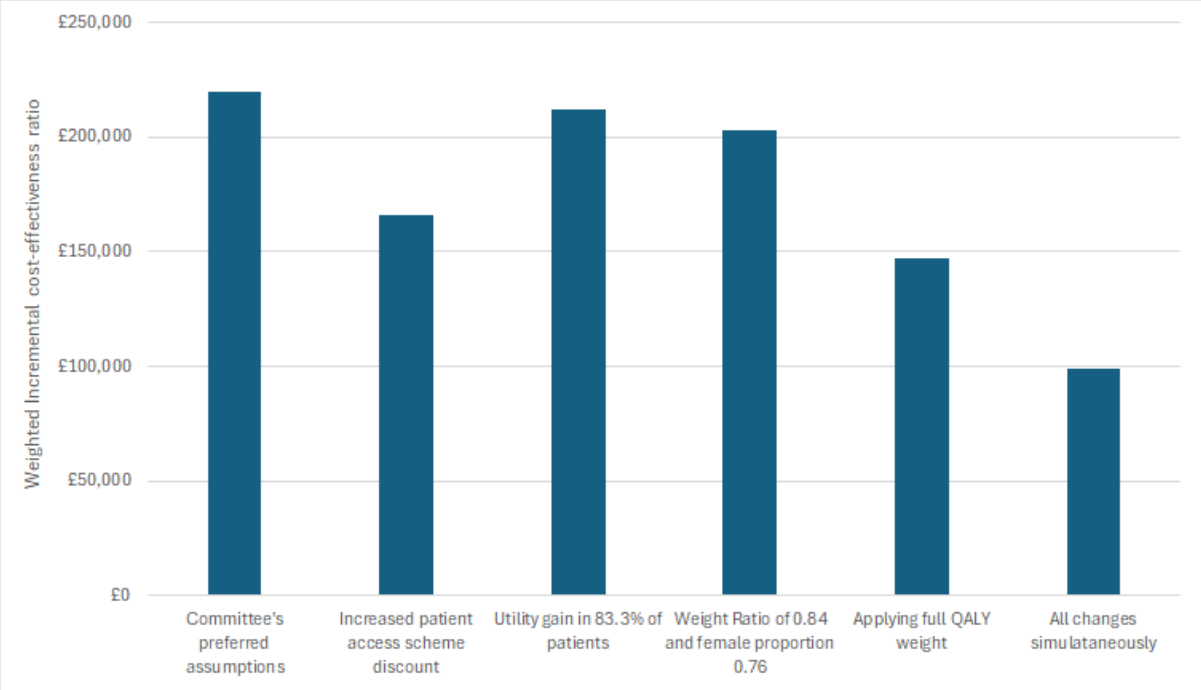
2. Changes made by the company to the previous EAG base case

The company assessed the 13 committee preferred assumptions that were provided in Section 3.22 of the July 2025 DGD. Of these 10 were accepted, but 3 were not, with the company proposing modifications to these "*in line with available evidence*".

For brevity, the EAG has not discussed the 10 committee-preferred assumptions that were accepted but has instead focussed on the 3 assumptions which the company believes should be modified. These are discussed individually in Section 2.1 to 2.3

However, in order to provide overall context, the EAG has shown how the increase in the PAS, and the proposed modifications to the committee's-preferred assumptions impacts on the ICER. Figure 1 shows that all three proposed modifications reduce the incremental cost-effectiveness ratio (ICER) with the application of the full QALY weight, rather than the half weight assumed by the Appraisal Committee has the largest impact, more so than the increase in the PAS discount. The three modifications reduce the Committee's preferred weighted ICER (with latest PAS discount) from a value of £165,807 to £98,804. The EAG comments that the changes made by the company in its response to the DGD has notably increased the incremental quality-adjusted life years (QALYs) gained which were [redacted] in the Committee's preferred base case and are [redacted] in the company's revised submission.

Figure 1: Detailing how the increased PAS discount and proposed modifications change the Committee's preferred deterministic ICER



2.1 Assuming that 83.3% of the pegzilarginase-treated patients have a utility gain rather than 48.5%

In the committee's preferred base case, 48.5% of patients receiving pegzilarginase were assumed to have a utility gain, despite the company using a value of 83.3% (10/12) based on real-world evidence from France.[5] The committee may have been influenced by the EAG critique,[3] (Section 2.9) that noted that (i) the company had moved from a threshold of 15% or more increased protein intake used in its original submission,[6] to any increase in protein intake, (ii) that only [redacted]%) patients in the treatment-naïve group increased protein intake by more than 15%, over a follow up period of 12 months and (iii) that any placebo response (18.2% of patients in the control arm of the PEACE study increased protein intake by over 15%) was disregarded.

The company contests that there would be a placebo response stating that "*the Committee's suggestion that dietary intake would improve in real life without access to pegzilarginase, corresponding to a placebo effect, is not supported by clinical practice. Outside of a controlled trial setting, it is highly unlikely that dietitians would recommend increased protein intake without the biochemical improvements demonstrated with treatment. Doing so would risk rising arginine levels, which are associated with a faster onset and progression of symptoms.*" As there are no new data provided by the company the EAG believes that this is a committee decision.

The company also states that "*the threshold of >15% increase in dietary protein tolerance excludes patients who experienced smaller but still clinically meaningful improvements . In the Company's view, all sustained increases in protein intake are relevant to quality of life. This applies to 83.3% of patients, not just the 66.7% who met the >15% threshold.*" The EAG comments that (i) the individual data for the patients reported in Arnoux *et al*.[5] is not available for the 12 patients with data on natural protein increases, so it is unclear whether all 10 patients had clinically meaningful improvements, and also that it unknown why 14 patients provided data for other outcomes, such as arginine levels, but only 12 provided data on protein intake and (ii) that the utility gain assumed by the company (of 0.04 per person) is likely to be a function of the threshold of increased protein increase, and that reducing the threshold required for an improved diet could be associated with a lower utility gain. As there are no new data provided by the company the EAG believes that this is a committee decision.

The company provided scenario analyses that indicated that the proportion of people with an improved diet was not a large driver of the ICER, with the company's base case of £98,804 (using a proportion of 83.3%) increasing to £99,959 (using 66.7%) and to 48.5% (using £101,903).

2.2 Assuming that the pegzilarginase-treated patients weigh 84% of the general population and that 76% of the cohort are female

In the committee's preferred base case, patients receiving pegzilarginase were assumed to weigh 90% of the general population weight and that 50% of patients would be female. The company has contested both points which will be described separately.

For the weight ratio, the company suggested that the average (rounded to 2 decimal places) of the company's preferred estimate of 0.782 and 0.900, which is 0.84 should be used. The rationale was that "*using 0.782 for all patients may underestimate the average weight. However, to use the Committee preferred assumption of 0.9 will overestimate the average weight*" The EAG comments that simply averaging the two values may not be correct. As described in Section 2.15 of a previous EAG report,[3] results from the Delphi panel appears more supportive of a higher value: "*In the Delphi panel, the clinicians were asked whether the weight of the average patient treated with continuous pegzilarginase would remain below 90% of population norms…. At this level, 5 clinicians agreed, 2 somewhat agreed and 1 was neutral, suggesting broad agreement with a value of 90%, which the EAG believes is a realistic value to use in sensitivity analyses. The EAG also notes that should pegzilarginase be recommended and treatment starts at a young age that the weight ratio in the future may be more similar to that of those patients currently under 13 years of age.*" As there are no new data provided by the company the EAG believes that this is a committee decision.

For the male/female ratio, the EAG agrees with the company that in order to be consistent with the preferred source of population data (the European Burden of illness study[7]) that using a proportion of patients who are female of 0.76 would be more appropriate. Making this change in isolation reduces the committee-preferred weighted ICER decrease from £165,807 to £153,068 applying the new PAS price.

2.3 Assuming that the full QALY weight should be used when calculating the weighted ICER

In the committee's preferred base case, the committee concluded that "*it could not apply the full QALY weighting as estimated by the economic model. This was primarily because of the very high uncertainty around key model parameters including:*

- *life expectancy for people treated with pegzilarginase*
- *whether disease progression occurs for some people on pegzilarginase*
- *how long people remain on pegzilarginase treatment*
- *the high quality-of-life gains for people treated with pegzilarginase compared to standard care*"

and requested further input on these issues.

For completeness, the EAG has reproduced the company's bullet points that were included in its response to the second DGD.[4]

> "*The Company has provided clarifications and further evidence to support the following key points. Together, these points provide a coherent and consistent case that pegzilarginase delivers sustained clinical benefit aligned with the HST criteria.*
>
> - *arginine is the key driver of disease in ARG1-D; sustained reductions in plasma arginine are associated with disease stabilisation and lowering elevated arginine concentrations has been shown to deliver meaningful clinical benefit. Sustained arginine control should be interpreted as a key indicator of stabilisation of disease progression*
> - *results from the pegzilarginase trials show that arginine levels can be reduced to normal level for all patients, and arginine levels will be kept within normal levels over time*
> - *the risk of hyperammonaemia is reduced in pegzilarginase-treated patients and less frequent and less severe HAC events are reported*
> - *the trials show that the reduced arginine levels, to within normal level, is associated with clinically relevant improvements in motor function with some patients reaching normal level of function*
> - *the improvement in symptoms or avoidance of any/further progression is expected to increase survival*
> - *very few patients are expected to discontinue pegzilarginase treatment*
> - *improved protein tolerance offers meaningful quality of life benefits and may enhance growth in younger patients*
> - *patient utility values are strongly correlated with symptom severity, reaching negative values when both motor function and cognition are severely impacted*
> - *patients treated with pegzilarginase will experience more years with improved QoL/utilities*
> - *the updated base case supports cost-effectiveness well within the HST threshold when the full QALY weight is applied.*
>
> *In summary, this response document provides clarification, evidence and scenario analyses addressing the key uncertainties raised by the Committee. The Company believes this should support the application of the full QALY weighting, as estimated by the model, in the final appraisal decision.*"

The EAG comments that there is little new data presented by the company, as would be expected given that longer-term data would need to come from the pivotal clinical studies, but more reiterations of the likely long-term benefits of pegzilarginase. The EAG has made no further comment on this but leaves this decision to the Committee.

3. Exploratory analyses undertaken by the EAG

3.1 Overview of the EAG's main exploratory analyses

The EAG undertook exploratory analyses to generate the weighted ICERs for 16 scenarios which combined the committee's preferences and the company's proposed changes for the following parameters:

- The proportion of patients with an improved diet resulting in utility gains (0.485 or 0.833)
- The assumed weight ratio between people treated with pegzilarginase and the general population (0.900 or 0.84)
- The proportion of pegzilarginase-treated patients that are female (0.50 or 0.76)
- QALY weighting (half or full)

All results use the latest PAS discount.

3.2 Results of the EAG's main exploratory analyses

Weighted ICERs for the 16 scenarios are shown in Figure 2. Deterministic results range from the Committee's preferred value (£165,807) to the Company's preferred value (£98,804) and probabilistic results (1000 iterations) from the Committee's preferred value (£169,650) to the Company's preferred value (£102,186). More detailed results for these two scenarios are presented in Table 1 (deterministic) and Table 2 (probabilistic). Probabilistic weighted ICERs are slightly greater than deterministic weighted ICERs, due to non-linearity in the impacts of the QALY weighting which can never be greater than 3 but can be markedly lower for some parameter value sets.

Figure 2: Detailing how changing assumptions affect the estimated ICER

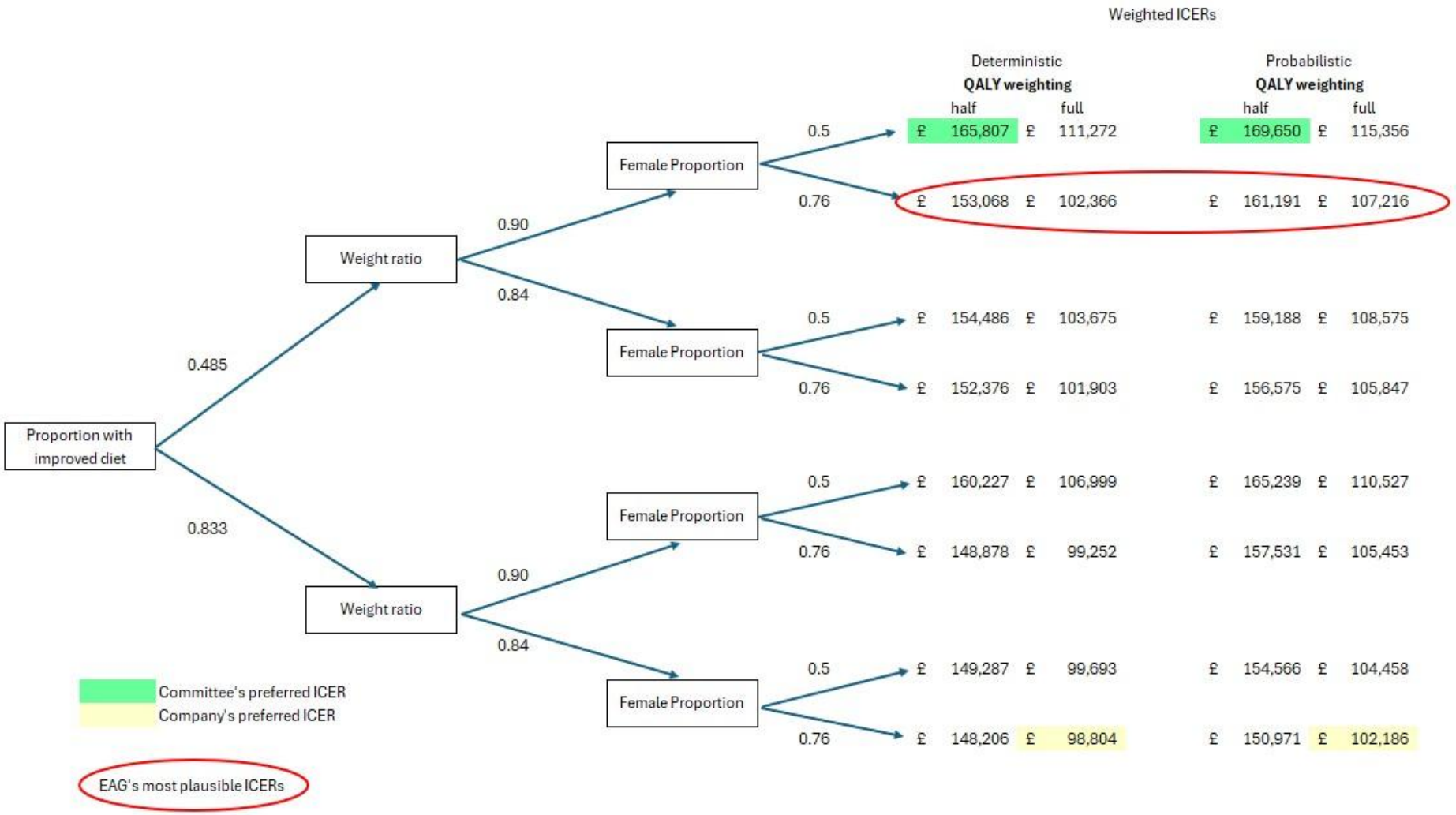


Table 1: Deterministic results from the Committee's preferred analyses and the Company's preferred base case

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs*	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
Committee's preferred base case									
Pegzilarginase	44.31	[redacted]	[redacted]	32.22	[redacted]	[redacted]	[redacted]	£165,807	[redacted]
IDM	12.10	[redacted]	[redacted]						
Company's preferred base case									
Pegzilarginase	45.43	[redacted]	[redacted]	32.09	[redacted]	[redacted]	[redacted]	£98,804	[redacted]
IDM	13.01	[redacted]	[redacted]						

*Undiscounted ** Calculated using the undiscounted QALY gains (not shown in the table)
IDM: Individualised disease management. LYG: life year gained; QALY: quality-adjusted life year

Table 2: Probabilistic results from the Committee's preferred analyses and the Company's preferred base case

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs*	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
Committee's preferred base case									
Pegzilarginase	44.36	[redacted]	[redacted]	31.71	[redacted]	[redacted]	[redacted]	£169,650	[redacted]
IDM	12.65	[redacted]	[redacted]						
Company's preferred base case									
Pegzilarginase	45.68	[redacted]	[redacted]	32.17	[redacted]	[redacted]	[redacted]	£102,186	[redacted]
IDM	13.51	[redacted]	[redacted]						

*Undiscounted ** Calculated using the undiscounted QALY gains (not shown in the table)
IDM: Individualised disease management. LYG: life year gained; QALY: quality-adjusted life year

3.3 Additional EAG sensitivity analyses

The EAG has explored the impact of two factors on the ICER. The first relates to the use of an average weight assumed to apply to all patients rather than a distribution of weight, the second concerns the standardised mortality rates (SMRs) used in the model. The analyses provided by the EAG are indicative of the change in the ICER using alternative assumptions, definitive answers cannot be provided due to the inherent uncertainty in the parameter values, although the EAG notes that the company may be able to provide more accurate data on the distributions of weight.

3.3.1 Exploratory analyses exploring the number of vials required per patient

The EAG notes that the company has used a point estimate for the average weight of patients per age band, rather than assuming a distribution of weight. This can cause inaccuracy in costing estimates where the point estimate lies close to a threshold weight where an additional vial is required.

For example, assuming that 76% of the population is female and using a weight ratio of 0.84 the weight for patients assumed to be between 25 and 34 years is assumed to be 63.6kg with the threshold (including a 10% margin) for requiring a fourth vial is 62.9kg. The company's approach assumes that all patients require 4 vials, whereas it is likely that a significant proportion of patients will weigh under 62.9kg, particularly the females within the cohort who tend to be lighter than females. The lighter patients would be associated with a reduced cost of 25% (as 3 vials would be used rather than 4). As shown in Figure 3, the 0.84 ratio has many points close to, but above, the threshold, potentially overestimating costs for patients aged 25 years and over. Conversely, at a 90% weight ratio, the costs may be underestimated for those aged 16 to 24 years. Inaccuracy in younger ages will be more influential due to the impacts of discounting.

When assuming that 50% of the population are female (as in Figure 4) the inaccuracy on costs appears smaller, mainly focussed on the 16- to 24-year-old group, with a potential underestimate of costs in the 0.84 weight ratio and a potential underestimate of costs in the 0.90 weight ratio.

Figure 3: Comparison of point estimate of weights and the thresholds for different number of vials of pegzilarginase assuming 76% of the population is female

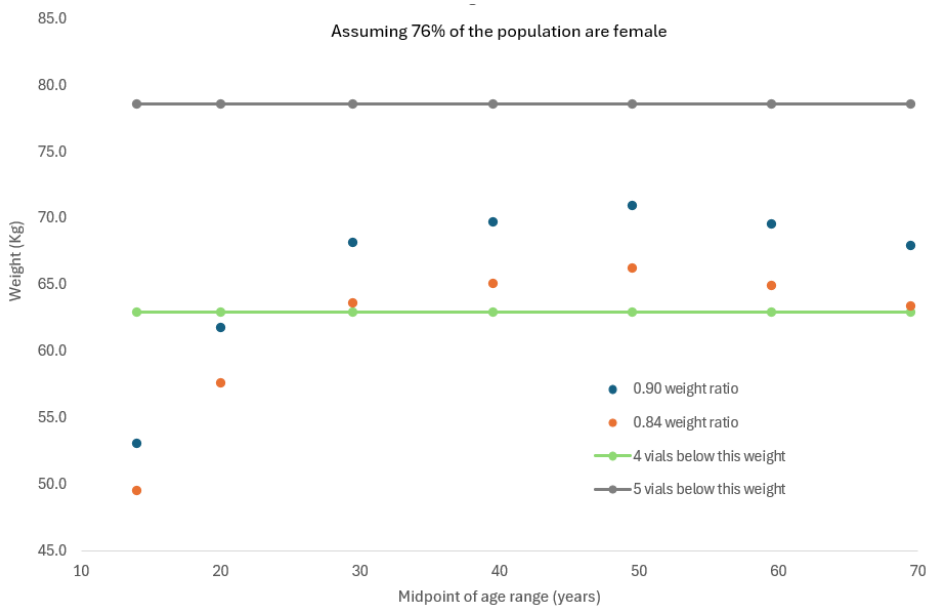
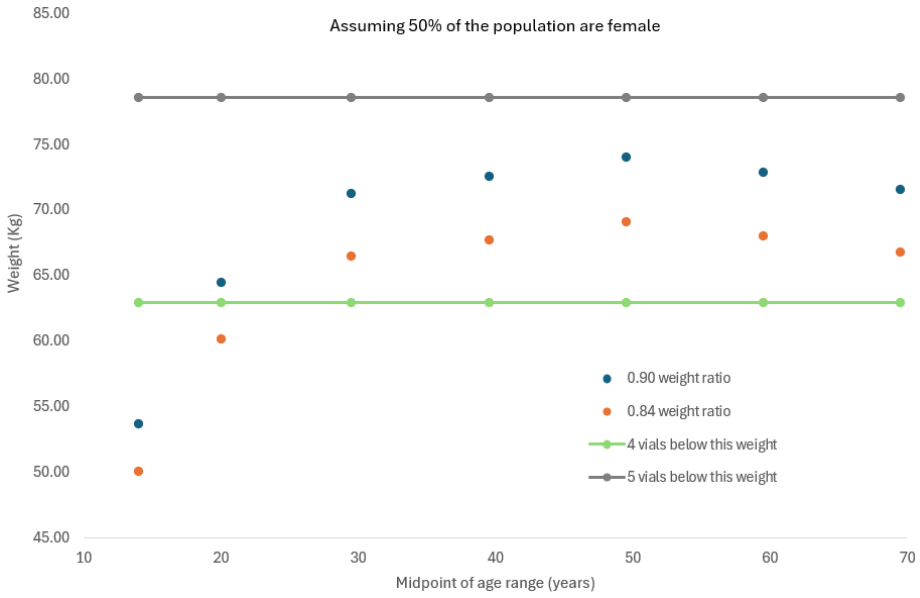


Figure 4: Comparison of point estimate of weights and the thresholds for different number of vials of pegzilarginase assuming 50% of the population is female



Ideally, the company would have used distributions of weight to accurately calculate the number of vials, although these distributions are likely to be sensitive to the proportion of patients that are male which given the small number of patients with ARG-1D could fluctuate considerably.

The EAG has explored modest changes in the costs of treatment with arbitrary values for chosen scenarios. For the company's base case, which assumes 76% female and a weight ratio of 0.84, a 5% reduction in cost has been assumed. For the committee's base case, which assumes 50% female and a weight ratio of 0.90, a 5% reduction in cost has also been assumed. For the EAG base case, which assumes 76% female and a weight ratio of 0.90, a 5% increase in cost has been assumed.

Table 3 provides the ICERs from the EAG's exploratory analyses. These results exhibit a lack of face validity between the Committee's preferred scenario and the EAG's most plausible scenario 1, as the EAG's ICER, should be lower than the Committee's ICER, as the only difference is in the proportion of female patients. This indicates that assuming changes of -5% (Committee) and +55 (EAG) are not correct. Despite the face validity error, the results have been maintained to provide the Committee with some indication of how variability in weight can affect the ICER. Detailed distributions of the number of vials used at each age range is required to provide accurate answers.

Table 3: Probabilistic ICERs from selected scenarios when the estimated acquisition costs are amended

	Proportion with improved diet	Weight Ratio	Female Proportion	QALY weighting	Assumed change in total costs	Probabilistic ICER (£)
Committee's preferred scenario	0.485	0.90	0.50	Half	-5%	162,629
Committee's preferred scenario (at full QALY weighting)	0.485	0.90	0.50	Full	-5%	110,898
Company's preferred scenario	0.833	0.84	0.76	Full	-5%	97,672
EAG's most plausible scenario 1	0.485	0.90	0.76	Half	+5%	167,523
EAG's most plausible scenario 2	0.485	0.90	0.76	Full	+5%	113,080

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

3.3.2 Exploratory analyses using alternative SMRs for patients receiving pegzilarginase

In its original company submission[6] the company assumed that SMRs related to metachromatic leukodystrophy[8] (adjusted for reduced toxicity) would be generalisable for patients with ARG1-D. However, in the most recent submission it was assumed that SMR in the more severe Gross Motor Function Classification System (GMFCS) health states were greatly increased (these data were marked as commercial in confidence). This had the impact of making those patients receiving pegzilarginase in the more debilitating and more expensive health states progress to death more quickly, which favoured pegzilarginase-treatment. Following discussions with the NICE technical team the EAG has run an exploratory analysis where the SMR for those receiving pegzilarginase was set to that in the company's initial submission. The relevant SMRs are shown in Table 4. The EAG notes that the SMRs for individualised disease management (IDM) were calibrated by the company and marked as commercial-in-confidence.

Table 4: The SMRs applied in different analyses

Health State	SMR (revised company base case)		SMR (EAG exploratory analyses)	
	IDM	Peg	IDM	Peg
GMFCS-I	[redacted]	[redacted]	[redacted]	1.16
GMFCS-II	[redacted]	[redacted]	[redacted]	1.32
GMFCS-III	[redacted]	[redacted]	[redacted]	1.80
GMFCS-IV	[redacted]	[redacted]	[redacted]	1.80
GMFCS-V	[redacted]	[redacted]	[redacted]	8.14

EAG: External Assessment Group; GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; Peg: pegzilarginase; SMR: standardised mortality ratio.

The results for selected scenarios when using the SMRs for the exploratory analyses (see Table 4) are provided in Table 5.

Table 5: Probabilistic ICERs from selected scenarios when the exploratory SMRs for pegzilarginase are used

	Proportion with improved diet	Weight Ratio	Female Proportion	QALY weighting	Probabilistic ICER (£)
Committee's preferred scenario	0.485	0.90	0.50	Half	189,892
Committee's preferred scenario (at full QALY weighting)	0.485	0.90	0.50	Full	123,013
Company's preferred scenario	0.833	0.84	0.76	Full	113,110
EAG's most plausible scenario 1	0.485	0.90	0.76	Half	178,765
EAG's most plausible scenario 2	0.485	0.90	0.76	Full	121,293

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

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