Single Technology Appraisal

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Contents:

The following documents are made available to stakeholders:

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 **Comments on the Draft Guidance from Immedica**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

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 **Consultee and commentator comments on the Draft Guidance** from: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

3. **Comments on the Draft Guidance from experts:**
   a. Zafar Aslam – Patient Expert, nominated by Metabolic Support UK
   b. Dr Arunabha Ghosh and Dr Reena Sharma – Clinical Experts, nominated by Metabolic Support UK

   Comments on the Draft Guidance received through the NICE website no comments received

4. **External Assessment Group critique of company comments on the Draft Guidance**

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **14 March 2025**.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 AB
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Immedica Pharma AB has no past or current links to, or funding from, the tobacco industry.
Name of commentator person completing form:	[redacted]

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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	**Company commitment to providing access to patients** 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 information to NICE and other relevant stakeholders, and urge 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 as quickly as possible. This will enable patients in England and Wales to have access to treatment like other patients across Europe, since pegzilarginase is now reimbursed in Germany, Italy and Spain. To address the uncertainties highlighted in the draft guidance, the Company has undertaken further analyses of trial data and conducted a Delphi panel, which included eight healthcare professionals, who cover 6/8 centres caring for [redacted] patients with ARG1-D in England and Wales.[1] Topics explored in the Delphi panel included mortality and disease trajectory of patients with ARG1-D on individual disease management (IDM), patient characteristics of patients with ARG1-D within the National Health Service (NHS), pegzilarginase dosing and patient weight, resource use and costs associated with ARG1-D, the quality of life (QoL) impact on caregivers of ARG1-D patients, and treatment discontinuation. Consensus was achieved for 35/38 statements (92%), with only three statements remaining unresolved. See the Delphi report for more details.[1] Specifically, the Company have addressed the key uncertainties (outlined in Section 1 of the draft guidance) by: • Verifying that, amongst those who would initiate treatment with pegzilarginase if it is available, the number of people grouped by disease severity is similar to that from the clinical trials and burden of illness (BOI) study pooled. • Identifying how age is correlated to Gross Motor Function Classification System (GMFCS) health state, informing revised transition probabilities for patients treated with IDM.

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	• Analysis of patient weight by time on treatment for those treated with pegzilarginase over time to address uncertainty in how pegzilarginase affects body weight. • Analysis of patient-level discontinuation data from the clinical trials to address uncertainty in how long people stay on pegzilarginase treatment. The Delphi panel further supported the following changes to the economic model base case to ensure it is better aligned with clinical practice in the United Kingdom (UK), namely: • Updated standardised mortality rates for IDM to better reflect the natural history of ARG1-D (mortality discussed in draft guidance 3.9). • Inclusion of 5% of patients treated with IDM per year who transition into GMFCS V from GMFCS II and GMFCS III due to severe hyperammonaemic crisis (HACs) (transition probabilities for IDM discussed in draft guidance 3.8). • Implemented a higher disutility for caregivers of more than one child with ARG1-D to better reflect the carer burden of ARG1-D (carer disutility discussed in draft guidance 3.14). • Validated the applied parametric extrapolation of trial data for time on treatment (discontinuation discussed in draft guidance 3.16). • Inclusion of end-of-life (EoL) costs to reflect the resource use and costs that occur at the end of a patient's life (costs discussed in draft guidance 3.15). • Implemented lower dietary management costs for patients receiving pegzilarginase to better reflect the reduction in need for these patients (costs discussed in draft guidance 3.15). Following further analyses of data, the Company have also made the following changes to the economic model to better align the base case with UK practice, namely: • Application of utility gain from diet liberalisation to a greater proportion of patients treated with pegzilarginase (from 24.7% to 83.3%; utility gain associated with improved diet discussed in draft guidance 3.12).

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	• Modelled cognitive progression independently to motor function deterioration and updated utility values to reflect this (disutility associated with cognitive disability discussed in draft guidance 3.13). • Application of a lower dose (0.14 mg/kg) during the long-term extension (LTE) period, based on the mean final dose across PEACE[2] and study 102A[3], supported by real-world evidence (RWE) (pegzilarginase dosing and drug wastage discussed in draft guidance 3.15).[4] • Application of compliance to pegzilarginase treatment costs using PEACE clinical trial data (costs discussed in draft guidance 3.15).[2,5] The Company have also provided the following scenario analyses: • Incremental cost-effectiveness ratio (ICER) weighted by age and severity (in line with the request listed in draft guidance 3.5). • IDM survival set so that 90% are dead by age 32 (in line with findings from the Delphi panel and the request for further analyses around standardised mortality rates listed in draft guidance 3.9). • Explore alternative parametric curves for time to treatment discontinuation of pegzilarginase patients (in line with the request listed in draft guidance Section 1). • Pegzilarginase standardised mortality rates set to 1/10 of IDM standardised mortality rates (in line with the request for further analyses around standardised mortality rates listed in draft guidance 3.9). • Set pegzilarginase survival to align with the original base case model (in line with the request for further analyses around standardised mortality rates listed in draft guidance 3.9). • Apply the utility gain from diet liberalisation to 100% of pegzilarginase treated patients (utility gain associated with improved diet discussed in draft guidance 3.12). • Assume no improvement in cognition for patients treated with pegzilarginase (modelling of cognitive ability discussed in draft guidance 3.5).

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	• Set baseline cognitive distributions so that more patients start in less severe cognitive states (modelling of cognitive ability discussed in draft guidance 3.5). • Application of an upper bound on patient utility (utility values discussed in draft guidance 3.11). • Application of Van Hout algorithm to cognitive utilities (disutility associated with cognitive disability discussed in draft guidance 3.13). • Reduce caregiver disutility for pegzilarginase treated patients in GMFCS I and II (carer disutility discussed in draft guidance 3.14). • Application of a 90/95% weight cap to adult and paediatric patients, respectively (pegzilarginase dosing discussed in draft guidance 3.15). • Set weight according to age at baseline for each GMFCS health state (pegzilarginase dosing discussed in draft guidance 3.15). • Exclusion of caregiver disutilities from quality-adjusted life years (QALYs; in line with the request in QALY weighing draft guidance 3.17). • Inclusion of disease progression costs (costs discussed in draft guidance 3.15). With the provision of the Delphi panel findings, additional evidence incorporated into the model, and scenario analyses, uncertainty in the benefits of pegzilarginase have been reduced. The Company conclude that a QALY weighting should be applied to ensure this medication can be made available to patients with ARG1-D in the UK. There is currently no available disease-modifying treatment for these patients. Current management focuses on dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers. In most, if not all cases, current management does not successfully normalise arginine levels and has a major impact on patients' lives.[6] ARG1-D is an inherited, progressive, and debilitating disease, leading to gradual loss of developmental milestones and spasticity, progressive neurological and motor deterioration, cognitive delays and

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	seizures. ARG1-D significantly impacts QoL for both patients and caregivers. With a lack of treatment options, there is substantial unmet need. Indeed, the Company welcomes the Committee's conclusion that ARG1-D is a debilitating condition associated with multiple comorbidities, poor survival, and a substantial impact on QoL for patients and carers. Furthermore, the Committee also concluded that there is an unmet need for a disease-modifying treatment for ARG1-D and that pegzilarginase can potentially fulfil this unmet need. With the updated economic model, pegzilarginase has an ICER of £88,595 relative to IDM (see Table 1 of accompanying Appendix). This demonstrates that pegzilarginase is a cost-effective treatment option for patients with ARG1-D. Moreover, the Company would like to reiterate that pegzilarginase offers hope to many ARG1-D patients and their families. Indeed, all clinical experts involved in the Delphi panel support the reimbursement of pegzilarginase for the NHS.
2	**Company's modelling approach for IDM (draft guidance 3.5)** During the Committee meeting, it was concluded that the current modelling approach does not reflect age at each GMFCS health state in clinical practice. To address this, the Company gained consensus on the average ages within each GMFCS health state from responses collated from key opinion leaders (KOLs) during a Delphi panel:[1] • GMFCS I: 11 years • GMFCS II: 12 years • GMFCS III: 16 years • GMFCS IV: 25 years KOLs confirmed that, amongst GMFCS health states I through IV, there is a trend of increasing age with increased disease severity. However, they noted that 5 to 10% of patients per year can transition into GMFCS V from GMFCS II and GMFCS III due to severe HACs, resulting in a permanent and substantial decline in their health. This results in patients having an average age of 15 in GMFCS V. Further to this, to reflect the prevalent NHS cohort and in line with the Committee request noted in the draft guidance, a scenario analysis has been provided where the ICER is weighted by the proportion of patients starting in each GMFCS health state, and where mean age at baseline is specified for each health state. Incremental costs and QALYs have been calculated to evaluate the cost-effectiveness of pegzilarginase when initiated in each GMFCS health state separately.

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	The scenario ICER is then calculated by weighting the incremental costs and QALYs by the distribution of patients eligible to start treatment with pegzilarginase within each GMFCS health state. Table 2 of the accompanying Appendix presents the weighted ICER by age and severity. Building on feedback from clinical experts provided in the draft guidance, if diagnosis (via metabolic or newborn screening) of ARG1-D were to improve, an even larger proportion of the population would be in less severe GMFCS health states (i.e., GMFCS I and II), given that patients will be identified prior to clinical presentation. In addition, newborn genetic screening is likely to become more routine within the NHS, with an estimated 100,000 newborns to be screened in England under the Generation Study (which includes screening for ARG1-D).[7] Therefore, the Company would like to emphasise the benefit of pegzilarginase for future patients, who are expected to initiate treatment at an earlier stage of disease.
3	**Starting distributions by GMFCS health states (draft guidance 3.6)** The Company does not agree with the Committee's conclusion that the starting distributions from the European BOI survey[8] is more representative of clinical practice in the NHS in England than the Company's approach (using pooled data from PEACE, Study 101A/Study 102A and European BOI). To reduce uncertainty around the current population with ARG1-D in the NHS in England, KOLs were asked whether the baseline distribution of people in GMFCS health states reflects the distribution of patients who would be initiated on pegzilarginase treatment in UK clinical practice. There was consensus amongst the KOLs that the pooled data from PEACE, Study 101A/Study 102A and European BOI survey reflects the distribution of patients with ARG1-D that would be initiated on pegzilarginase treatment in UK clinical practice.[1] Therefore, the baseline health state distribution is reflective of UK clinical practice in the Company's base case. Updating the starting distributions in line with the Committee's preferred assumption (informed by the European BOI survey[8]) increases the ICER by £567. The Company notes the feedback from clinical experts provided in the draft guidance that most people in the more severe GMFCS IV and GMFCS V health states are likely to be adults. However, as outlined in Section 2, feedback from KOLs during the Delphi panel highlighted that 5 to 10% of patients can enter GMFCS V from GMFCS II and GMFCS III due to severe HAC. Therefore, the assumption that

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	patients progress through all of the GMFCS health states linearly does not hold true. Furthermore, based on this movement to GMFCS V (discussed in more detail in Section 4), KOLs agreed that the average age in GMFCS V is 15 years, which is lower than GMFCS III (16 years) and GMFCS IV (25 years). Evidence from published literature also supports that there is variability in disease severity across ages.[9] The Company would like to clarify that whilst approximately 50% of patients with ARG1-D are adults in England, this does not directly correlate to a higher proportion of adult patients being in the most severe health state.
4	**Transition probabilities for standard care arm (draft guidance 3.8)** In the draft guidance, it is reported that the Committee considered the External Assessment Groups base case approach to modelling transition probabilities for IDM more reflective of clinical expert estimates of the time taken to progress to more severe GMFCS health states than the Company's estimates. The Committee concluded the following assumptions were appropriate for decision making: • The mean PEACE, Study 101A/Study 102A used as the starting Gross Motor Function Measure-88, Part D (GMFM-D) and Gross Motor Function Measure-88, Part E (GMFM-E) score for people in the GMFCS I health state. • Reduction in GMFM-DE score of 2.66 per year. • Inverse of time spent in GMFCS health state converted to a probability. To address uncertainty in the transition probabilities for IDM, the Company gathered insights from KOLs in a Delphi panel,[1] in which consensus was reached that: • The average age at diagnosis is 5.1 years. • The average age within each health state is 11 for GMFCS I, 12 for GMFCS II, 16 for GMFCS III, 25 for GMFCS IV and 15 for GMFCS V (see Section 2). • 5-10% of patients transition from GMFCS II or GMFCS III to GMFCS V per year. • The age at which 90% of patients would be dead (excluding death due to HAC) is 32 years.

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	Given the consensus gained on trajectory of disease for patients treated with IDM from KOLs during the Delphi, the approach to modelling disease progression has been revised. Firstly, as described in Section 2, the non-linear progression of patients from GMFCS II and GMFCS III to GMFCS V per year is captured independently from the progression through the sequential health states in the model. KOLs gained consensus that 5-10% of patients progress from GMFCS II or GMFCS III to GMFCS V per year, based on clinical observations that patients may experience early disease progression from severe HACs in early childhood. Therefore, it has been conservatively assumed that 5% of patients will transition to GMFCS V from GMFCS II or III per year. For patients treated with IDM, this 5% annual progression directly to GMFCS V does not exceed the model's annual HAC event probability of 28.66%. Therefore, the Company considers it clinically plausible that approximately a sixth of patients experiencing a HAC would also experience early progression as a consequence of the event. Secondly, for the linear trajectory of GMFCS I-IV, the change in GMFM-DE score was updated to a reduction of 3.17 per year (which assumes patients will move from the maximum GMFM-DE score [111] to the minimum [0] over 35 years). This results in the relationship between age and GMFM-DE score being revised to: $$GMFM\text{-}DE = 111 - age \times 3.17$$ Then, the GMFM-DE thresholds for each GMFCS health states I-IV were redefined to ensure that the average age in each state reflected the consensus gained in the Delphi, resulting in an updated estimate of the time spent in each health state. As the upper and lower bounds of GMFM-DE score are derived to ensure that the average age occurs halfway through the time spent in each GMFCS health state, the thresholds for the upper and lower bounds will change if the average age within the GMFCS health state is altered. Additionally, as the average age in GMFCS IV is higher than the average age in GMFCS V, the lower bound of GMFM-DE for GMFCS IV was conservatively derived to reflect that the 32 is the average age of patients who have progressed from GMFCS IV. This aligns with the consensus from clinicians that 90% of patients will be dead by age 32. Since clinicians noted during the Delphi panel that patients are likely to remain in GMFCS IV for an extended period, the Company considers the assumption, that patients progressing from GMFCS IV have an average age of 32 years, to be clinically plausible.

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	Together, these changes ensure that the modelled disease trajectory of standard care is in line with the trajectory of disease described by clinicians. The changes to the calculation of disease progression resulted in the following characteristics being modelled for IDM: • GMFCS I: upper bound GMFM-DE, 78; lower bound GMFM-DE, 75; average age within state: 11. To note, the upper bound for this health state is derived based on the average age in GMFCS I. If the average age in GMFCS I is lowered, the upper bound will increase up to a maximum of 111 reflecting a longer duration spent in GMFCS I before patients progress to GMFCS II. • GMFCS II: upper bound GMFM-DE, 75; lower bound GMFM-DE, 67; average age within state: 12 • GMFCS III: upper bound GMFM-DE, 67; lower bound GMFM-DE, 46; average age within state: 16 • GMFCS IV: upper bound GMFM-DE, 46; lower bound GMFM-DE, 21; average age within state: 25 Given the lack of published data on the disease trajectory for patients treated with IDM, this is the most appropriate approach to characterise disease trajectory.
5	**Mortality (draft guidance 3.9)** ARG1-D is associated with high morbidity and early mortality.[10,11] The Committee noted the lack of survival data from the clinical trials used to inform mortality in the economic model, questioning the Company's approach of using standardised mortality rates to model mortality. In the base case, the Company used the standardised mortality rates from metachromatic leukodystrophy and applied a multiplier to the pegzilarginase arm to estimate a standardised mortality rate for the IDM arm that was 800 times greater than that of the pegzilarginase arm. This resulted in 0.0008% of people alive at age 35 in the IDM arm. To address concerns from the Committee regarding standardised mortality rates for IDM, the Company have gathered insights from KOLs in a Delphi panel.[1] During the Delphi panel, consensus was reached on the following topics: • The average age at diagnosis is 5.1 years.

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	• The proportion of patients managed with IDM that die within each GMFCS health state (excluding death due to HAC) is 5.3% in GMFCS I, 6.1% in GMFCS II, 13.9% in GMFCS III, 32.3% in GMFCS IV and 42.3% in GMFCS V. • The age at which 90% of patients would be dead (excluding death due to HAC) is 32 years in the IDM arm. One KOL treating adult patients stated that their eldest patient is age 35, however, the majority do not live beyond mid-30s, a point the other KOLs concurred with. Despite this, clinical advice to the EAG suggested that it was unlikely that nearly all people would die by age 35. One clinical expert highlighted that some people would be expected to live beyond age 35 with current standard care, even without pegzilarginase. The Committee concluded that the scenario analysis in which nearly all people in the standard care arm die at age 50 is appropriate. Therefore, in the updated base case, the Company have taken a hybrid approach, whereby the standardised mortality rates for IDM have been revised to align with the proportion of patients dying from each health state (as described by KOLs) and the Committee's preferred assumption for age by which nearly all patients would be dead (excluding death due to HAC). This was implemented via a Visual Basic for Applications (VBA) function to ensure the data utilised in the model reflects the whole trajectory of disease. • In the first step, the distribution is set to 100% in GMFCS I and the age at baseline is set to 5.1 years, capturing the beginning of disease observed. The average age in GMFCS I is also set to 5.1 years, to ensure that the average time spent in GMFCS I from diagnosis is captured. • An overall standardised mortality rate for IDM is then identified via goal-seek to ensure that by age 50, 99% of patients are dead (excluding death due to HAC), in line with the Committee's conclusion that the scenario analysis in which nearly all people in the standard care arm die at age 50 is appropriate. • Then, multipliers for each health state to the overall standardised mortality rate were identified via goal-seek to ensure that the proportion of all deaths (except HAC) from each GMFCS health state aligned to the feedback collected in the Delphi panel.

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	• The outputs of the calibration are then stored on the Settings page to verify fit of data to the data reported in the Delphi. The proportion of patients dying from each health state (excluding death due to HAC) in the model closely matches the reported Delphi data, differing by no more than 0.6%. • The model is then returned to its baseline settings. The resulting standardised mortality rates applied in the model are 67, 84, 193, 1,414 and 118 for GMFCS I through to GMFCS V, respectively (see Appendix Table 3). The use of these standardised mortality rates in the base case settings is appropriate as they are applied constant in time and are calculated according to the whole disease trajectory of patients with ARG1-D. To note, these standardised mortality rates exclude death due to HACs. Additionally, the Committee requested further scenario analyses around standardised mortality rates in the model. As outlined above, KOL feedback indicates that the majority of patients with ARG1-D do not live beyond mid-30s. Therefore, the Company have provided a scenario whereby 90% of patients treated with IDM are dead by age 32, as described by KOLs during the Delphi panel. The standardised mortality rates used for this analysis were calculated using a method aligned to the base case, see Appendix Table 3. The results of this scenario are presented in Table 20 of the Appendix. It should be acknowledged that, if the pegzilarginase standardised mortality rates remain unadjusted from the Company's original base case, patients treated with pegzilarginase show significantly improved overall survival due to updated time on treatment assumptions (See Section 11; implemented in line with feedback from the Delphi panel that no patients would discontinue treatment after one year of initiating pegzilarginase) compared to the Company's original base. Therefore, in the updated base case, the Company have conservatively set the pegzilarginase SMRs in GMFCS III-V to half that of those treated with IDM in the same GMFCS state. This reflects that patients treated with pegzilarginase in latter GMFCS states would have improved survival, but prevents survival returning to near general population norms. As noted by clinicians in the Delphi panel, patients treated with pegzilarginase in GMFCS I and II are likely to reach full or near-full health, therefore the Company considers it appropriate to maintain an SMR of 1.16 in GMFCS I and 1.32 in GMFCS II as in the Company's original base case.

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	The Company acknowledge that the survival of patients treated with pegzilarginase was not validated during the Delphi panel. Therefore, to explore the impact of pegzilarginase survival on cost-effectiveness, the Company have conducted the following scenario analyses, which are presented in the Appendix:
	• Choice of the parametric curve for time to treatment discontinuation of pegzilarginase patients.
	  o The base case choice of parametric curve is Gompertz, which reflects minimal discontinuation in the long-term (see Appendix Figure 6).
	  o The alternative choices for parametric curve have increased rates of discontinuation in the long-term. This affects the proportion of patients who transition back to IDM and resume the natural progression of the disease, which has increased mortality compared to treatment with pegzilarginase.
	• Aligning pegzilarginase survival with the survival estimates in the Company's original base case.
	  o The Committee concluded the pegzilarginase standardised mortality rates may be appropriate.
	  o Therefore, a multiplier to the pegzilarginase standardised mortality rates was calculated to ensure that life years gained in the new base case match the life years gained in the previous Company base case.
	• Assuming pegzilarginase standardised mortality rates are 1/10 of the updated IDM standardised mortality rates (see Appendix Table 4).
	  o The Company's previous base case assumed proportionality in the risk of death within each GMFCS health state for patients treated with pegzilarginase compared to IDM.
	  o In the updated base case, this proportionality is lost to match the projected rates of death from each GMFCS health state.
	The Company believe that the updated standardised mortality rates for IDM accurately capture the life expectancy of patients with ARG1-D. Moreover, there is a lack of evidence to inform standardised mortality rates for patients treated with pegzilarginase; however, the

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	Company have taken a conservative approach to align the survival of pegzilarginase treated patients more closely with the Company's original base case. The results of the scenarios described above are provided in Table 20 of the Appendix and indicate that pegzilarginase is a cost-effectiveness treatment option in every case.
6	**Distribution of peak ammonia levels during hyperammonaemic crisis (draft guidance 3.10)** The EAG highlighted that there is *considerable* uncertainty around the peak ammonia levels during a HAC when treated with pegzilarginase. In the Company's base case model, peak ammonia levels during a HAC were informed by four data points which implies that peak ammonia levels greater than 500-1000 µmol/L would unlikely happen for people on pegzilarginase treatment. The clinical experts highlighted that pegzilarginase reduces the severity of HACs and that HACs do not occur in people whose condition is controlled on pegzilarginase. The Committee considered that it is likely that a few instances of high levels of peak ammonia may still occur with pegzilarginase but the values in the EAG's scenario were potentially too high. Given the lack of additional data to inform peak ammonia during a HAC when treated with pegzilarginase, and to address the Committee's concerns, the distribution of high levels of peak ammonia in the pegzilarginase arm has been adjusted in the updated base case to reflect values that fall between the Company's original base case and the EAG's scenario analysis. These values are provided in Table 5 of the accompanying Appendix.
7	**Utility gain with improved diet for pegzilarginase patients (draft guidance 3.12)** PEACE data indicated that by Week 24, 42.9% of pegzilarginase treated patients were able to increase their total protein consumption by more than 15%, compared to 18.2% of placebo treated patients.[2] This was despite the fact that the protocol for diet liberalisation during PEACE was extremely strict, with sites instructed to minimise dietary protein prescription changes. Furthermore, RWE data from France has indicated that 83.3% of pegzilarginase treated patients were able to increase their average daily amount of natural protein with a mean of +3.8 g/day (+20.6%) at 6 months (n=12), and +8.9 g/day (+44.9%) at 12 months (n=3).[4] The model incorporates a utility gain of 0.04, which is assumed to be half the decrement of a fully restricted diet, based on HST13 data. The

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	RWE data demonstrating that 83.3% of pegzilarginase patients had increased natural protein intake suggests that this utility gain (0.04) should be applied to 83.3% of pegzilarginase patients rather than only 24.7% of patients. Indeed, the Delphi panel supported this rationale as it was suggested that pegzilarginase allows for diet liberalisation amongst the vast majority of patients. The liberalisation of severe protein-restricted diets in patients would remove a large psychosocial burden to patients thus improving the health-related quality of life (HRQoL). Therefore, the Company deem it appropriate to apply the utility gain from improved diet to 83.3% of pegzilarginase patients, based on French RWE. Given that feedback from KOLs during the Delphi panel suggested that pegzilarginase allows for diet liberalisation among the vast majority of patients, the Company have provided a scenario applying this utility gain to 100% of patients treated with pegzilarginase. The results of this scenario are presented in Table 20 of the Appendix and indicate that the Company's base case of applying this utility gain to 83.3% of pegzilarginase treated patients is conservative.
8	**Cognition (draft guidance 3.13)** ARG1-D is associated with developmental delay as the earliest clinical manifestation, with affected children typically experiencing slowed linear growth, cognitive decline, and developmental regression between 1-3 years of age, which persists if left untreated. Currently, the model assumes that the rate of cognitive deterioration is associated with GMFCS health state, with more severe GMFCS health states containing more patients with severe cognitive impacts. Although cognitive decline is correlated with disease severity, it does not capture the cognitive decline that can occur independent of disease progression in patients treated with IDM. Moreover, it does not capture that progression of cognition decline is halted or reversed in patients treated with pegzilarginase. Indeed, in the draft guidance it is acknowledged that the improvement in cognitive ability with pegzilarginase was plausible. Regression analyses from the European BOI study indicated that with time, cognitive score declines with IDM, as presented in Figure 1 of the accompanying Appendix. Additionally, clinical advice to the Committee suggested that improvement in cognitive ability is plausible with pegzilarginase, and experts also raised that improvement in attention span, school results and communication has been demonstrated with pegzilarginase. Therefore, the Company deem it appropriate to model cognitive progression for ARG1-D patients independently to motor deterioration.

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	To implement cognitive deterioration independently of motor deterioration in the model, transition probabilities for IDM were generated from the regression analysis of the BOI data (see Table 6 in the Appendix) and converted to per-cycle transition probabilities. Based on clinical advice to the Committee raised in the draft guidance, in the updated base case, it was assumed that pegzilarginase treatment is associated with a nominal 2% improvement from mild to no cognitive impairment and 1% from moderate/severe to mild, continuing until 36 months, consistent with the timeframe for GMFCS improvement in the model (see Appendix Table 7). A scenario analysis is provided whereby no improvement in cognition is assumed for pegzilarginase treated patients. The baseline cognitive distributions across all GMFCS health states are shown in Table 8 of the Appendix. Based on findings from the BOI, these distributions are based on the assumption that as GMFCS health state worsens, cognitive impairment worsens.[12] Due to the varying mortality rates across GMFCS health states and the assumed distribution of cognitive impacts at baseline, cognitive impact must be modelled independently of GMFCS health states as patients in more severe health states have a higher risk of death. Therefore, it is assumed that during GMFCS transitions, patients stay within their cognitive health state (none, mild, or moderate/severe), and vice versa. The data from the BOI study categorised cognitive impacts as none, mild, or moderate/severe, which varies from the categorisation in the original submission (none/mild, moderate, or severe).[12,13] Therefore, the reference case for cognitive impact is updated from the previous base case, in which the reference patients have no cognitive impacts rather than no or mild cognitive impact in the previous base case. This would mean that the reference patients have a higher utility in the new base case compared to the previous. As such, the utility values in the economic model were updated to represent the different categorisation of cognitive impairment.[8] There is utility data available from the BOI which categorises health state utility values according to GMFCS state and cognitive impairment. However, the data are insufficient for use in the model as not all states are reported and there are inconsistencies in the trends for cognitive and functional decline. However, data from the BOI is available to inform the overall health state utility values for patients with no, mild, and moderate/severe cognitive impairment, which can then be used to

	inform the gains in utility according to reduced levels of cognitive impairment (see Appendix Table 9). To that end, the utility values for patients with moderate/severe cognitive impairment within each GMFCS health state were assumed to be the average of the utility values used for the moderate and severe groups in the original Company submission. To calculate the utility values in the no and mild cognitive impairment categories, the utility gain from improved cognitive function as reported from the BOI was applied to the moderate/severe utilities. The final utility values are presented in Table 10 of the Appendix; subsequent disutility values for all GMFCS health states for mild and moderate/severe cognitive impairment are -0.271 and -0.526, respectively. To note, the health state utility value for GMFCS I with normal cognitive function is 0.966 (see Appendix Table 10). The Company believe it is clinically plausible for a patient with no cognitive impairment and minor physical disability to rate their QoL higher than the general population, given that there were patients in the BOI study reporting perfect health for worse states. As a scenario, the Company have implemented an upper bound of 0.94 on patient utility, in line with Szende et al. (2014), see Appendix Table 11.[14] The base case utility values were derived from BOI data using the Hernández et al. (2023) mapping function (see Appendix Table 12), in line with the NICE reference case.[15] A scenario is presented using BOI utilities derived from the outdated Van Hout mapping method (see Appendix Table 13).[16] An additional scenario analysis is provided whereby no improvement in cognition is assumed for pegzilarginase patients, although this does not align with conclusions in the draft guidance and clinical expert opinion. Moreover, since there is variance in symptom severity among patients,[12] a scenario has been included whereby baseline cognitive distribution allows a higher proportion of patients to begin in less severe cognitive states (see Appendix Table 14). The results of the four scenarios are presented in Table 20 of the Appendix. Whilst only the scenario in which the baseline cognitive distribution is altered shows greater cost-effectiveness for pegzilarginase, the Company would like to emphasise that the current approach of assuming an improvement in cognition for pegzilarginase treated patients, applying a health state utility value of 0.966 for GMFCS I with normal cognitive function, and using the Hernández

	tariff to derive utility values from the BOI data are appropriate, based on the reasons stated above. Of note, a minor error was identified in the trace for pegzilarginase and IDM in the application of cognitive disutilities. This has also been corrected in the revised economic model. Modelling cognitive progression independently to motor deterioration and updating the utility values accordingly provides a more realistic depiction of cognitive progression, and a more accurate estimate of the cost-effectiveness of pegzilarginase compared to IDM.
9	**Carer disutility (draft guidance 3.14)** The model currently does not account for the HRQoL decrement to caregivers who care for more than one child with ARG1-D. The European BOI study indicated that there is a greater disutility to caregivers who care for more than one ARG1-D patient compared to those caring for one patient only.[8] Given that ARG1-D is an inherited disease, families with one ARG1-D patient often have a family member with ARG1-D too. In the draft guidance, it was acknowledged that there is uncertainty in the caregiver disutility values. Therefore, the Delphi aimed to address this uncertainty, explore whether an additional disutility to caregivers of two or more children with ARG1-D can be applied in the model, and understand what proportion of children with ARG1-D have a sibling with ARG1-D in the UK. KOLs identified that 63% of children with ARG1-D in the UK have a sibling with ARG1-D.[1] This is representative of UK clinical practice as KOLs represent the majority of centres who manage ARG1-D patients in the UK. The European BOI study demonstrated that caregivers of only one child have a mean EQ-5D-5L utility of 0.843, whilst caregivers of two or more children have a utility of 0.674.[8] Therefore, the estimated disutility for caregivers of two or more children with ARG1-D compared to caregivers of one child only is -0.169 (see Appendix Table 15). During the Delphi panel, KOLs agreed that the additional HRQoL impact for caring for multiple children will be most significant for patients in GMFCS III onwards. Additionally, consensus was reached on the appropriate scaling factor and disutilities to apply to caregivers of more than one child according to the child's GMFCS health state. A disutility of -0.169 was applied for patients in GMFCS V and for the other health states the disutility was lower; these are presented in Table 16 of the Appendix.

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	In the updated base case, an additional disutility was applied to caregivers who care for two or more children with ARG1-D. As the model considers the costs and outcomes per patient treated with pegzilarginase, the additional disutility was applied to the proportion of patients with a sibling, since their caregiver will bear the additional burden of caring for more than one patient with ARG1-D. The Company would like to emphasise that this additional QoL burden for caregivers of two or more children is critical to incorporate into the model to accurately capture the full burden that caregivers of patients with ARG1-D face in the UK. Importantly, this additional disutility for caregivers of two or more children is only applied for one caregiver only until the patient reaches 16 years of age. Paediatric ARG1-D patients aged 16 years and below may require care from two caregivers, and as such the caregiver burden may remain underestimated. Further to the burden of caring for multiple patients with ARG1-D captured in the base case, a scenario has been explored where the burden of caring for patients with ARG1-D is reduced when patients are treated with pegzilarginase. From the BOI study, it is noted that caregiver burden may worsen from the knowledge that there is little a parent can do to alleviate their child's progression through the course of the disease. Pegzilarginase, as noted by clinicians in the Delphi panel, can return patients treated in GMFCS I and II to full or near-full health. Therefore, it is anticipated that the burden will be reduced to carers of patients within these health states. This reduction may be attributed to decreased caregiving demands, improved patient independence, and a lower need for ongoing medical or supportive care. For this reason, a scenario is included whereby the disutility to caregivers of patients receiving pegzilarginase is reduced by 50% in GMFCS I and II health states. The results of this scenario are presented in Table 20 of the Appendix and indicate that the Company's base case approach of assuming no reduction in caregiver disutility for pegzilarginase treated patients in GMFCS I and II health states is in fact conservative.
10	**Pegzilarginase dosing and drug wastage (draft guidance 3.15)** *Dose* In the original submission, the Company assumed an average pegzilarginase dose of 0.14 mg/kg per week for the first 24 weeks, increasing to 0.16 mg/kg afterwards based on PEACE data only. The mean dose of pegzilarginase at the end of Study 102A and PEACE was [redacted] mg/kg/week (range: [redacted] mg/kg/week) and [redacted]

	mg/kg/week (range [redacted] mg/kg/week), respectively. When pooled, this is a collective mean of 0.14 mg/kg. French RWE also demonstrates that the dose of pegzilarginase in clinical practice is lower than the average dose at Week 24 in the PEACE clinical trial, with an average pegzilarginase dose of 0.14 mg/kg/week at 6-month follow-up.[4] The RWE confirms that arginine levels were normalised in 92.9% of patients with an average pegzilarginase dose of 0.14 mg/kg/week. In the treatment naïve group, plasma arginine fell from 384.4 µmol/L at baseline to 121 µmol/L at 3 months (n=8) and to 136.9 at 6 months (n=8). In patients previously treated with pegzilarginase in PEACE, plasma arginine fell from 175.2 µmol/L at baseline to 110.8 µmol/L at 3 months (n=6) and to 69 µmol/L at 6 months (n=6). In both patient groups, the RWE suggests that lower doses of pegzilarginase (0.14 mg/kg/week) maintain reductions in plasma arginine at a steady level.[4] As demonstrated from RWE, the efficacy of pegzilarginase is maintained even at the pooled mean dose from Study 101A/Study 102A and PEACE and supports the argument that a lower dose of pegzilarginase would show the same effect in UK clinical practice. Therefore, the updated base case applies the pooled mean dose of 0.14 mg/kg/week (based on the mean final dose across PEACE and Study 101A/Study 102A) across the LTE period of the model. Additionally, the PEACE study protocol specifies that dose adjustments will generally be made if a subject's plasma arginine level—measured 168 hours after administration but before the next dose—falls outside the range of 50 to 150 µM.[2] Consequently, in clinical practice, where protocols may be less stringent than in the trial setting, dose modifications will likely occur when plasma arginine levels drop below 200 µM, the target level of arginine in ARG1-D.[17] Clinical advice to the Company highlighted it is likely that once initial doses of pegzilarginase have cleared the elevated plasma arginine, a reduced dose may be sufficient to maintain plasma arginine within normal levels.[18] *Compliance* The original Company submission did not include compliance. However, compliance is important to accurately capture pegzilarginase treatment costs in the model. Therefore, the Company have updated the model's base case to include compliance data from both the PEACE double-blind phase and LTE (see Table 17 in Appendix). Compliance data for Study 101A/Study 102A was insufficient and, as a result, was excluded from the calculation.

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	Drug wastage The Committee considered the level of drug wastage, including 10% weight margin, uncertain in the model. However, results from the Delphi panel suggest that the current assumption is conservative. Consensus was gained among KOLs that dose adjustments will be made to eliminate drug wastage with pegzilarginase in UK clinical practice.[1] Therefore, the Company believe the scenario tested by the EAG which removed the 10% margin and another assuming no drug wastage is inappropriate. Furthermore, clinical advice to the EAG stated that concerted efforts would be made to reduce drug wastage, including using an additional vial every 2 weeks should the optimal dose indicate using half a vial a week. The Company believe that the EAG scenarios do not align with how pegzilarginase will be used in UK clinical practice and that the Delphi panel, which concluded drug wastage would be eliminated, addresses the uncertainty raised by the Committee. Therefore, the current 10% weight margin assumption is conservative. *Patient weight* In the Company's previous base case, patients with ARG1-D are assumed to weigh less than an age- and sex-matched population. For patients under 16 years of age, the reduction was assumed to be 9%; for patients aged 16 years or over, the reduction was assumed to be 23%. The Committee have requested additional data (from trials and clinical expert opinion) on the impact of pegzilarginase treatment on patient weight. A post-hoc analysis of longitudinal PEACE trial data indicated that there is no trend for increasing weight compared to the general population over time in patients aged ≥13 years treated with pegzilarginase (see Appendix Figure 2); there was a trend suggesting reducing weight compared to the general population after an initial rise following treatment initiation. For patients who start treatment aged <13 years, their weight tends to slowly approach population norms (see Appendix Figure 3). Given that the average age at baseline in the model is 13 years, patients will not start treatment early enough to benefit from growth improvements. Therefore, in the updated base case, the Company have set the average weight ratio to the general population as 0.782 for all patients, which is the average weight ratio to the general population amongst patients aged ≥13 across all observations across time.

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	A scenario analysis is provided whereby patients starting treatment below the age of 13 years have an average weight ratio of 0.9139, which is the average weight ratio to the general population of patients <13 years (see Appendix Figure 3). The base case model assumes all patients enter the model at 13 years, thus this scenario has no impact on the base case ICER. However, the scenario impacts the ICER when it is weighted by age and severity (provided by the Company as an additional scenario). In this weighted ICER scenario, the average ages in GMFCS I and II are 11 and 12 years, respectively. Therefore, the average weight ratio of 0.9139 applies to patients who begin treatment in these health states as they are younger than 13 years old. The results of this scenario are presented in Table 20 of the Appendix and indicate an increase in the ICER of £12,982. The Company's assumptions are supported by the Delphi panel whereby KOLs gained consensus that the weight of the average patient treated with pegzilarginase and IDM would remain below 90% of population norms with continued treatment. The Company firmly believes that the NICE technical team's preferred scenario—assuming patients with ARG1-D would weigh 95% of the expected general population weight—is highly unrealistic. Untreated patients with ARG1-D are typically frail, often wheelchair-bound, and have difficulty with eating and gaining weight.[19] Data from the French RWE study reported that in treatment-naïve patients, the average daily intake of natural protein increased from [redacted] g protein/kg per day at baseline to [redacted] g protein/kg per day at 3 months (n=7) and [redacted] g protein/kg per day at 6 months (n=8) (see Appendix Figure 4 and 5 for treatment naïve patient weight and protein consumption per day). This increase in natural protein intake still remains below the recommended daily protein intake for adults (0.83 g protein/kg per day), confirming that the changes in diet are insufficient to allow such weight gain.[20] To further support the assumption in the Company's updated base case that the average weight ratio to the general population of all patients is 0.782, the Company have gathered insights from clinicians who treat adult patients with ARG1-D. One clinical expert stated that even with pegzilarginase treatment, patients are unlikely to gain significant weight from baseline.[18] Another clinician highlighted that the increased protein intake associated with pegzilarginase would not alter muscle mass, as patients are unable to exercise due to spasticity.[18] Furthermore, another clinical expert stated that in the long-term, the dose of pegzilarginase is unlikely to increase if arginine is well controlled. The expert highlighted a case study of one patient

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	who is slightly 'underdosed' based on actual weight and still has well controlled plasma arginine.[18] The Company would also like to emphasise that adults who begin treatment later in life would be unable to achieve population norm weight, as their growth would have already been stunted before treatment initiation. An additional scenario analysis has been included based on feedback from the Delphi panel, whereby a weight cap has been implemented to ensure that weight is not sampled above 95% and 90% for paediatric and adult patients, respectively. The results of this scenario are presented in Table 15 of the Appendix. To note, the results do not differ from the base case results; this weight cap only reduces the ICER when wastage is assumed.
11	**Pegzilarginase treatment discontinuation (draft guidance 3.16)** The NICE technical team highlighted that the assumption around the rate of treatment discontinuation in the pegzilarginase arm has a large impact on the cost-effectiveness estimates. In the Company's base case model, a 1% annual discontinuation rate was assumed. The Committee questioned whether using 1% discontinuation rate in the model was appropriate. It concluded that a 2% pegzilarginase discontinuation is appropriate, but uncertain. To address the uncertainty in how long people stay on pegzilarginase, the data for time on treatment with pegzilarginase from the PEACE and Study 101A/Study 102A clinical trials were pooled to generate a Kaplan-Meier curve. Parametric curves were fit to the Kaplan-Meier data to extrapolate time on treatment. These curves are shown in Figure 6 of the accompanying Appendix. The Gompertz curve estimates that by 1 year, ~92% of patients (who were initiated and deemed suitable for pegzilarginase) will remain on pegzilarginase unless they die. This remains constant over the remainder of the model time horizon, whereby at 40 years ~92% of patients will remain on pegzilarginase. This curve is the best suited curve to fit the current clinical trial data (which found the number of patients that remain on treatment [91.7%] plateaued after the first year). During the Delphi panel, KOLs agreed that the Gompertz curve was the most clinically plausible and this aligns with the consensus statement from the Delphi panel that it is unlikely that patients will discontinue treatment after 1 year of initiating pegzilarginase.[1] The Gompertz curve is therefore the most clinically plausible in UK clinical practice. As such, in the updated base case, the discontinuation of

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	pegzilarginase is aligned to the expected use in UK clinical practice, with Gompertz used as the selected extrapolation curve. Scenario analyses are presented in Table 20 of the Appendix, which use alternative parametric curves to extrapolate time on treatment (Weibull and Log-logistic). Given that both scenarios show greater cost-effectiveness for pegzilarginase, the Company would like to emphasise that the current approach assuming no patients discontinue treatment after one year of initiating pegzilarginase is in fact conservative. The Company agrees with the Committee's comment on the practical application of pegzilarginase start and stop rules in clinical practice. The Committee's conclusion that the absence of an analysis based on responders and non-responders to pegzilarginase treatment in the model is acceptable as this would be difficult to implement with the available data. Clinically relevant stopping rules were explored in the Delphi panel, however, KOLs agreed that it is unlikely that patients will discontinue treatment after 1 year of initiating pegzilarginase.
12	**EoL costs** Based on the Delphi panel, EoL costs are considered in the updated model's base case. The importance of EoL costs has been indicated by the Decision Support Unit (2020)[21] which highlights how these costs can be substantial and can confound the relationship between age and unrelated costs, and therefore it is important to include them. The Delphi panel confirmed that a paediatric EoL cost of £30,286.75[22] and an adult EoL cost of £45,537.55 (average cost of spending at least 20 days in intensive therapy unit [codes XC01Z to XC07Z from NHS reference costs 2023/24[23]], see Appendix Table 18) are appropriate to include in the model. One KOL highlighted that hospital admissions normally increase when patients reach adolescence and, therefore, it is intuitive that the adult EoL cost is higher than the paediatric EoL cost. Therefore, the Company's updated base case includes EoL costs as a one-off cost for progressing into the dead health state.
13	**Diet cost savings for ARG1-D patients treated with pegzilarginase** Pegzilarginase treatment has been shown to improve the consumption of natural proteins and reduce essential amino acid (EAA) supplements.[2] The Committee deemed it appropriate to apply a utility gain associated with improved diet in pegzilarginase treated patients. Therefore, the Company believe it is appropriate to include a reduction

	in diet costs (i.e., protein substitute) in pegzilarginase treated patients. In the Delphi panel, KOLs highlighted how controlled arginine levels with pegzilarginase treatment would allow for reductions in prescribed protein substitutes and low protein foods and result in an increase in natural protein intake.[1] KOLs gained consensus that pegzilarginase would reduce the need for diet management by 40%. Therefore, the Company have updated the model base case to apply a 40% reduction to the diet costs in the model, which include the EAA supplements required by patients with ARG1-D. KOLs indicated that the requirement for dietitian management would remain unchanged, thus these have not been altered as they are included in the health care costs.
14	**Disease progression costs** As a scenario analysis, disease progression costs have been included to capture the economic burden associated with ARG1-D progression to the NHS and Personal Social Services. One-off costs for disease progression to a more severe health state were included in a previous HST NICE submission (HST9) in hereditary transthyretin-related amyloidosis (hATTR). The appropriateness of these costs when considering ARG1-D was confirmed during the Delphi panel. Therefore, the Company has explored the impact of including one-off disease progression costs (including walking aids, hoists and other home modifications; see Appendix Table 19) as a scenario in the model. Resources suggested by KOLs may overlap with health state costs in the model, and therefore, have been provided as a scenario analysis to reduce the risk of double counting. The results of this scenario are presented in Table 20 of the Appendix. During the Delphi panel, KOLs submitted which individual healthcare resource use a patient with ARG1-D is likely to require when progressing from GMFCS I to II, GMFCS II to III and GMFCS III to IV. KOLs discussed that patients would require walking aids such as crutches and walking frames from GMFCS II onwards. Therefore, these costs (crutches: £12.50[24] and walking frame: £12.50 [assumed the same cost as crutches]) have been applied for the progression from GMFCS I to II. Furthermore, consensus was reached that home modifications would be required from GMFCS IV onwards. These home modifications include the implementation of hoists, walking rails, movement of the patient's bedroom to the ground floor, and adaptations to the bathroom to ensure wheelchair accessibility. Therefore, these costs (rails: £1,000[25]; hoists/home extensions/bathroom adaptations: £30,000[26]) have been applied for progression from GMFCS III to IV only. Although KOLs identified that

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	wheelchairs (both manual and motorised) are required from GMFCS III onwards, these costs are already captured within the health state costs. Therefore, one-off costs associated with progressing from GMFCS II to III are not included. It is important to note that for patients that progress from GMFCS II and GMFCS III straight to GMFCS V, one-off disease transition costs are still incurred for the states they have bypassed. This is because patients in GMFCS V require all the additional disease progression resources (i.e., those acquired from GMFCS I to II, GMFCS II to III and GMFCS II to IV progression), which was validated by KOLs in the consensus meeting.[1]
15	**QALY weighting (draft guidance 3.17)** The Committee stated that for a QALY weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. The Committee agreed that there was evidence of significant QALY gains in most scenarios, however concluded that it could not apply a QALY weighting at this stage because of the high uncertainty around key model parameters. The EAG highlighted that it is unclear whether the calculation of incremental QALYs should include carer QALYs to estimate the QALY weighting. The Committee concluded it is appropriate to exclude caregiver disutility from the QALY weighting calculation. The Company would like to highlight that the impact of excluding carer QALYs from the incremental QALY calculation is inconsequential in their updated base case ([redacted] when included and [redacted] when excluded). A QALY weight of [redacted] can therefore be applied in both scenarios. As presented in Sections 2-14, the Company have addressed uncertainties raised by the Committee and EAG. Of note, clinical expert opinion has been leveraged to mitigate the following key uncertainties: • Whether the number of people grouped by disease severity is similar to that in NHS clinical practice. o During a Delphi panel, KOLs agreed that the pooled data from PEACE, Study 101A/Study 102A and European BOI survey reflects the distribution of patients with ARG1-D that would be initiated on pegzilarginase treatment in UK clinical practice.[1]

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	• How age varies in NHS clinical practice at the start of each disease severity group.
	  o A ICER has been adjusted to reflect the prevalent NHS cohort, with transition probabilities for IDM updated based on average age in each GMFCS health state and a scenario presenting the ICER weighted by age and severity.
	• How pegzilarginase affects body weight and levels of ammonia in the blood.
	  o Post-hoc analysis of PEACE data indicated that patients aged >13 treated with pegzilarginase treated patients weigh 78.2% of the age- and gender- matched general population weight.
	  o During a Delphi panel, KOLs agreed that the average patient treated with pegzilarginase plus IDM would remain below 90% of population norms with continued treatment.[1] Indeed, clinical expert advice to the Company indicated that ARG1-D patients struggle to gain muscle mass due to spasticity and the inability to exercise.
	  o A scenario analysis is provided in which the distribution of high levels of peak ammonia in the pegzilarginase arm is between the values used in the Company's base case and EAG's scenario analysis.
	• How long people stay on pegzilarginase treatment.
	  o Post-hoc analysis of the trial data illustrates that the Gompertz curve is the best suited curve to fit the current clinical trial data, which found that the number of patients that remain on treatment [92%] plateaued after the first year.
	  o During a Delphi panel,[1] KOLs agreed on the following:
	  ▪ It is unlikely that patients will discontinue treatment after 1 year of initiating pegzilarginase.
	  ▪ The Gompertz curve is the most plausible distribution in UK clinical practice.

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	Under the updated base case, pegzilarginase treatment is associated with [redacted] undiscounted incremental QALYs. Therefore, the Company believe that the QALY weight of [redacted] should be applied.
16	**Revised base case** The updated model includes the following amendments to its base case assumptions: • Revised the modelling approach for patients treated with IDM to reflect average age in state reported by KOLs in the Delphi panel. • Model progression of 5% of patients treated with IDM from GMFCS II/III to GMFCS V per year. • IDM standardised mortality rates based on Delphi panel and assumes 99% dead by 50 years. • Pegzilarginase standardised mortality rates in GMFCS III to V are half IDM standardised mortality rates. • Set peak ammonia levels during HAC to be between EAG SA8 and Company's original base case. • Application of utility gain from diet liberalisation to patients treated with pegzilarginase from 24.7% to 83.3%. • Modelled cognitive deterioration independent of GMFCS health state and updated health state utility values to represent this. • Nominal 2% improvement from mild to no cognitive impairment and 1% from moderate/severe to mild for patients treated with pegzilarginase, continuing until 36 months. • Modelled cognitive deterioration in patients treated with IDM based on data from the BOI study. • Correction of cognitive utilities in trace. • Implementation of a disutility for caregivers with two or more children with ARG1-D. • Application of a lower dose (0.14 mg/kg) post 24 Weeks. • Compliance data added based on both PEACE double-blind and LTE data. • Average weight of patients ≥13 years treated with pegzilarginase are 78.2% of the age- and gender- matched general population weight. • Pegzilarginase discontinuation is in line with PEACE and Study 101A/Study 102A clinical trials, utilising a Gompertz curve. • Inclusion of paediatric and adult specific EoL costs. • Diet costs reduced for pegzilarginase patients.

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	• Implementation of a higher disutility for caregivers with two or more children with ARG1-D. The results from the updated base case demonstrate an ICER of £88,595 for pegzilarginase compared to IDM (shown in Table 1 in the Accompanying Appendix), which clearly demonstrates that it is cost-effective for the treatment of ARG1-D. Pegzilarginase is the first disease-modifying drug for ARG1-D to show normalisations of plasma arginine and improvements in functional mobility, providing substantial improvement in quality and quantity of life. A positive recommendation for pegzilarginase would fulfil a longstanding treatment gap for ARG1-D and will transform the care of ARG1-D patients.

Insert extra rows as needed

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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.

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Pegzilarginase for treating arginase-1 deficiency [ID4029]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **14 March 2025**. Please submit via NICE Docs.

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Appendix: New evidence

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Updated cost-effectiveness results

Table 1: Deterministic base-case results

Technology	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	Weighted incremental QALYs	ICER (£)
Pegzilarginase + IDM	[redacted]	22.756	[redacted]	--	--	--		
IDM	[redacted]	8.745	[redacted]	[redacted]	14.011	[redacted]	[redacted]	£88,595

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

Starting distributions by GMFCS health states

Table 2: ICER weighted by age and population distribution

GMFCS health state	Age at baseline	Proportion of patients at baseline (%)	Incremental Costs (£)	Incremental QALYs
GMFCS I	11	48.44	[redacted]	[redacted]
GMFCS II	12	34.38	[redacted]	[redacted]
GMFCS III	15	3.13	[redacted]	[redacted]
GMFCS IV	25	12.50	[redacted]	[redacted]
GMFCS V	15	1.56	[redacted]	[redacted]
All GMFCS health states			[redacted]	[redacted]
			Weighted ICER: £85,083	

Abbreviations: GMFCS – Gross Motor Classification System; ICER – incremental cost-effectiveness ratio; QALY- quality-adjusted life year

Mortality

Table 3: IDM SMRs

From	Base case SMRs (SMRs based on Delphi panel, assuming 99% dead by age 50)	Scenario (SMRs based on Delphi panel, assuming 90% dead by age 32)
GMFCS-I	67.42	71.11
GMFCS-II	83.71	88.28
GMFCS-III	193.22	204.76
GMFCS-IV	1,414.46	1,673.32
GMFCS-V	118.12	370.74

Abbreviations: GMFCS – Gross Motor Classification System; SMR – standardised mortality ratio; yrs – years

Table 4: Pegzilarginase SMRs

From	Base case SMRs (pegzilarginase SMRs in GMFCS III-V are half of IDM SMRs)	Scenario (pegzilarginase SMRs are 1/10th of IDM SMRs)	Scenario (pegzilarginase survival aligned to previous model)
GMFCS-I	1.16	6.74	4.37
GMFCS-II	1.32	8.37	4.98
GMFCS-III	96.61	19.32	6.79
GMFCS-IV	707.23	141.45	6.79
GMFCS-V	59.06	11.81	30.68

Abbreviations: GMFCS – Gross Motor Classification System; IDM – individual disease management; SMR – standardised mortality ratio

Distribution of peak ammonia levels during hyperammonaemic crisis

Table 5: Distribution of peak ammonia from HAC events - pegzilarginase arm

	PEACE pegzilarginase	Total: EAG SA8	Updated base case: scenario requested by NICE
≤200 µmol/liter	3	3.25	3.125
>200-500 µmol/liter	1	1.25	1.125
>500-1000 µmol/liter	0	0.25	0.125
>1000 µmol/liter	0	0.25	0.125
Total	4	5	4.5

Abbreviations: EAG – External Assessment Group; HAC – hyperammonaemic crisis; NICE – National Institute for Health and Care Excellence; SA – scenario analysis

Cognition

Figure 1: Regression analyses using baseline data for cognition in BOI study

Abbreviations: BOI – burden of illness

Table 6: Cognition transition matrix for IDM based on BOI regression analysis

From:	None	Mild	Moderate/Severe
None	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate/Severe	[redacted]	[redacted]	[redacted]

Abbreviations: BOI – burden of illness; IDM – individual disease management

Table 7: Cognition transition matrix for pegzilarginase for first 36 months

	To		
From	**None**	**Mild**	**Moderate/Severe**
None	100.0%	0.0%	0.0%
Mild	2.0%	98.0%	0.0%
Moderate/Severe	0.0%	1.0%	99.0%

Table 8: Base case starting distribution across all GMFCS health states and cognitive impairment

	GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
None	100%	75%			
Mild		25%	50%	25%	
Moderate/Severe			50%	75%	100%

Abbreviations: GMFCS – Gross Motor Function Classification System

Table 9: European BOI utilities by cognitive impairment

No cognitive impairment	0.832
Mild cognitive impairment	0.561
Moderate/Severe cognitive impairment	0.306

Abbreviations: BOI – Burden of illness

Table 10: Updated base case health state utility values

	Normal Cognitive Function	Mild Impairment	Moderate/Severe Impairment
GMFCS I	0.996	0.725	0.470
GMFCS II	0.705	0.434	0.179
GMFCS III	0.404	0.133	-0.122
GMFCS IV	0.282	0.011	-0.244
GMFCS V	0.276	0.005	-0.250

Abbreviations: GMFCS – Gross Motor Function Classification System

Table 11: Scenario health state utility values with cap

	Normal Cognitive Function	Mild Impairment	Moderate/Severe Impairment
GMFCS I	0.940	0.725	0.470
GMFCS II	0.705	0.434	0.179
GMFCS III	0.404	0.133	-0.122
GMFCS IV	0.282	0.011	-0.244
GMFCS V	0.276	0.005	-0.250

Table 12: Utility weights for no, mild and moderate to severe/extreme cognitive impairment across GMFCS levels using the Hernandez tariff.[1] Patients, N=16

	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS IV-V (n=3)
0-10=no cognitive impairment	0.832 SD=0.138 (n=6)	--	--
11-20=mild cognitive impairment	0.856 SD=0.222 (n=1)	0.925 SD=NA (n=1)	-0.098 SD=NA (n=1)

	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS IV-V (n=3)
21-52=moderate to severe/extreme cognitive impairment	0.231 SD=NA (n=1)	0.523 SD=0.2152 (n=4)	-0.092 SD=0.049 (n=2)

Abbreviations: GMFCS – Gross Motor Function Classification System; SD – standard deviation

Table 13: Utility weights for no, mild and moderate to severe/extreme cognitive impairment across GMFCS levels. Van Hout Crosswalk tariff.[2] Patients, N=16

n	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)

*Three patients reported no cognitive impairment (all in GMFCS I)
Abbreviations: GMFCS – Gross Motor Function Classification System; SD – standard deviation

Table 14: Scenario analysis – baseline cognitive distribution set so more patients start in less severe cognitive states

	GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
None	100%	75%			
Mild		25%	75%	75%	
Moderate/Severe			25%	25%	100%

Abbreviations: GMFCS – Gross Motor Function Classification System

Carer disutility

Table 15: Mean EQ-5D-5L utility for caregivers from the European burden of illness survey

Number of persons with ARG1-D	Utility (EQ-5D cross walk)	Disutility
1 child	0.843	N/A
2 or more	0.674	-0.169

Source: European BOI[3]

Table 16: Base case - additional caregiver disutility for caregivers with two or more children with ARG1-D according to the child's GMFCS health state

GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
-0.002	-0.002	-0.135	-0.152	-0.169

Abbreviations: GMFCS – Gross Motor Function Classification System

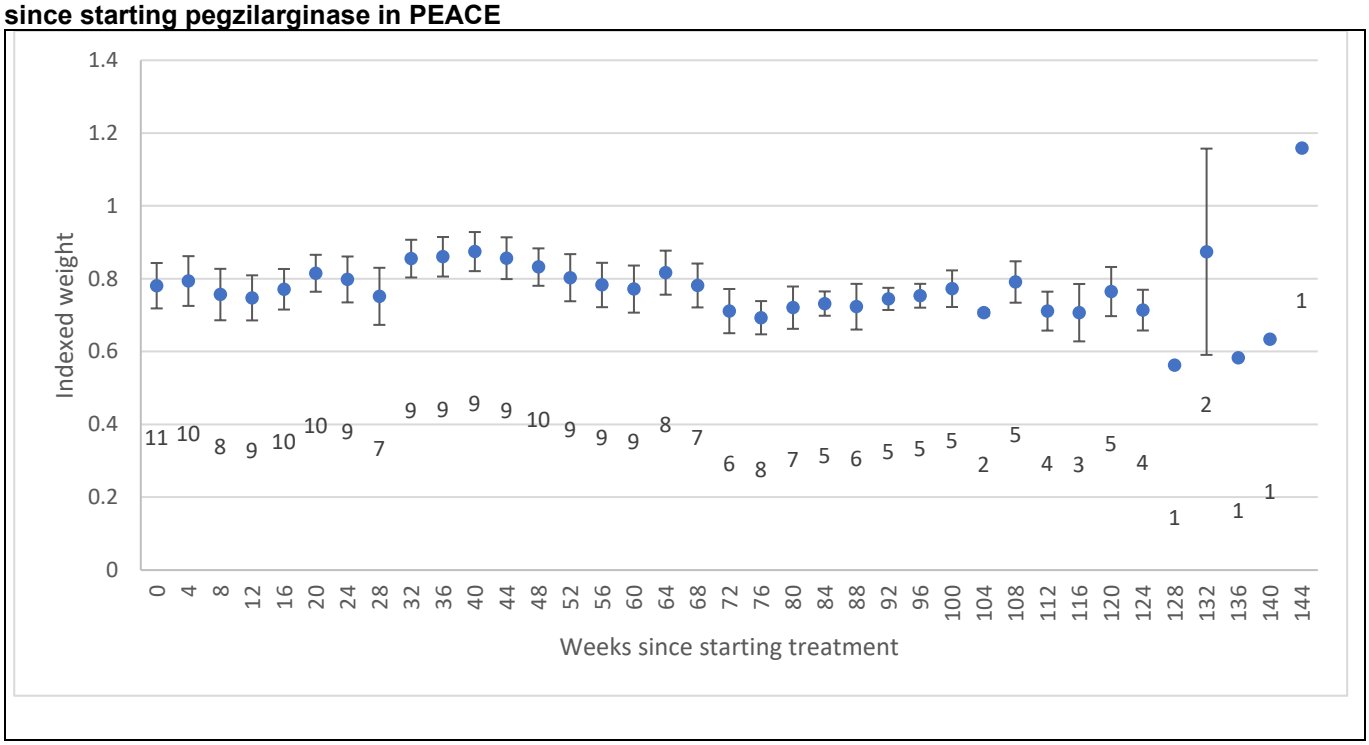
Pegzilarginase dosing and drug wastage

Table 17: Summary of dosing compliance across PEACE used in the model

	Double-Blind Period		Long-Term Extension	
	Pegzilarginase (n=20)	**Placebo (n=11)**	**Pegzilarginase/Pegzilarginase (n=20)**	**Placebo/ Pegzilarginase (n=11)**
Mean dosing compliance	94.1%	N/A	[redacted]	

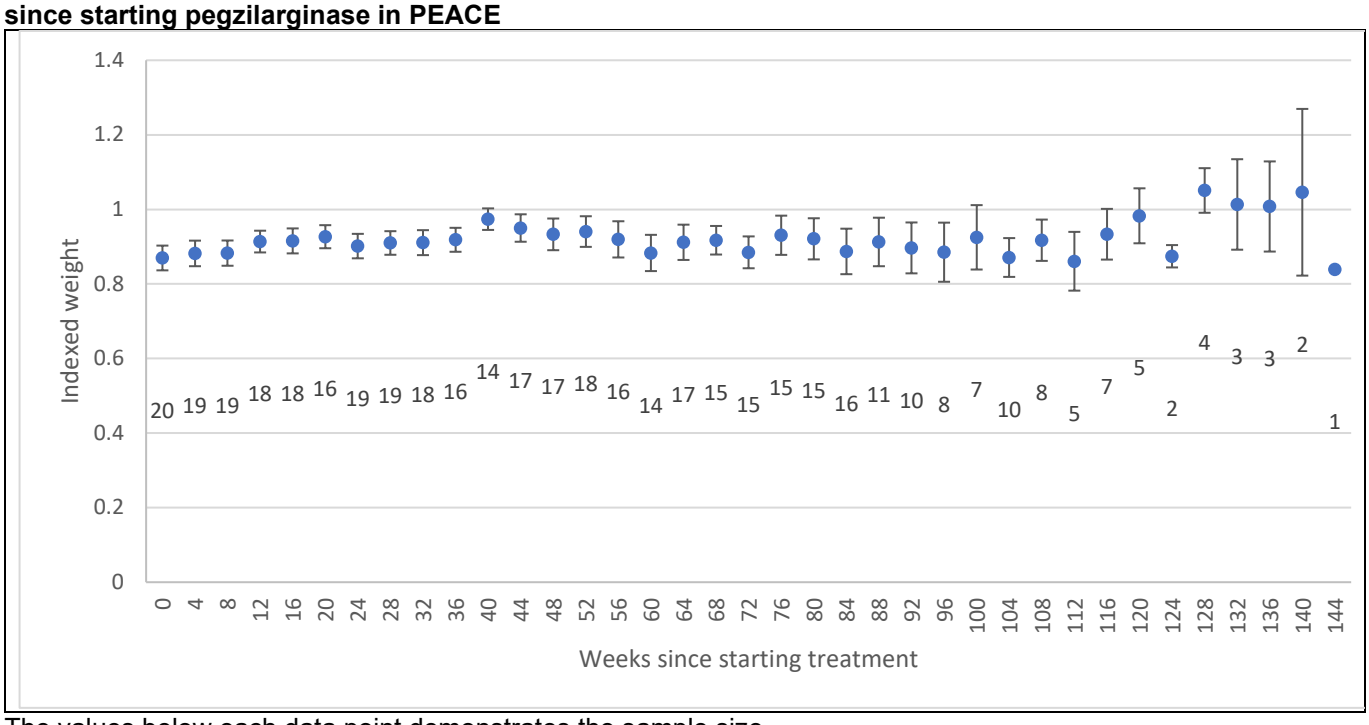
Abbreviations: Max – maximum; Min – minimum; SD – standard deviation
Source: Table 54 and Table 61, PEACE CSR[4].

Figure 2: Weight of patients ≥13 years as a percentage of the general populations' weight according to time since starting pegzilarginase in PEACE



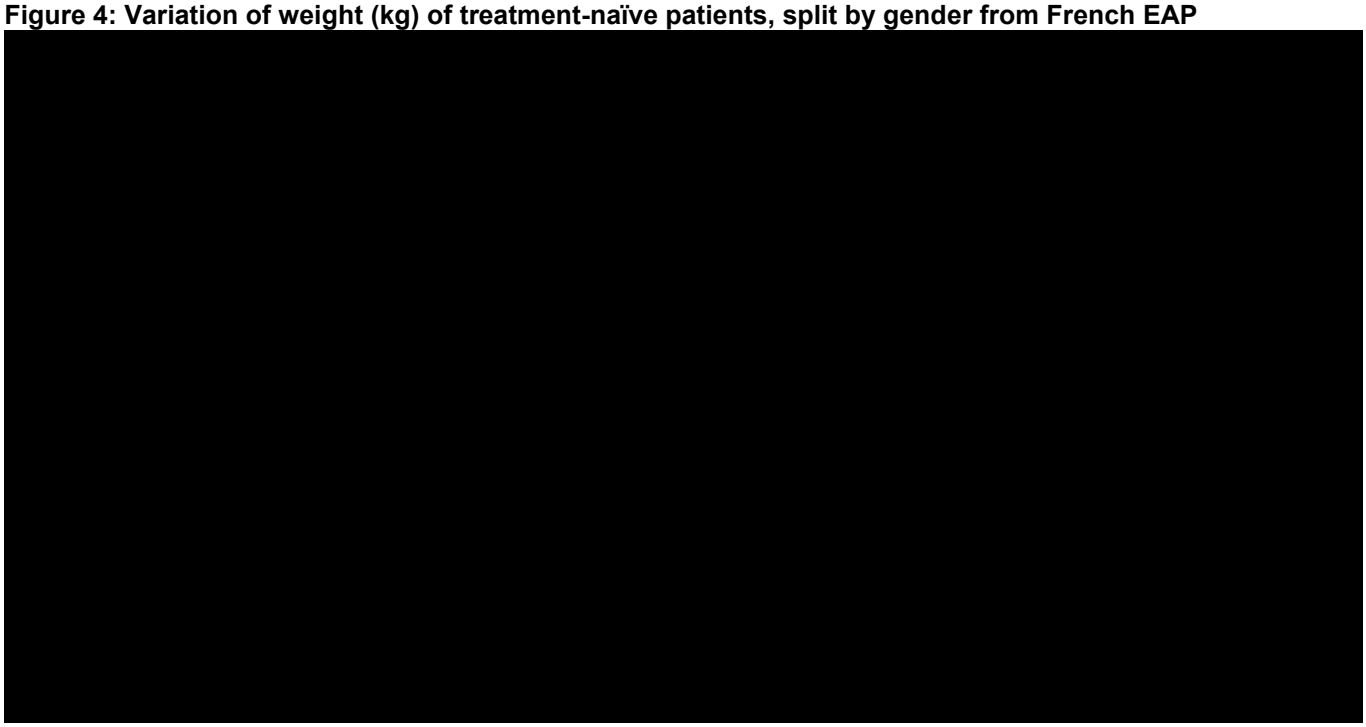
The values below each data point demonstrates the sample size.

Figure 3: Weight patients <13 years as a percentage of the general populations' weight according to time since starting pegzilarginase in PEACE



The values below each data point demonstrates the sample size.

Figure 4: Variation of weight (kg) of treatment-naïve patients, split by gender from French EAP



Abbreviations: EAP – Extended Access Programme
Source: Data on file[5]

Figure 5: Variation of natural protein intake (g/day) of treatment-naïve patients, split by gender from French EAP

Abbreviations: EAP – Extended Access Programme
Source: Data on file[5]

Discontinuation extrapolation

Figure 6: Time to discontinuation of pegzilarginase

End of life costs

Table 18: Adult ICU costs

Service code	Service description	Activity	Unit costs
XC01Z	Adult Critical Care, 6 or more Organs Supported	8,203	£3,227
XC02Z	Adult Critical Care, 5 Organs Supported	32,409	£3,274
XC03Z	Adult Critical Care, 4 Organs Supported	113,839	£3,126
XC04Z	Adult Critical Care, 3 Organs Supported	266,351	£2,714
XC05Z	Adult Critical Care, 2 Organs Supported	350,589	£2,399
XC06Z	Adult Critical Care, 1 Organ Supported	488,918	£1,738
XC07Z	Adult Critical Care, 0 Organs Supported	49,702	£1,622
		Weighted average	**£2,276.88**
		Total cost of 20 days	**£45,537.55**

Abbreviations: ICU – intensive therapy unit
Source: 2023/24 NHS Cost Collection[6]

Table 19: Disease progression costs (scenario analysis)

Resource	Unit cost	Source	GMFCS progression stage
Walking aids			GMFCS I to II
Crutches	£12.50	North Yorkshire Clinical Commissioning Group[7]	
Frames	£12.50	Assumed the same as crutches	
Home modifications			GMFCS III to IV
Rails	£1,000	NHS home adaptations[8]	
Hoists	£30,000	GOV.UK Disabled Facilities Grants[9]	
Extension e.g., downstairs bedroom			
Wet room			

Abbreviations: GMFCS – Gross Motor Classification System; NHS – National Health Service; PPSRU – Personal Social Services Unit

Scenario analysis

Table 20: Scenario analyses

Parameter	Scenario number	Base case	Scenario	Incremental costs	Weighted Incremental QALYs	ICER
Mortality	1	IDM SMRs based on Delphi panel, assuming 99% are dead by age 50	SMRs based on Delphi panel, assuming 90% are dead by age 32	[redacted]	[redacted]	£93,152
	2	Pegzilarginase SMRs in GMFCS III-V are half of IDM SMRs	Pegzilarginase survival aligned to previous model	[redacted]	[redacted]	£92,716
	3		Pegzilarginase SMRs are 1/10th of IDM SMRs	[redacted]	[redacted]	£89,516
Utility gain with improved diet for pegzilarginase patients	4	Apply utility gain from diet to 83.3% of patients	Apply utility gain from diet to 100% of patients	[redacted]	[redacted]	£87,965
Cognition	5	Improvement in cognition for pegzilarginase treated patients	No improvement in cognition for pegzilarginase treated patients	[redacted]	[redacted]	£89,582
	6	No upper bound cap on patient utility	Apply upper bound cap on patient utility	[redacted]	[redacted]	£92,354
	7	Apply Hernandez algorithm to cognitive utilities	Apply Van Hout algoirthm to cognitive utilities	[redacted]	[redacted]	£92,549
Caregiver disutility	8	No reduction in caregiver disutility for pegzilarginase treated patients	Reduction in caregiver disutility for pegzilarginase treated patients	[redacted]	[redacted]	£87,811
Pegzilarginase dosing and drug wastage	9	Set weight ratio to 0.782 for all patients	Set weight ratio according to age at baseline	[redacted]	[redacted]	£101,577
	10	No weight cap	Apply a 90%/95% weight cap to adult	[redacted]	[redacted]	£88,595

			and paediatrics, respectively			
Treatment discontinuation	11	Gompertz curve	Log-logistic	[redacted]	[redacted]	£87,361
	12		Weibull	[redacted]	[redacted]	£87,286
Disease progression costs	13	Exclude disease progression costs	Include disease progression costs	[redacted]	[redacted]	£88,346
QALY weighting	14	Include caregiver disutilities in QALYs	Exclude caregiver disutilities from QALYs	[redacted]	[redacted]	£93,522

Abbreviations: BOI – burden of illness; HST – highly specialised technology; ICER - incremental cost-effectiveness ratio; IDM – individual disease management; QALYs - quality adjusted

Table 21: Probabilistic base-case results

Technology	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	Weighted ICER (£)
Pegzilarginase + IDM	[redacted]	55.75	[redacted]	-	-	-	-
IDM	[redacted]	11.90	[redacted]	[redacted]	43.857	[redacted]	£92,926

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

Figure 7: Incremental cost-effectiveness plane

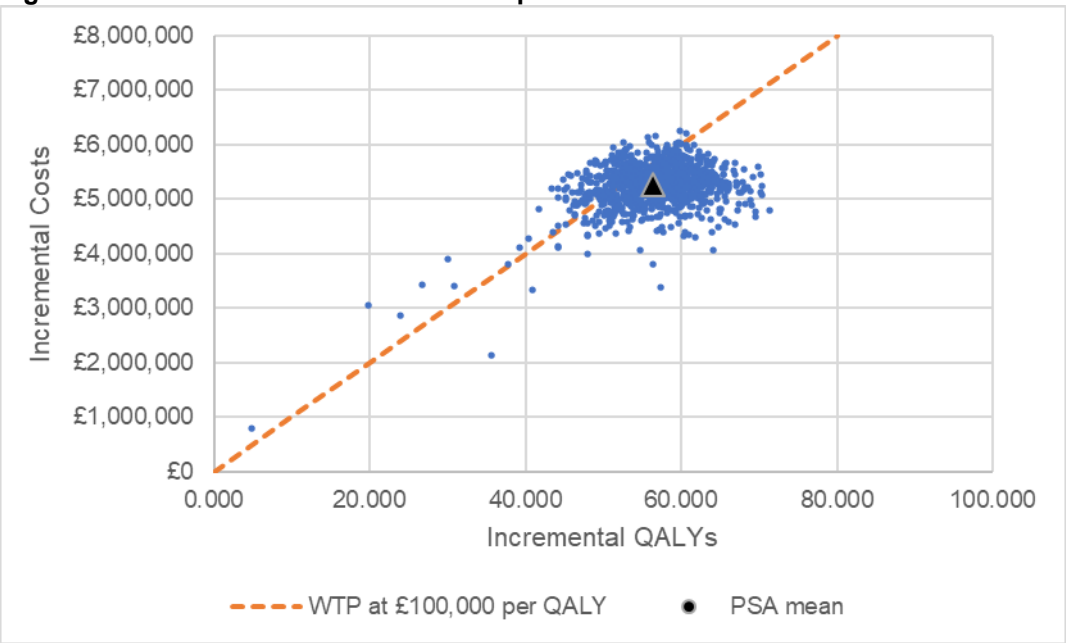


Figure 8: Cost-effectiveness acceptability curve

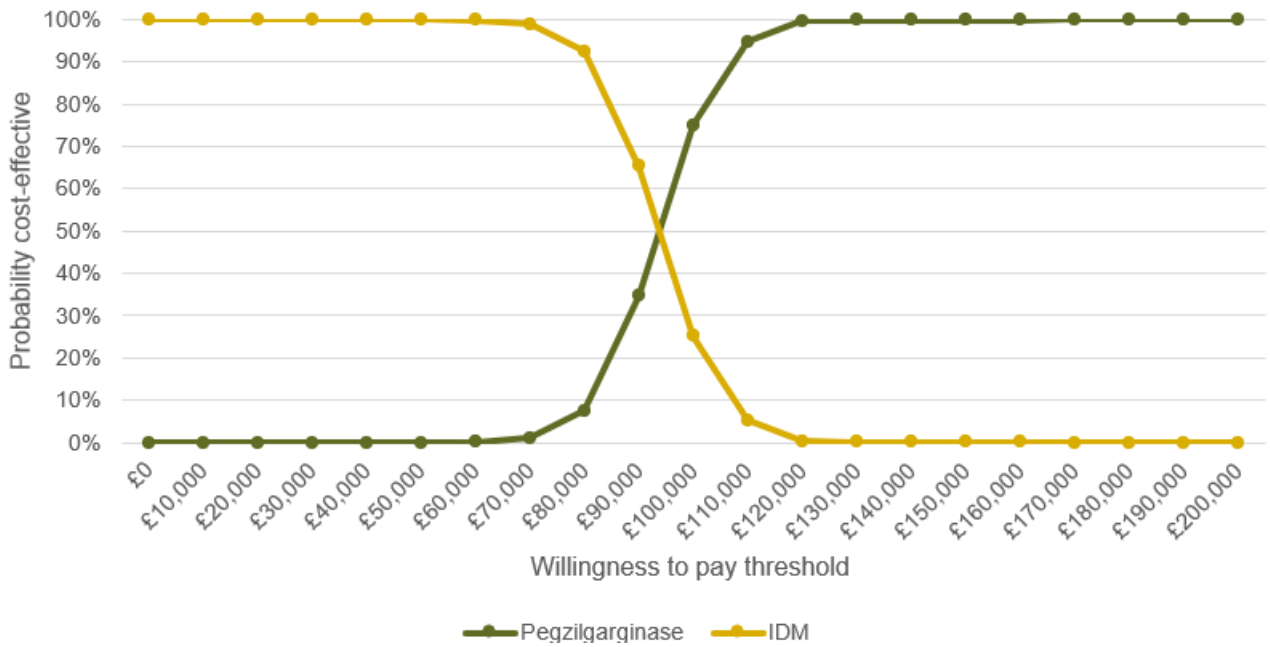
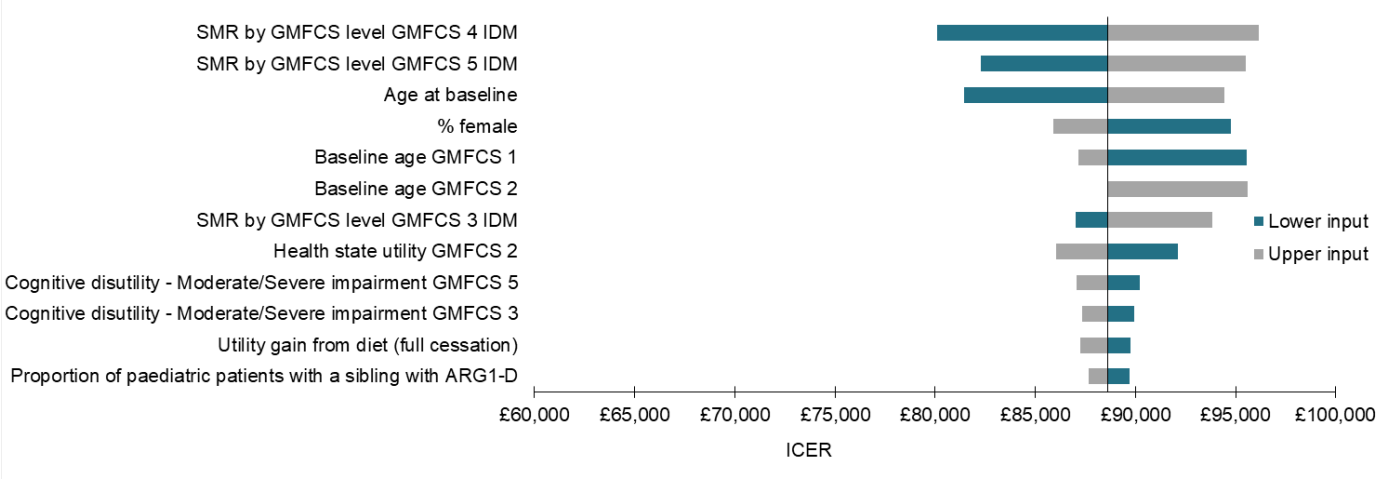


Table 22: One-way sensitivity analysis

	ICER		
Parameter	**Lower bound**	**Upper bound**	**Difference**
SMR by GMFCS level GMFCS 4 IDM	£80,096	£96,158	£16,062
SMR by GMFCS level GMFCS 5 IDM	£82,270	£95,527	£13,258
Age at baseline	£81,462	£94,433	£12,971
% female	£94,746	£85,902	£8,845
Baseline age GMFCS 1	£95,560	£87,169	£8,391
Baseline age GMFCS 2	£88,595	£95,590	£6,995
SMR by GMFCS level GMFCS 3 IDM	£87,014	£93,857	£6,843
Health state utility GMFCS 2	£92,139	£86,041	£6,098
Cognitive disutility - Moderate/Severe impairment GMFCS 5	£90,206	£87,062	£3,144

Cognitive disutility - Moderate/Severe impairment GMFCS 3	£89,921	£87,334	£2,587
Utility gain from diet (full cessation)	£89,736	£87,269	£2,467
Proportion of paediatric patients with a sibling with ARG1-D	£89,692	£87,664	£2,029

Figure 9: Tornado diagram



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NICE National Institute for Health and Care Excellence

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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

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NICE National Institute for Health and Care Excellence

Pegzilarginase for treating arginase-1 deficiency [ID4029]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to declare.
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 are concerned that in not recommending pegzilarginase for the treatment of arginase 1 deficiency (ARG1d), that the Committee has not fully understood or 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. Pegzilarginase has shown meaningful impact on the lives of patients, and their families, as detailed in previously provided evidence by patients and carers, who took the time to share their lived experience, their everyday challenges and the significant, and meaningful way in which pegzilarginase has improved their health and quality of life. To address the uncertainties identified by the committee, we surveyed our community and clinicians. Our community survey received responses from four carers and one individual living with ARG1d. The five responses covered a total of eight individuals living with ARG1d, seven adults (age range: 20-33) and one child (age: [redacted]). Respondents resided in England (n=4) and the United States of America (n=1). Two of the respondents indicated they had experience with pegzilarginase. Both are currently 33 years of age. One received pegzilarginase for 2 years [redacted], the other received pegzilarginase for 3 year, with a 1.5 year gap and is back on treatment as of [redacted]). Our clinical survey received 12 responses from clinicians, treating a total of 24 paediatric ARG1d patients and 19 adult ARG1d patients. Respondents practice in England (n=7), USA (n=4) and Austria (n=1). Eight respondents treat

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	paediatric patients (England: n=4 HCPs; n=9 patients) and four respondents treat adult ARG1d patients (England: n=3 HCPs; n=12 patients). A total of 15 paediatric ARG1d patients had experience with ARG1d (England: n=5 patients) treated by seven different HCPs (England: n=3 HCPs) and four adult ARG1d patients (England: n=1 patient), treated by two different HCPs (England: n=1 HCP). HCPs were asked to only comment on patients under their care to avoid double-counting in centres where several HCPs see ARG1d patients.
2	We understand that there is 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 (draft guidance, page 3). We asked the ARG1d **community** to comment on this. The two respondents with pegzilarginase experience both indicated that they noticed improvements to the mobility of the person living with ARG1d once they were receiving pegzilarginase. They indicated that they stopped seeing further mobility improvements after 3-6 months. The type of mobility improvement observed differed substantially due to the difference in initial mobility. One of the individuals could walk with mobility aids prior to receiving pegzilarginase. Due to pegzilarginase, their stamina improved and they can now stand and walk for long periods of time (up to 10 hours per day) where this was previously limited. Their spasticity also decreased. The other individual required a wheelchair as a mobility aid prior to pegzilarginase treatment, and continued to use a wheelchair while on treatment. Their carer noticed improvements to the range of movement in the legs, as well as reduced swelling of the legs. Most notably, where the individual used to sleep in a fetal position due to muscle spasticity, they were able to sleep in a fully relaxed position. Additionally, previously obtained testimonies from families shared the following mobility impacts observed while the individual with ARG1d was on pegzilarginase: “She regained strength, she quit falling and her seizures stopped. We all noticed [she] was able to walk better and further. She could be active for longer amounts of time and her gait was much smoother. She was no longer dragging her toes and had so much more control over her body.” – carer of a 12-year-old living with ARG1d “Both my daughters' mobility had improved. They were not as fatigued, and could walk for a longer period of time before being tired. My daughters were no longer feeling ill and this was during the pandemic. We were blessed to have finally come across a medicine that was helping my daughters.” – carer of a 34 and 37-year-old living with ARG1d

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	"My son too was super excited to discover how this drug was giving him a chance to enjoy life as normally as possible by improving his walking abilities, running, catching up to his friends and not feeling singled out." – carer of an individual living with ARG1d We also asked HCPs in our **clinical** survey to comment on mobility as measured by GMFCS levels. The paediatric HCPs indicated that no improvement as measured by GMFCS were observed as all paediatric patients were at GMFCS level 1 when they enrolled. However, they also detailed that for this population, GMFCS was not sufficiently detailed to measure mobility improvement. Free text responses detailed that paediatric patients did not detoriarate and generally had an improved gait as a result of treatment. The adult HCPs indicated that either no GMFCS level improvement or 1 GMFCS level improvement was observed. The 1 GMFCS level improvement was observed over a period of 12 months where patients improved from a GMFCS level 4 to a level 3. No GMFCS level improvement was observed in a patient with GMFCS level 5. Additionally, we asked clinicians after how many years of pegzilarginase treatment initiation they expect an ARG1d patient to plateau (draft guidance, section 3.7). Both paediatric and adult HCPs provided responses ranging between one and five years. Six HCPs responded that they did not see any worsening after three years (no experience: n=3), two paediatric HCPs responded that they continued to observe improvements after three years (no experience: n=4, no further improvement: n=3). Worsening was only observed after ARG1d patients were taken off pegzilarginase treatment.
3	We understand that there is uncertainty around cognitive improvements in people living with ARG1d as a result of pegzilarginase, including how large these benefits are and how long they will last (draft guidance, page 3). We asked the ARG1d **community** to comment on this. The two respondents both indicated that they noticed improvements to the cognitive abilities of the person living with ARG1d once they were receiving pegzilarginase. They indicated that they stopped seeing further cognitive improvements after 3-6 months. The type of cognitive improvement observed differed substantially due to the difference in initial cognitive ability. One of the individuals indicated that while not receiving pegzilarginase, their "cognitive abilities were adequate". Once they started on pegzilarginase, they experienced an "improved ability to focus and handle multiple tasks simultaneously and ability to complete highly technical and precise functions without issue." They also added "Pegzilarginase was the key to me being able to transition from part-time work to full-time work. I was able to live a normal and functional life.". The other individual mainly improved their speech, which became "a lot clearer and she was much easier to understand."

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	Additionally, previously obtained testimonies from families shared the following mobility impacts observed while the individual with ARG1d was on pegzilarginase: "[She] made giant strides at school and her teachers were shocked that anyone could gain so much in such a short time. She was learning so much quicker and was almost able to keep up with her friends." – carer of a 12-year-old living with ARG1d "After pegzilarginase, [he had] increase in sustained attention, functional communication, length of sentences with vocalizing a variety of nouns and verbs, clarity in speech" – carer of a 26-year-old living with ARG1d We also asked HCPs in our **clinical** survey to comment on cognitive improvements. The paediatric HCPs responses included indications that there was no data on this or "no cognitive impairment present" to three HCPs who did observe cognitive improvements in a subset of their patients. Improvements were observed over a period of 6-18 months and described as "More focused and able to understand. Better academic performance in school", "Increased interaction and attention; noticeably improved school performance" and "Not formally assessed but better attention span, engagement". One adult HCP commented on the cognitive improvements. They indicated that all three of their adult ARG1d patients experienced cognitive improvements, which were achieved during the first six months of treatment and described as "Improved mood, more attentive, more interested in life activities, more outgoing." As outlined in relation to the mobility uncertainties, HCPs expect ARG1d patients to plateau between one and five years after pegzilarginase treatment initiation (draft guidance, section 3.7). Worsening was only observed after ARG1d patients were taken off pegzilarginase treatment.
4	We understand that the committee would like further details on the current population with ARG1d in the NHS in England to determine whether this is comparable to the numbers provided in the economic model (draft guidance, page 3 and section 3.6). We asked HCPs practicing in England to share details about their cohorts' current GMFCS levels via our clinical survey and were provided with the following: Paediatric GMFCS: - level 1 – 7 patients - level 2 – 1 patient - level 3 – 0 patients - level 4 – 0 patients

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	- level 5 – 1 patient This covers patients from Birmingham Children's Hospital, Manchester University NHS FT and Great Ormond Street Hospital. Adult GMFCS: - level 1 – 2 patient - level 2 – 1 patient - level 3 – 3 patient - level 4 – 2 patient - level 5 – 4 patient This covers patients from Queen Elizabeth Hospital Birmingham, Salford Royal NHS FT and UCL Hospitals NHS FT. As we did not receive responses from all NHS FTs approached, we cannot comment on the generalisability of these numbers across England. All NHS FTs of community members who responded to our community survey, responded to the clinical survey. No questions about GMFCS levels were put forward to the community through our community survey.
5	We understand that there are uncertainties around the assumptions on how age varies in NHS clinical practice at the start of each disease severity group (draft guidance, page 3 and section 3.5). We asked all HCPs to share details about the starting age per GMFCS level for the patients in their cohort, which has been outlined below. The data for ARG1d patients suggests that there is an increasing trend in terms of starting age per GMFCS level, which includes overlap in starting ages between GMFCS levels. Paediatric GMFCS (England): - level 1 starting age – from birth: no problems/motor deterioration (7 patients) - level 2 starting age – 1.2 years (1 patient) - level 3 starting age – No data - level 4 starting age – No data - level 5 starting age – 10.9 year (1 patient) International responses supplied the following additional starting ages: Paediatric GMFCS: - level 1 starting age – 0-4 years (2 patient) - level 2 starting age – 4 years (2 patients) - level 3 starting age – 6-12 years (3 patients) - level 4 starting age – No data - level 5 starting age – No data Adult GMFCS (England): - level 1 starting age – from birth (1 patient)

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	- level 2 starting age – 19 years (1 patient) - level 3 starting age – 16 years (1 patient) - level 4 starting age – 24-28 years (2 patients) - level 5 starting age – 25-31 (4 patients) One HCP commented that the three adults under their care had remained in the same GMFCS levels (level 1 and level 3) since before they transitioned to adult care at age 17-18.
6	We understand that there is uncertainty around the weight of people living with ARG1d and the impact pegzilarginase may have (draft guidance, page 3 and section 3.15). All respondents to our survey reported that the weight of the individuals living with ARG1d is impacted by the disorder. The way in which it is impacted varies 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. Respondents (n=5) to the community survey indicated that at a young age, the individual living with ARG1d was generally underweight. Other respondents (n=3) did not comment on weight status at a young age. Some individuals remain underweight (n=3). Another respondent reported that the individual's deterioration in mobility resulted in gradual weight accumulation leading to them becoming obese (n=1). Other respondents reported that the HCP chose to address weight by fitting a PEG which aids in administering high-calorie, low-protein diets. Individuals who had a PEG fitted all successfully gained weight (n=2), including one respondent detailing that the individual became overweight. For one individual it was reported that "it has been challenging to stay a healthy weight", nonetheless, they reported they were at a normal weight. The two respondents to the community survey with experience of pegzilarginase had different experiences with weight changes. One individual detailed they were at a normal weight prior to initiating treatment and maintained this while on treatment. The other individual detailed they were at normal weight, close to being underweight (approx. size 8) prior to initiating treatment and became overweight while on treatment (approx. size 20). This was lost again after treatment cessation. The clinical survey suggested that three of the 15 paediatric ARG1d patients were underweight prior to pegzilarginase treatment initiation. Two out of three paediatric ARG1d patients reached normal weight once on pegzilarginase. Five HCPs commented that they did not observe any other weight related changes; while one HCP detailed a better appetite among trial participants was noticed. One paediatric HCP did not comment. Among the adult ARG1d patients, none were underweight. One international HCP noted that "all patients did gain weight

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	as there was a tendency to liberalize diet (both in protein intake and total calories) despite being asked not to change diet per study protocol".
7	We understand that the committee is uncertain about how pegzilarginase affects levels of ammonia in the blood, and, specifically, what the distribution of peak ammonia levels during hyperammonaemic crises while on pegzilarginase looks like (draft guidance, page 3 and section 3.10). Through both our community and clinical survey, we asked trial participants and HCPs to share their experience of the impact of pegzilarginase on hyperammonaemia. We also queried whether pegzilarginase led to the loosening or relaxing of usual treatment (i.e. increased protein allowance or decreased need for ammonia scavengers). Both respondents to the community survey indicated that the person living with ARG1d experienced hyperammonaemic episodes while on pegzilarginase. The individual who was on pegzilarginase for three years indicated that they had occasional hyperammonaemic episodes during the early stages of treatment, when the proper dose and administrative pathways were still being determined. They estimated they had a total of five episodes over three years of treatment and disclosed that levels generally ranged from 50-100 umol/L, with one episode at 250 umol/L. The other individual who was on pegzilarginase for two years indicated that they experienced more than 10 episodes over two years, but that it was unclear whether these were associated with pegzilarginase treatment or severe constipation. Paediatric HCPs responded that three of the 15 paediatric patients (England, n=2) experienced hyperammonaemic episodes; two of them had recurrent hyperammonaemic episodes. In the first year, the following distribution of hyperammonaemic episodes among the three paediatric patients was reported: - ≤200 umol/L (n=3 episodes) - 200-500 umol/L (n=3 episodes) - 500-1000 umol/L (n=0) - >1000umol/L (n=0) For the following years, only one HCP had experience with a paediatric patient who continued to have hyperammonaemic episodes. In year 2, they reported one episode in the 200-500 umol/L range; in year 3, four episodes <200 umol/L; and, in year 4, three episodes <200 umol/L. Adult HCP responded that three out of four adult ARG1d patients experienced hyperammonaemic episodes. All three had recurrent hyperammonaemic episodes. In the first year, 10 hyperammonaemic episodes were reported among the three adult ARG1d patients (range 2-4 per adult patient), with all episodes reported to be <200 umol/L. In the second year, nine hyperammonaemic episodes were reported among the three adult ARG1d patients (range 2-4 per

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	adult patient), with all episodes reported to be <200 umol/L. No ARG1d patients were reported to have an ammonia >500 µmol/L while on pegzilarginase. In terms of loosening or relaxing usual care treatments, only one respondent to the community survey responded to this question. They indicated that the amount of ammonia scavengers they were on were reduced while they were on the trial, but their protein limit remained the same. HCPs responded that seven of the 15 paediatric ARG1d patients saw their ammonia scavenger prescription reduced while on pegzilarginase. One of these was a patient based in England. Additionally, one HCP based in England commented that their had been limited opportunity to do this because the trial closed just after prescription amendments were allowed on the study. Similarly, six of the 15 paediatric ARG1d patients had their protein allowance increased (England, n=1 patient); including a comment that the opportunity to do this had been limited due to the trial protocol and subsequent cessation. Among the four adult patients, none had their ammonia scavengers reduced; with a comment from the international HCP (with n=3 adult patients on pegzilarginase) that changes had not been allowed per protocol. The one patient based in England saw their protein allowance increase by 50%, which was due to alignment with the patient's weight gain. We also asked HCPs to comment on their expectation to reduce ammonia scavengers and/or increase protein allowance. Seven out of nine HCPs indicated that they expected to reduce the dose of ammonia scavengers in ARG1d patients (n=6 for paediatric HCPs and n=1 for adult HCPs). HCPs argued that based on their clinical experience, they expected to be able to reduce or eliminate the need for ammonia scavengers. One of the HCPs who did not expect to reduce the dose of ammonia scavengers in ARG1d patients indicated that in their experience, pegzilarginase does not clearly improve urea cycle function. All nine HCPs indicated that they expected to increase the protein allowance of ARG1d patients receiving pegzilarginase. They supported this based on either their own experience, or based on reasoning; i.e. "the arginine levels are the primary target of the protein restriction. With therapy, they can maintain arginine levels while increasing the protein intake. The limiting factor on therapy will be ammonia and glutamine levels, but these patients are more tolerant of protein in terms of causing hyperammonemia compared to other urea cycle defects."
8	We understand that the committee is uncertain about the duration over which people with ARG1d would stay on pegzilarginase treatment (draft guidance, section 3.16). We queried this in our clinical survey, including whether any ARG1d patients were taken off treatment during the clinical trial, whether they

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	believe any ARG1d patients in their cohort would be unsuitable for pegzilarginase, and what stopping rule should be attached to pegzilarginase. Questions were put forward to HCPs with pegzilarginase experience only (n=8): - All HCPs who responded (n=8) to the duration of treatment question indicated that they would expect the treatment to be lifelong. - HCPs indicated that three (all based in England, out of 15) paediatric patients stopped pegzilarginase treatment for personal reasons. None of the adult patients were reported to have been taken off treatment for any other reason that trial cessation. - Two paediatric HCPs indicated that they would not consider one of the paediatric patients eligible for pegzilarginase; one because the condition is "relatively mild without cognitive or ambulatory impairtment" and one because the patient has "profound disability secondary to hyperammonaemia and I would expect this to be irreversible; her disability is not because of chronic hyperargininaemia". One adult HCPs (international, currently caring for 7 adult ARG1d patients) indicated that all of the adult ARG1d patients in their cohort would be considered eligible. The other HCP (based in England, currently caring for 8 adult ARG1d patients) commented that they had two patients they would consider unsuitable for pegzilarginase, as they are both "very advanced in their neurological disease and do not suffer from recurrent episodes of hyperammonaemia." - HCPs suggested stopping rules related to worsening (of motor function or increased hyperammonaemic episodes, n=5), no response (n=5), severe adverse events (n=3) and poor compliance (n=1). The suggested time period over which this is measured varied between responders, some suggested stopping after at least one year of treatment was given while another suggested at least 3 years of treatment should be explored.
9	The committee noted that some of the trial participants were identified through newborn screening and that this is not routine practice in the NHS (draft guidance, section 3.3). We queried HCPs in England on the cause of diagnosis, as well as age at diagnosis, to establish a more complete picture of English diagnostic practices. Of the 24 ARG1d patients HCPs shared details on (including those who passed away), five were diagnosed as the result of family history and 19 were diagnosed due to clinical presentation. Those with a family history were generally diagnosed at a young age (2 years or less), while those who presented clinically were diagnosed anywhere from infancy (incl. several before the age of one) to adulthood.

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10	We understand that there is unclarity around the life expectancy of ARG1d patients, including the impact of pegzilarginase on life expectancy (draft guidance, section 3.4 and 3.9). We queried HCPs on this, including whether any of the patients under their care passed away and what the cause of their passing was. - Paediatric and adult ARG1d HCPs agreed that ARG1d patients are likely to live into adulthood. Life expectancy was estimated to be between 20 and 60 years, with the expectation that some die younger due to significant hypermamonaemic crises and other medical comorbidities. - Seven HCPs reported that one or two ARG1d patients under their care passed away (total, n=9, England, n=7). The age at which patients passed away ranged from 6 months to 37 years (median=17; England range 12-34, median=17). - There were several causes of death, with hyperammonaemia (n=4; England n=3) and sepsis (n=2, all England) the most common causes. Other causes included compartment syndrome (n=1 in England), viral illness with acute respiratory failure (n=1) and pulmonary embolism (n=1 in England). - Eight HCPs with experience of treating ARG1d patients with pegzilarginase responded to a question about whether they expect the life expectancy of ARG1d patients to be positively affected by pegzilarginase. Seven HCPs indicated that they expected the life expectancy of ARG1d patients to be positively affected by pegzilarginase; one indicated that they did not expect life expectancy to be impacted. Those who expected life expectancy to be impacted and commented on the duration, indicated they thought this could extent from “many years” to “normal lifetime” (n=5). They attributed this to stabilisitation of functional mobility (n=2) and improved quality of life (n=3).
	Finally, we are concerned about the negative impact the decision to not recommend pegzilarginase has on our community. It is a community who have closely followed the development of pegzilarginase, and contributed much of their time through clinical trial participation, quantitative and qualitative surveys, as well as by speaking at conferences and presenting posters. It is a community that is well-connected and knows the impact pegzilarginase can have and is therefore all the more desperate to gain access. This progressive disease has a marked effect on the mental health of patients and families. The knowledge that there is a treatment, a treatment that works, but

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	one they cannot access it, is causing long-term stress and anxiety for all ARG1d patients and their families. "[She] has always dreamed of one day being married and having her own family. My biggest fear is for my daughter not to be able to fulfill this dream with the current circumstances. All I want is for both of my daughters to be healthy again. I fear that I will lose [my other daughter] if she continues to decline. I worry my daughter could become depressed if she is unable to live an independent life." – carer of a 34- and 37-year-old living with ARG1d "Just when [her] life journey seemed to be bright and full of hope, the unthinkable happened. […] [She] and her parents were devastated, as the lifeline they had found was suddenly snatched away. As [she] was taken off the treatment, her health began to decline rapidly. Terrible muscle cramps and weakness plagued her, making it hard for her to walk again. Each day became a new battle as she struggled to maintain her balance, falling more often than not. How do you tell anyone but especially a young pre-teen that the drug that was saving her life could no longer be given?" – carer of a 13-year-old with ARG1d "The treatment stopped abruptly and [her] ability to walk and run stopped within a few months of the last treatment. The lack of this medication has not only been detrimental for [her] physically, but also to her emotional well-being. Due to [her] inability to walk and run like other children her age has caused [her] to experience depression and withdraw from society. As a mother I feel powerless every time I must help my daughter bathe, do her bowel movements and so forth." – carer of an 11-year-old with ARG1d "[She] was able to receive this medicine for the past 2.5 years. This was the biggest blessing we could have ever prayed for. Our little girl finally had a chance to live a better life. […] She has been off the drug for almost 4 months and we have noticed a significant difference. [Her] spasticity has returned. She also has frequent nosebleeds again. This reminds me of all we were going through when she was first diagnosed. I feel helpless and desperate to get her back on the medication that was once helping her." – carer of a 9-year old with ARG1d "Pegzilarginase was the key to me being able to transition from part-time work to full-time work. I was able to live a normal and functional life, without it, I am unable to. I saw great improvements on it and major regression without it. Losing access to pegzilarginase in 2023 cost me my job and social life" – 33-year-old with ARG1d

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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- 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.
- 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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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Zafar Aslam, Patient Export self-nominated via Metabolic Support UK

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Name of commentator person completing form:	Zafar Aslam

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	**Daily Life with Arginase Deficiency** I am a parent and carer of a young adult patient with Arginase Deficiency. The information below is from both personal experience and information shared from a global network patient & families affected by arginase deficiency. My child, my family and I are concerned that in not recommending pegzilarginase for the treatment of arginase 1 deficiency (ARG1d), that the Committee has not fully understood or considered the high level of unmet health and medical needs, as well as the high physical and psychological burden ARG1d has on both patients, their carers, and their families, how this impacts each of their quality of life. Patients treated with pegzilarginase had reduced and normalised levels of arginine. In the absence of treatment, over the life of the patient, the health and medical needs, and physical and psychological burden increases, resulting in patients become increasingly isolated from others. The lives of carers and patients' families' evolve around the patient, affecting everyone's mental well-being. Evidence from patients and carers demonstrates that pegzilarginase has hugely beneficial impact on the lives of patients, and their families, resulting in significant, improvement in both their health and quality of life (mobility, cognitive, mental, and social).

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	Patients and families are holding onto <u>hope</u> for ADG1d treatment and improvement in health and quality of life, that is only possible from receiving pegzilarginase treatment.
2	**Mobility Improvement** My child with ARG1d has had progressive decline in lower limb mobility with the passage of time, with accompanying balance issues. ARG1d patient was walking ' frequently stumbling and tripping over' at birth. Appearance of abnormal walking gait from age 5/6 onwards. and progressively worsened, with difficulty walking and standing for long periods of time, losing balance and falling over. From the age of 10, needed wheelchair from walking more 100 meters and not able to place feet flat on the ground. From age 15 onwards, required walking frame for standing or walking short distances with abnormal walking gait and on toes, to maintain balance. This lower limb spasticity caused by ARG1d, leg and feet muscles became tight. From age of 16 onwards, very difficult walking with frames, and dependent upon wheelchair, and from age 18 onwards, legs very visibly not able to extend fully. Mobility aids include walking frame, wheelchair, foot splints, special supportive shoes, bath seat, ramps and handles around the house. Therapies included physiotherapy therapy (PT), occupational therapy (OT), with hospital teams and community teams. Patients and families have informed us that pegzilarginase treatment resulted in significantly improved mobility, especially lower limb spasticity improvements – becoming less dependent upon walking aids, improved standing, improved walking gait, walking longer distances. Pegzilarginase treatment resulted overall in being able to live more of a normal life like their age groups, coming out of the ARG1d-caused isolation, and being able to integrate, mix, interact and socialise again. This provided a motivation and life boost to patients, and hugely improved mental well-being of both patients, carers, and family members.
3	**Cognitive Improvement** My child with ARG1d is lively, funny and communicative at home with parents and siblings, however otherwise very shy. Cognitive ability noted as behind from early age and always remained behind that of her peer group to date. Did not meet developmental milestones, and inherently poor gross and fine motor skills, and struggled with basis daily life tasks such as getting dressed (doing up buttons), washing and bathing, combing hair. Struggled to understand and learn at mainstream school from early age due to ARG1d. Eventually moved to a special needs school at age 11/12 and hated it as patient was in classes with severely

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	disabled children. Cognitive ability has remained behind that of peers in early teens to current age (20), but with mental age of 13 or less (patient repeatedly failed by local council SEN team: SEN assessments and statements, this has escalated to local MP). Patients interests at age 20 include drawing and colouring (pictures that a 6/7-year-old would do) and enjoys making Lego sets for age 7 (Lego sets for age 8 are difficult for patient). Patients and families have informed us that pegzilarginase treatment has resulted in significantly improved cognitive abilities, such as improved concentration and focus, handling more complex tasks than before treatment, noticeable improvement in learning ability and educational performance, improved language communication skills and clarity of communication. Pegzilarginase treatment resulted overall in being able to live more of a normal life like their age groups, coming out of the ARG1d-caused isolation, and being able to integrate, mix, interact and socialise again. This provided a motivation and life boost to patients, and hugely improved mental well-being of both patients, carers, and family members.
4	**Patient Weight** Patient was underweight between ages of 5 to 18, and now sometimes slightly over-weight from age of 20 (due to short height, and high calorie feeds). Very fussy eater, and gastro-PEG is crucial to maintain dietary need, including supplements and medications. Patients and families have informed us that pegzilarginase treatment has resulted in significantly improved appetite and weight of patients on the treatment.
5	**Hyperammonemic Episodes** Patient had first hyperammonemic episode age 7-8 (including cortical blindness), second episode age 16 (4 times in 2 weeks during post-sepsis recovery, including cortical blindness), then monthly for a year in 2021 triggered by bowel disease medication (medication stopped, and episodes stopped.), then on average 3-4 times a year, and now currently monthly episodes (10 days prior to monthly cycle), or when having poor appetite. Thus, we see there are a multitude of triggers (diet management, infections, unwellness, stress, other medications). Frequently hyperammonemic episodes lead to visits to hospital A&E/ER, and sometimes admissions.

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	Pegzilarginase is the only hope for patients to treat their life threatening and life limiting ARG1d condition, and potentially reduce the incident of hyperammonemic episodes.
6	**Pegzilarginase Recommendation** The ARG1d community has closely and eagerly followed the pegzilarginase trails, giving their time and focus to the study to research its health benefits, from patients fortunate enough to have received pegzilarginase. The global ARG1d community is small but well connected, and fully aware of the huge positive impacts it can have for patients, can have and is therefore even more desperate to gain access. Therefore, the ARG1d community is more desperate to gain access to pegzilarginase to receive the recorded health benefits. ARG1d is a progressive disease having a hugely significant negative effect on the mental health of patients and families. The knowledge that there is a treatment, a treatment that works, but one they cannot access it, is causing long-term stress and anxiety for all ARG1d patients and their families. **Patients and families are holding onto hope for ADG1d treatment and improvement in health and quality of life, that is only possible from receiving pegzilarginase treatment.**

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.
- 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

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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.

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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):	Nominated clinical experts (Dr Reena Sharma, Dr Arunabha Ghosh)

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Arunabha Ghosh 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.
1	The committee requested further information from clinicians on a number of points. In order to support our response, an online survey was developed with the support of Metabolic Support UK. This was sent to clinicians in the UK and abroad. Clinicians were asked to respond on behalf of their centres, to avoid double-counting of patients where multiple clinicians see patients with ARG1D. Responses were received from a total of 12 clinicians. Eight paediatric clinicians responded to the survey, of whom 4 were from England and managed a total of 9 patients. Four adult clinicians responded to the survey, of whom 3 were from England and managed a total of 12 patients. Of these, 7 clinicians (3 from England, 4 international) had experience with paediatric patients on pegzilarginase (15 patients, 5 from England, 10 international); and 2 adult clinicians (1 from England, 1 international) had experience with adult patients on pegzilarginase (1 from England, 3 international).
2	We understand that the committee have requested further details with regards to the current population with arginase-1 deficiency in the NHS in England (section 3.6 of draft guidance). In the clinician survey, we asked for numbers of patients under active review, stratified by GMFCS level. A total of 12 adult patients and 9 paediatric patients were reported to be under review at the responding specialist metabolic centres in England. (Paediatric centres – Manchester University FT, Birmingham Children's Hospital, Great

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	Ormond Street Hospital. Adult centres – Queen Elizabeth Hospital, Birmingham, Salford Royal Hospital, UCL Hospitals NHS FT). **The overall age range of patients under active review was 2 months – 34 years.** **GMFCS scoring of England population:** Paediatrics: GMFCS level 1 = 7 GMFCS level 2 = 1 GMFCS level 3 = 0 GMFCS level 4 = 0 GMFCS level 5 = 1 Adults: GMFCS level 1 = 2 GMFCS level 2 = 1 GMFCS level 3 = 3 GMFCS level 4 = 2 GMFCS level 5 = 4 As expected, adults are more severely affected.
3	We understand that the committee have asked for further details on the age distribution of patients at the start of each GMFCS level. In the clinician survey, we asked for details of the range of ages at which patients entered each GMFCS level throughout their lifetime. Paediatric GMFCS (England): - level 1 starting age – from birth: no problems/motor deterioration (7 patients) - level 2 starting age – 1.2 years (1 patient) - level 3 starting age – No data - level 4 starting age – No data - level 5 starting age – 10.9 year (1 patient)* *This patient experienced a severe and protracted hyperammonaemic crisis which resulted in profound disability, having previously been at GMFCS level 1. International responses supplied the following additional starting ages: Paediatric GMFCS: - level 1 starting age – 0-4 years (2 patient) - level 2 starting age – 4 years (2 patients) - level 3 starting age – 6-12 years (3 patients)

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	- level 4 starting age – No data - level 5 starting age – No data Adult GMFCS (England): - level 1 starting age – from birth (1 patient) - level 2 starting age – 19 years (1 patient) - level 3 starting age – 16 years (1 patient) - level 4 starting age – 24-28 years (2 patients) - level 5 starting age – 25-31 (4 patients) One physician commented that the three adults under their care had remained in the same GMFCS levels (level 1 and level 3) since before they transitioned to adult care at age 17-18. Overall, the starting age at each GMFCS level tended to increase, though there is considerable overlap, with the youngest patient entering GMFCS level 2 being 1.2 years old. With the exception of one patient experiencing a profound hyperammonaemic crisis, no paediatric patient was reported to have entered GMFCS level 4 or 5.
4	The committee requested additional data from clinical expert opinion on the impact of pegzilarginase on patient weight (section 3.15 of the draft guidance). In the clinician survey, of a total of 15 paediatric patients treated with pegzilarginase, only 3 were reported to be underweight prior to starting pegzilarginase. Two of these were reported to no longer be underweight since receiving treatment. The third patient discontinued pegzilarginase treatment (family choice) and no data on pegzilarginase impact on weight was provided. Only one other clinician commented on changes in weight during treatment – this patient was noted to have started gaining weight before enrolling in the clinical trial and continued on this trajectory during the course of the trial, even during the placebo-controlled arm, so the weight gain was considered to be unrelated to pegzilarginase. Of a total of 4 adult patients treated with pegzilarginase, none were reported to be underweight prior to starting treatment. However, one clinician responded that their 3 patients did gain weight while on treatment, as there was a tendency to liberalise diet and caloric intake (despite being advised not to change as per the clinical trial protocol). The only UK adult patient reported gained weight while on pegzilarginase and then lost it after discontinuation as the trial stopped. The patient had multiple admissions to the hospital since cessation of the trial, including worsening dystonia. She has gained weight again now without pegzilarginase treatment and

	has reached the weight that was at the end of the trial without any additional dietary intervention. It was therefore concluded that the change in weight was not linked to the treatment. Overall, there were no significant concerns about weight gain related to pegzilarginase treatment. One must bear in mind that in paediatric population there would be some change in weight as the patients are still in growing age . From the dose perspective, it is common practice in England for adult patients for other HST, i.e. enzyme replacement therapies for lysosomal storage diseases, to cap the dose of ERT at a BMI of 27.
5	The committee requested further information regarding the peak levels of ammonia during hyperammonaemic episodes, considering a scenario in which distribution of high levels of peak ammonia in the pegzilarginase arm is between the values used in the company's base case and EAG's scenario analysis (section 3.10 of the draft guidance) **Paediatric patients** Of the 15 paediatric patients reported on in the survey, 3 were reported to have had at least one episode of hyperammonaemia while on treatment with pegzilarginase. (**None of the UK paediatric patients treated had an episode of hyperammonaemia while on treatment**). Of these 3 patients, only 2 had recurrent hyperammonaemic episodes. For these 3 patients, we asked for details on the distribution of peak ammonia concentration during hyperammonaemic episodes during the first year on treatment, which were reported as follows: - ≤200 µmol/L (n=3 episodes) - 200-500 µmol/L (n=3 episodes) - 500-1000 µmol/L (n=0) - >1000 µmol/L (n=0) One clinician described that their patient who experienced a hyperammonaemic episode did so in the context of undergoing major spinal surgery. We also asked for details on the distribution of peak ammonia concentrations during the second year of treatment. This was only described in a single patient, who was reported to have had one episode in the 200-500 µmol/L range in year 2, 4 episodes <200 µmol/L in year 3 and 3 episodes <200 µmol/L in year 4. On further contact with this clinician, they described that the pegzilarginase was started soon after treatment, but the patient had an 18-month lapse in treatment after the end of the clinical trial, before re-starting. They described that the

	severity of the episodes was significantly reduced when on pegzilarginase; stating that [during treatment with pegzilarginase] : **"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…"** *Ammonul – intravenous preparation of combined sodium benzoate and sodium phenylacetate (ammonia scavengers) **Adult patients** Of the 4 adult patients treated with pegzilarginase, 3 had at least one hyperammonaemic episode. One patient, (described by a UK clinician), had a single episode of high ammonia (though <150 µmol/L) at the beginning of the clinical trial. A second clinician reported 2 patients who each had 2-4 episodes of high ammonia in the first year on treatment, and 2-4 episodes of high ammonia in the second year on treatment, with peak ammonia concentrations in all episodes being <200 µmol/L. **Overall summary** 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**.
6	In the clinician survey, we invited clinicians to comment on their experience of relaxation of ammonia scavenger treatment and dietary therapy while on treatment with pegzilarginase. **Ammonia scavenger treatment:** Of the 15 paediatric patients treated with pegzilarginase, 7 were reported to have had their ammonia scavenger prescription reduced while on treatment (of whom 1 was an English patient). One UK clinician commented that they had limited opportunity to relax ammonia scavengers, as the trial closed just after prescription amendments were allowed on the study. Of the 4 adult patients treated with pegzilarginase, none had their ammonia scavenger dose reduced.

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	We invited clinicians to comment on whether they expected to be able to reduce ammonia scavenger prescriptions while on treatment with pegzilarginase. Six of the seven paediatric clinicians, and one of the two adult clinicians with experience of pegzilarginase stated that they would expect to do so, and, commenting variously that: - "one patient is on maximum ammonia scavenging therapy… this escalated significantly while off [pegzilarginase]. I intend to reduce the dose and administration frequency if tolerated now that [pegzilarginase] has been restarted] - "in patients with no hyperammonaemia episodes, scavengers can probably be discontinued; in patients with hyperammonaemia episodes we have left them on about 50% of the dosage before pegzilarginase treatment" - "I expect to stop one of the two drugs gradually" - "I would expect the need to for ammonia scavengers to be minimized or become completely unnecessary" -"patients may increase their protein allowance first, and then reduce the ammonia scavengers" One adult clinician did not expect to reduce ammonia scavengers, stating that "pegzilarginase does not clearly improve urea cycle function as it is not taken up into hepatocytes where the urea cycle actually occurs" **Dietary therapy:** Of the 15 paediatric patients treated with pegzilarginase, 7 had their protein allowance increased (including 1 English patient). Clinicians commented that: -"tried in one prior patient and was successful in increasing protein allowance with normal levels of arginine" -"protein intake has been slowly increased, until reaching about double the amount of pre-pegzilarginase treatment" -"we have already achieved that, and the patient is currently on higher than safe amounts of protein" Of the 4 adult patients treated with pegzilarginase, only 1 (English patient) had their protein allowance increased (from 20g to 30g), though the patient also had significant weight gain. Another adult clinician commented that no changes were allowed during the study for their 3 patients. We invited clinicians to comment on whether or not they expected to increase the protein allowance in patients on pegzilarginase therapy. All 7 paediatric clinicians, and both adult clinicians responded that they would do so, commenting variously that: -"The arginine levels are the primary target of the protein restriction. With therapy, they can maintain arginine levels while increasing the protein intake. The limiting factor on therapy will be ammonia and glutamine levels, but these

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	patients are more tolerant of protein in terms of causing hyperammonaemia compared to other urea cycle defects" -"will increase as tolerated" -"if arginine levels remain low on pegzilarginase treatment, potentially protein allowance could be increased at least in some patients" -"we had planned to increase the protein allowance but did not execute this as the study closed and patient lost access to treatment" -"if improved metabolic stability, can potentially increase protein intake" **Overall summary** Just under half of the paediatric patients treated with pegzilarginase have already had their ammonia scavenger dose reduced. Almost all clinicians expect to be able to do this on patients on treatment. Relaxation of protein allowance has been achieve in just under half of paediatric patients, and all clinicians agree that this should be possible in patients on treatment.
7	The committee note that there is uncertainty around the improvements in mobility and how large these benefits are (page 3, section 1 of the draft guidance). In the clinician survey, UK paediatric clinicians reported experience of a total of 5 patients treated with pegzilarginase, of whom 3 discontinued treatment for personal reasons, and 1 stopped treatment at the end of the clinical trial. There was no deterioration in mobility in any of the patients during treatment (baseline GMFCS was level 1 for the 2 patients who continued treatment throughout the clinical trial). International respondents reported experience of a total of 10 paediatric patients treated with pegzilarginase. 5 patients stopped treatment at the end of the clinical trials, and 2 had an 18 month lapse in treatment. **Of these two, one was described to deteriorate with spasticity and fatigue while off treatment.** Six of the patients treated with pegzilarginase internationally were reported to improve in mobility while on treatment. One survey respondent described an improvement of 1 GMFCS level over 6 months (in 3 patients), and another described improvements in spasticity and mobility, steadier gait and faster ambulation (in 2 patients), though this was too broad to be captured by GMFCS level. A further respondent described improvement from GMFCS level 2 to level 1 over 12 months in one patient. Their other 2 patients were GMFCS level 1 at baseline and did not deteriorate. UK adult clinicians reported experience of only 1 patient on pegzilarginase, who was GMFCS level 5 at baseline and did not change. An international adult clinician described stabilisation of motor decline while patients were on treatment

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	(3 patients treated), noting that 2 patients improved from GMFCS level 4 to level 3 over 12 months, but deteriorated again from level 3 to level 4 since stopping treatment. This clinician also commented that "pegzilarginase is an effective therapy for arginase deficiency… gross motor function will not miraculously improve given the length of time most patients have had their disease without a specific therapeutic intervention but will stabilize and further declines will be unlikely." Overall, the reports from clinicians with pegzilarginase suggest that there is no deterioration in mobility in GMFCS level 1 patients while on pegzilarginase, that patients with some mobility impairments have clinically observable improvements while on treatment. **Worsening of mobility was only reported in patients who were taken off pegzilarginase treatment**.
8	We understand that there is uncertainty around the cognitive improvements associated with pegzilarginase, how large the benefits may be and how long they may last. In the clinician survey, 6 out of 7 paediatric clinicians with experience of pegzilarginase treatment commented on whether cognitive improvements were observed. Two respondents commented that there was "no data available yet" or that "no cognitive impairment was present" [at baseline]. Three respondents described cognitive improvements (in 4 patients), over a period of 6-18 months. These were variously described as: - "more focussed and able to understand, better academic performance in school" - "increased interaction and attention; noticeably improved school performance" -"Not formally assessed but better attention span, engagement" Of the two adult clinicians with experience in pegzilarginase, one respondent (UK clinician) described no change in cognitive status (this was a patient at GMFCS level 5 at baseline). An international adult clinician reported cognitive improvements over 6 months in 3 patients, describing "improved mood, more attentive, more interested in life activities, more outgoing."
9	The committee requested further analysis around standardised mortality rates in the model (section 3.9 of the draft guidance). We requested information in the clinician survey with regards to age at death and cause of death. The overall age of death varied from 6 months to 34 years, and the cause of death was variable, though a number of patients died with hyperammonaemia. There were a total of 5 deaths reported in paediatric patients. One patient (non-UK) died at 6 months of age due to viral illness and respiratory failure. Four

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	English paediatric patients died (age at death 12-17 years). Cause of death was hyperammonaemia in 3 cases and sepsis in 1 case. There were three deaths in adulthood (all English patients, aged 19-34 years) – one was due to pulmonary embolism, one was due to pneumonia and adult respiratory distress, and one was due to multifactorial causes with sepsis and compartment syndrome.
10	We understand that there is uncertainty around the life expectancy of patients with arginase deficiency, and around the potential impact of pegzilarginase on life expectance. In the clinician survey, we invited comments on the life expectancy of patients and whether they believed this would be impacted by pegzilarginase treatment. Paediatric and adult clinicians agreed that patients are likely to live into adulthood, though estimates of life expectancy varied from 20-60 years. One clinician stated that life expectancy would be "highly variable and depends on other medical comorbidities." Another pointed to outliers due to "significant hyperammonaemic crises earlier in life." Eight clinicians responded to a question about whether they expect the life expectancy of ARG1d patients to be positively affected by pegzilarginase. Seven HCPs indicated that they expected the life expectancy of ARG1d patients to be positively affected by pegzilarginase; one indicated that they did not expect life expectancy to be impacted. Those who expected life expectancy to be impacted and commented on the duration, indicated they thought this could extent from "many years" to "normal lifetime" (n=5). They attributed this to stabilisation of functional mobility (n=2) and improved quality of life (n=3). One adult clinician noted that **"the primary driver of mortality is the limited mobility. Once their motor function declines to level 5, infection risk goes up. Improving and maintaining mobility will equate to increased life expectancy."**
11	We understand that there is uncertainty with regards to the duration of time for which patients are expected to stay on pegzilarginase treatment. In the clinician survey, we asked clinicians with experience of pegzilarginase whether any patients were taken off pegzilarginase treatment. We also invited comments as to whether they thought any patients in their cohort may be unsuitable for pegzilarginase treatment, and also whether they would suggest any stopping rules to be attached to pegzilarginase treatment.

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	Eight clinicians responded with regards to expected duration of treatment. All indicated that they would expect the treatment to be lifelong ng. Three out of 15 paediatric patients (all English patients) stopped pegzilarginase treatment for personal reasons. All adult patients stopped treatment due to cessation of the clinical trial and loss of access to treatment. Two paediatric clinicians commented that they each had one patient they would consider unsuitable for pegzilarginase. One (non-UK clinician) commented that this was because the patient is “relatively mild without cognitive or ambulatory impairment” and another because the patient has “profound disability secondary to hyperammonaemia and I would expect this to be irreversible; her disability is not because of chronic hyperargininaemia”. One adult clinician commented that they would treat all their patients, if the treatment was available and the patients agreed. A second adult clinician (UK) commented that they had 2 patients they would consider unsuitable for pegzilarginase, as they are both “very advanced in their neurological disease and do not suffer from recurrent episodes of hyperammonaemia.” **Stopping rules** Clinicians suggested stopping rules related to worsening (of motor function or increased hyperammonaemic episodes, n=5), lack of response (n=5), severe adverse events (n=3) and poor compliance (n=1). The suggested time period over which this is measured varied between responders, some suggested stopping after at least one year of treatment was given while another suggested at least 3 years of treatment should be explored.
12	The committee requested input on the relevance of metachromatic leukodystrophy and familial chylomicronaemia syndrome to arginase-1 deficiency (section 3.9 and sections 3.11 to 3.14 of the draft guidance). No disease could exactly mimic Arginase 1 deficiency. Metachromatic leukodystrophy is a close comparator from the mobility and the cognitive impact of the disease but it does not cover the risks of hyperammonaemia. Familial chylomicronaemia syndrome (FCS) makes a reasonable comparison with the utility for impact on quality due to diet restriction. However, FCS diet could potentially bring the levels to normal or close to normal, if adhered to, while this is not possible in arginase 1 deficiency due to contribution by endogenous production and toxic effects of the accumulated arginine continue.
13	The committee invites comments as to whether the recommendations are considered to be sound and a suitable basis for guidance to the NHS.

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	As clinical experts, we feel that the negative draft recommendation is **not** a suitable basis for guidance to the NHS. ARG1D is a condition associated with progressive neurological deterioration for which standard treatment is inadequate and patients continue to decline despite therapy. Pegzilarginase represents a clear step change in management. We sought real-world experience of pegzilarginase in our clinician survey and this is supportive of the assertion that treatment with pegzilarginase leads to observable clinical benefits. This includes improvement in mobility, more subtle improvements in cognition (improve attention, engagement), and reduction of severity of hyperammonaemic crises. Notably, patients were not described to have deteriorated while on pegzilarginase, but some clinicians have reported decline when taken off treatment. Without pegzilarginase treatment we would expect patients to continue to deteriorate and experience continuing reduction of quality of life as the impact of neurological disease progression becomes severe.

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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- Do not use abbreviations.
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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 **27 September 2024**. Please submit via NICE Docs.

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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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

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Declared competing interests of the authors

None of the authors have any 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.

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Contributions of authors

Matt Stevenson and Sunhong Kwon critiqued all aspects of the company's response to the Appraisal Consultation Document (ACD) and conducted the exploratory and sensitivity analyses. Matt Stevenson led the team. Both authors were involved in drafting and commenting on the final 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).

The company submitted 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 Delphi panel appeared to be conducted well and involved 8 clinicians practicing in the UK who had experience of managing and treating ARG1-D, these represent a large proportion of the practicing clinicians in the UK. As such, this group would have a very good knowledge of the condition, but even so, may provide imprecise answers where there are no data currently available (for example, in predicting values associated with long-term pegzilarginase treatment). Specific answers from the Delphi panel and the association with variables in the model will be discussed under the relevant individual point, however, the EAG notes the over-arching decision that a consensus was assumed if 75% or more of respondents responded with one of the following options: 'somewhat agree'; 'agree'; or 'strongly agree'. Whilst this may appear reasonable, it does mean that a consensus would be declared when to a neutral observer this might be questionable. Examples of this are provided in Table 1, with the question number relating to that in the Delphi report.[2]

Table 1: Examples of questionable consensuses

	Question 1	Question 8	Question 23	Question 28
Disagree	-	-	-	1
Somewhat disagree	-	-	1	-
Neutral	2	-	1	1
Somewhat agree	3	6	2	3
Agree	3	1	3	2
Strongly Agree	-	-	1	1

Whilst the EAG highlights this issue, this does not mean that the company could have done a better job, just that there remains considerable uncertainty in whether the value reached by consensus is correct and also that there can be wide variations in the agreement of individual clinicians to the questions asked.

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, the EAG's critique of to provide a critique of this change, and where relevant, suggestions of alternative assumptions that, where possible, have been used by the EAG in sensitivity analyses. Section 3 describes further considerations that were either not within the EAG's base case but had been flagged as important sensitivity analyses or are new points identified since the DGD. Section 4 presents the results of the exploratory analyses undertaken by the EAG.

The EAG acknowledges that there remains considerable uncertainty within the most appropriate data values and that provision of a robust EAG base case is not possible. The approach taken by the EAG is to group changes within the EAG's sensitivity analyses into 3 categories (C1, C2 and C3) as described in Table 2.

Table 2: Classification of EAG changes

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

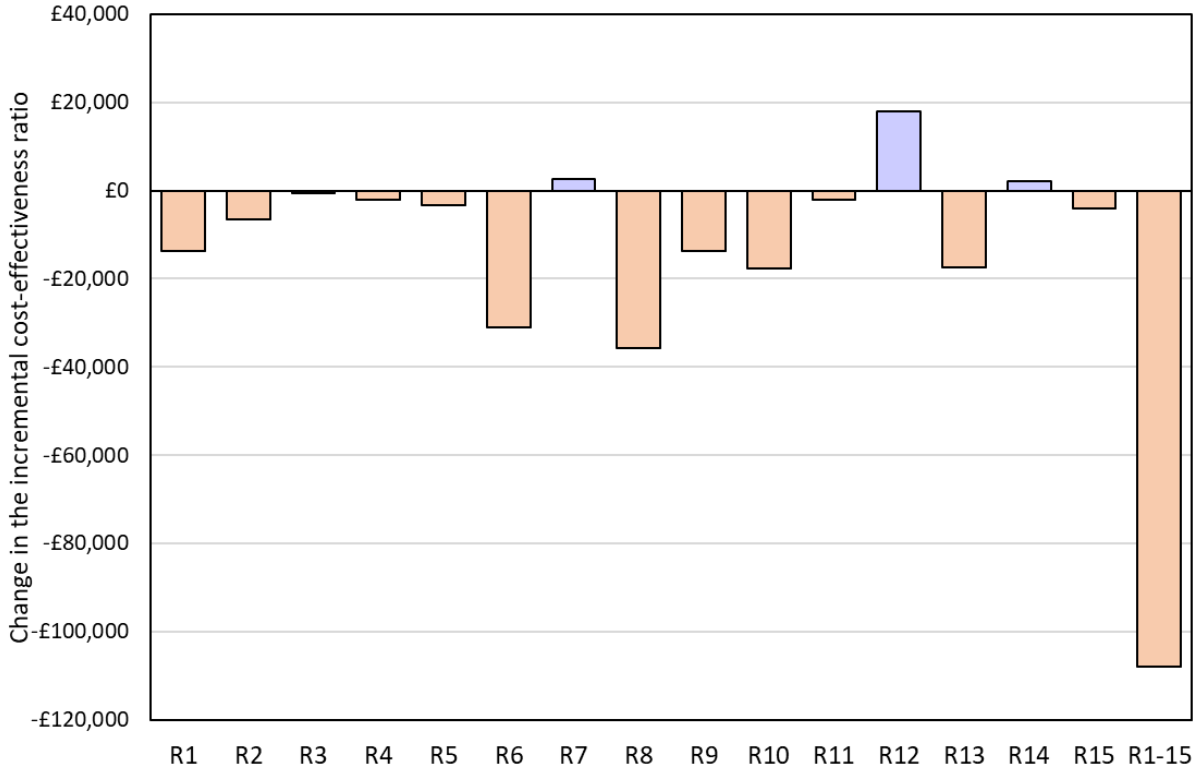
The EAG has provided an analysis where all C1 changes are made simultaneously as it believes this represents a more plausible ICER than that provided by the company. Further to this, C2 and C3 changes are made independently to both the company's base case, and the EAG analysis where all C1 changes have been simultaneously implemented. The EAG anticipates that it is unlikely to have generated an ICER using the committee's preferred assumptions, as the number of permutations of assumptions are very large. The EAG can run this analysis once the committee's preferred assumptions are established.

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

The company made a multitude of changes to the EAG base case which are described in individual sub-sections. Figure 1 presents a bar chart showing the change in the ICER associated with each modelling change based on the EAG's previous base case. Note, that the company increased the PAS discount after the initial submission and EAG report, resulting in an updated cost of [redacted] per 2mg vial (a discount of [redacted]) and therefore, the base case ICER in Figure 1 is lower than in the EAG's main report.[3]

The ordering in Figure 1 is aligned with that contained within the company's model and has not been prioritised by the EAG. The cumulative changes made by the company have considerably reduced the ICER, which is [redacted] (unweighted) and £88,595 (weighted).

Figure 1: The change in ICER (weighted) associated with each change made the company to the EAG base case



List of revisions

R1. Adjusting the compliance assumed for those receiving pegzilarginase treatment (Section 2.1)

R2. Changing the discontinuation rate associated with pegzilarginase (Section 2.2)

R3. Adding in costs associated with death (Section 2.3)

R4. Adjusting the costs associated with diet management for patients receiving pegzilarginase (Section 2.4)

R5. Including additional disutility for carers with more than one child with ARG1-D (Section 2.5)

R6. Adjusting the long-term dose for patients receiving pegzilarginase and reiteration that a 10% weight margin for dosing is appropriate (Section 2.6)

R7. Setting the distribution for peak ammonia level for patients treated with pegzilarginase to be halfway between the company's initial distribution and the EAG's scenario analysis (Section 2.7)

R8. Altering the methodology used to determine the utility of patient with no impairment in each GMFCS health state and the impact of cognitive impairments (Section 2.8)

R9. Increasing the proportion of patients who receive a utility gain due to an improved diet whilst on pegzilarginase treatment to 83.3% (Section 2.9)

R10. Revising the time spent in each health state for patients on IDM (Section 2.10)

R11. Assuming that each year 5% of patients move from GMFCS-II and -III to GMFCS-V (Section 2.11)

R12. Changing the standardised mortality rates for patients receiving IDM (Section 2.12)

R13. Setting the SMR for pegzilarginase-treated patients to half that of IDM-treated patients for those in GMFCS-III to GMFCS-V (Section 2.13)

R14. Correcting a minor error in the trace for pegzilarginase and IDM when applying cognitive disutilities (Section 2.14)

R15. Amending the ratio of weight between people with ARG1-D treated with pegzilarginase and the age-matched general population (Section 2.15)

R1-15. R1 to R15 combined

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 EAG's base case and are [redacted] in the company's revised submission.

2.1 Adjusting the compliance assumed for those receiving pegzilarginase treatment

In its original base case, the company assumed that all patients received the full dose of pegzilarginase. In its response to the DGD, the company has reduced 'dose compliance' stating that in PEACE that only 94.1% of the full pegzilarginase dose was taken in the double-blind period, and that this value was [redacted] in the long-term extension. These values have now been included in the model rather than an assumption of 100%. No reason has been given for the reduced compliance, which would be favourable to pegzilarginase if this was related to not allowing drug wastage (see Section 2.6)

The EAG notes that it is common to align costs with the observed benefits, which would imply that using the dose that was actually taken would be appropriate. However, the level of many of the benefits have come from the Delphi panel and may therefore be disconnected from the dosage within the PEACE study; in these circumstances the appropriateness of the change in dose compliance is more questionable. The EAG has not changed the company's base case but notes that reverting to 100% dose compliance would increase the company's weighted base case ICER from £88,595 to £95,734 (an increase of 8%.

2.2 Changing the discontinuation rate associated with pegzilarginase

In its original base case, the company assumed that 1% of patients would discontinue pegzilarginase each year. The company quotes the DGD which states that "*The Committee questioned whether using 1% discontinuation rate in the model was appropriate.*" and that "*It* [the Appraisal Committee] *concluded that a 2% pegzilarginase discontinuation is appropriate, but uncertain.*" To address the uncertainty in discontinuation rates the company fitted distributions to discontinuation data from PEACE and Study 101A / Study 102A. These fits are replicated in Figure 2. The company chose the Gompertz distribution whereby approximately 92% of patients have discontinued at year 1, with no material discontinuations thereafter. The company states that this aligns with clinical study data where 91.7% of patients remain on treatment after 1 year, with a plateau thereafter (the follow-up duration was not stated but appears to be approximately [redacted] years from data shown in Figure 2, although the data may be from very small patient numbers). Additionally, clinicians "*agreed that the Gompertz curve was the most clinically plausible and this aligns with the consensus statement from the Delphi panel that it is unlikely that patients will discontinue treatment after 1 year of initiating pegzilarginase.*" The company performed sensitivity analyses using log-logistic and Weibull distributions which reduced the ICER by approximately £1000. However, if the exponential distribution that best fitted the Kaplan-

Meier data is used the weighted ICER is £108,230, although the clinicians forming the Delphi panel suggest that such a high discontinuation rate would be highly unlikely.

Figure 2: The distributions considered by the company plus the 2% discontinuation rate per year mentioned in the DGD

From personal communication with NICE, the EAG understands that the committee's preferred discontinuation rate in the DGD was 2% per year. The EAG has used this discontinuation rate (2% per annum) in sensitivity analysis, although the EAG comments that this value does not fit the initial years of the Kaplan-Meier well, due to the initial number of discontinuations and then a plateau, however, there is considerable uncertainty due to the small number of patients in whom data are collected. The EAG prefers the log-logistic distribution as it believes that it is unlikely that there would be effectively no discontinuations after the first year of treatment. This belief was also shown by some clinicians in the Delphi panel, where question 23 asked "*The data within the Kaplan-Meier curve in pre-read slide 13 (presented in Appendix A) shows that no more patients will discontinue treatment after 1 year of initiating pegzilarginase. Do you agree/disagree that this would be similar in UK clinical practice?*" and produced the responses of 1 somewhat disagree, 1 neutral, 2 somewhat agree, 3 agree and 1 strongly agree. The loglogistic distribution estimates a discontinuation percentage of approximately [redacted] at 30 years.

2.3 Adding in costs associated with death

In its original base case, the company assumed no costs associated with death. In the revised submission, costs of death were included which were £30,287 for a paediatric death (inflated from Noyes *et al.*[4]) and £45,538 for an adult death, which was calculated assuming 30 days in an intensive therapy unit (weighting codes XC01Z to XC07Z from the 2023/24 NHS Reference costs).[5] These costs were applied to all patients, irrespective of the cause of death, which may be unfavourable to pegzilarginase. As the inclusion of costs of death had only a modest impact on the ICER and that there was a general consensus amongst expert clinicians that such costs were appropriate, the EAG did not change the company's assumption.

2.4 Adjusting the costs associated with diet management for patients receiving pegzilarginase

In its original base case, the company assumed costs for diet management for patients that were identical for patients receiving pegzilarginase and patients receiving individualised disease management (IDM). However, the company states that as the Appraisal Committee deemed it appropriate to apply a utility gain associated with improved diet in patients treated with pegzilarginase then it would be "*appropriate*" to include a reduction in diet costs for these patients, as less protein substitutes would be needed. The clinicians in the Delphi panel agreed (4 somewhat agree and 3 agree) that a 40% decrease in dietary management costs would be appropriate. This reduced the annual costs of dietary management by £3627 in GMFCS-I, -IV and -V, by £2901 in GMFCS-II and by £3264 in GMFCS-III (the initial value in each GMFCS state was calculated based on data from patients in the burden of illness (BOI) study). As the inclusion of costs of death had only a small impact on the ICER and that there was a general consensus amongst expert clinicians that such costs were appropriate the EAG did not change the company's assumption.

2.5 Including additional disutility for carers with more than one child with ARG1-D

In its original base case, the company assumed that the caregiver disutility values associated with patients with metachromatic leukodystrophy (MLD), apparently from an Institute for Clinical and Economic Review paper,[6] were appropriate for patients with ARG1-D. The company also assumed that 2 caregivers were needed for patients aged under 16 years of age. In the DGD, it is stated that "*The committee considered the uncertainty in the carer disutility values but concluded that values used in the base-case model are acceptable for decision making.*"

Post-DGD, the company aimed to address the uncertainty in caregiver utility, explore the additional utility of carers with more than one child with ARG1-D and ascertain the proportion of children with ARG1-D who also had a sibling with ARG1-D. The company used the values in its original submission with an additional decrement associated with having more than 1 child with ARG1-D. The value of the decrement was sourced from the BOI survey conducted by the company[7] which produced an EQ-5D-

5L utility of [redacted] for carers with one child with ARG1-D (n=[redacted]) and a value of [redacted] for carers with more than one child (n=[redacted]). No further details were provided that would allow the EAG to explore if there were other key differences between the groups such as the GMFCS state of the children. The EAG comments that the EQ-5D-5L values obtained in the BOI study have not been mapped into EQ-5D-3L values.

The company assumed that the difference between these numbers ([redacted]) was the maximum additional disutility associated with more than one child with ARG1-D with this value 'scaled' based on the patient's GMFCS state with scaling values of: 0.01 for GMFCS-I and -II; 0.8 for GMFCS-III; 0.9 for GMFCS-IV and 1.0 for GMFCS-V. The additional disutility values for each GMFCS health state are shown in Table 3. The company assumed that the proportion of children with more than one sibling with ARG1-D is 63.5% and applied this percentage to calculate the additional disutility associated with more than 1 child in the family with ARG1-D.

Table 3: Caregiver disutility values used in the model

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

ARG1-D: Arginase 1 deficiency EAG: External Assessment Group; GMFCS: Gross Motor Function Classification System; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy.

The EAG notes that the difference in utilities for those, with and without, a second child with ARG1-D from the BOI study was not statistically significant (95% CI [redacted] to [redacted], p-value [redacted]; calculation undertaken by the EAG). Without further details on the patient characteristics, the EAG cannot provide a robust estimate of any utility difference associated with more than one child with ARG1-D.

The EAG notes that obtaining the proportion of siblings with ARG1-D who have a sibling with ARG1-D is likely to overestimate the number of families with more than one child with ARG1-D. Consider that there are 3 people with ARG1-D, 2 in one family and 1 in a separate family. Here, the number of families with more than 1 child with ARG1-D is 50%, however the number of children with a sibling with ARG1-D would be 67% (2 out of 3). It is unclear whether this distinction was made by clinicians in the Delphi panel, but the EAG highlights that as the question is written, the over-estimation, as shown in the example would be likely to occur. Further, the percentage of families with more than one child with ARG1-D was [redacted]%, notable lower than the [redacted]% assumed by the company which was increased

from the [redacted]% mean in the round two responses with the company stating that "*The final percentage of [redacted]% accounted for patients in KOLs care who were unable to participate in the Delphi Panel and consensus meeting, as this missing data was provided by Immedica.*".

Additionally, the inclusion of a second child with ARG1-D would increase the disutility associated with a child in GMFCS-V by [redacted] regardless of whether the other child was in GMFCS-I or GMFCS-V. The impact on carer disutility is driven by the more severe GMFCS health states, and the EAG notes that this will occur more for patients on IDM rather than pegzilarginase treatment.

The EAG identified programming errors in the application of caregiver disutility related to more than one child. In calculating caregiver QALY loss on a per-cycle basis, the company directly applied the disutility values (as presented in the farthest right column of Table 3) without adjusting them to account for cycle duration (3 months) essentially increasing the QALY loss associated with multiple children with ARG1-D by a factor of 4. This issue was corrected in the revised version of the EAG's model.

Whilst the EAG acknowledges that there will be additional disutility associated with caring for more than one child with ARG1-D, it is not confident that the methodology used by the company is correct or that the data used by the company is robust, particularly given the small number of observed data points in the BOI study. The EAG suspects that the company's approach will over-estimate the caregiver burden, although it is difficult to ascertain by how much. The EAG preferred an assumption where the percentage of families with more than one child with ARG1-D is [redacted]%, which was the mean response in round two of the Delphi panel, a value which lies between the [redacted]% from the BOI study, and the [redacted]% assumed by the company. The EAG additionally provided arbitrary scenario analyses, where the additional caregiver disutilities, when there is more than one child with ARG1-D, has been quartered, halved, and set to three-quarters of the values assumed by the company.

The caregiver disutilities by GMFCS health state in the EAG scenario analysis are discussed in Section 4.5.2.13 in the EAG report[3] based on data in Sevin *et al*.,[8] which suggests a disutility value of 0.062 compared with the general population which was assumed to apply to GMFCS-III and more severe health states as shown in Table 3. These values have been used in a scenario analysis.

2.6 Adjusting the long-term dose for patients receiving pegzilarginase and reiteration that a 10% weight margin for dosing is appropriate

In its original base case, the company assumed that the dosage required for patients receiving pegzilarginase after 24 weeks was 0.16mg/kg which was estimated using regression and a random effects model from the 20 patients who received pegzilarginase treatment in the PEACE study. In the response to the DGD, the company has pooled PEACE data with Study 102A data which results in a

mean dose of 0.14mg/kg, although no uncertainty in this value was presented by the company. The company states that real-world evidence (RWE) from France (n=14),[9] suggests that a dose of 0.14mg/kg "*maintain reductions in plasma arginine at a steady level*". The company also highlights that "*Clinical advice to the Company highlighted it is likely that once initial doses of pegzilarginase have cleared the elevated plasma arginine, a reduced dose may be sufficient to maintain plasma arginine within normal levels*" citing email correspondence with clinical experts. The EAG comments that the range in dose in the French RWE study was [redacted] to [redacted] mg/kg and that this was from 14 patients only.

In its original submission the company applied a '*10% weight margin*'. In this, pegzilarginase wastage is assumed to occur but is tempered by the assumption that if the weight of a patient was less than 10% above the threshold weight for a certain number of vials then an additional vial would not be opened, and the patient receives a slightly lower dose. Further details are provided in Sections 4.2.4.10.1 and 4.5.2.7 of the EAG report.[3] Clinical advice received by the EAG stated that from three options contained in the model, that the company's chosen approach "*was most appropriate, although there is uncertainty around the true level of drug wastage.*" The three options assumed: 1) 10% margin with all patients with the same weight at each age; 2) no drug wastage using a distribution for weight at each age; 3) and full drug wastage using a distribution for weight at each age.

In Table 4, the EAG has shown the weight thresholds for which a specified number of vials are appropriate when a 10% margin is applied. For example, assuming a dose of 0.14mg/kg, 3 vials per week would be appropriate for patients weighing over 31.4kg and less than, or equal to, 47.1kg.

Assuming a fixed average weight, the number of vials required by age ranges, conditional on the assumed dose and the assumed weight ratio (see Section 2.15 for further details) are presented in Table 5. To aid interpretation, assuming a dose of 0.14mg/kg, a weight ratio of [redacted], and all patients at the average weight, then patients between the ages of [redacted] and [redacted] years would require 3 vials. If no margin was applied, then the weight thresholds at which additional vials would be needed would be lower (data not presented). Assuming a distribution of weight would alter the average number of vials needed, which could increase or decrease.

Table 4: The weight associated with the numbers of vials required each week

No. of vials per week (Total dose)	**Weight threshold applying a 10% margin after 24 weeks (kg)**	
	Dose=0.16mg/kg	**Dose=0.14mg/kg**
1 (2mg)	13.5	15.7
2 (4mg)	27.0	31.4
3 (6mg)	40.5	47.1
4 (8mg)	54.0	62.9
5 (10mg)	67.5	78.6

No. of vials per week (Total dose)	Weight threshold applying a 10% margin after 24 weeks (kg)	
	Dose=0.16mg/kg	Dose=0.14mg/kg
6 (12mg)	80.7	94.3

Table 5: The age associated with the numbers of vials required each week

No. of vials per week (Total dose)	Age range (years) associated with the weight threshold			
	Weight ratio=[redacted]		Weight ratio=[redacted]	
	Dose=0.16mg/kg	Dose=0.14mg/kg	Dose=0.16mg/kg	Dose=0.14mg/kg
1 (2mg)	[redacted]	[redacted]	[redacted]	[redacted]
2 (4mg)	[redacted]	[redacted]	[redacted]	[redacted]
3 (6mg)	[redacted]	[redacted]	[redacted]	[redacted]
4 (8mg)	[redacted]	[redacted]	[redacted]	[redacted]
5 (10mg)	[redacted]	[redacted]	[redacted]	[redacted]
6 (12mg)	[redacted]	[redacted]	[redacted]	

Ideally, the EAG would have preferred an approach which used a distribution for weight and maintained the 10% weight margin, however this was not possible within the company's model. Therefore, previous scenarios assuming a distribution of weight (without the application of the 10% weight margin) have been run at full drug wastage and no drug wastage to inform the Appraisal Committee.

In an attempt to explore the potential impact of variation in the number of vials required by a patient rather than assuming all have a fixed number of vials, and the potential contradiction related to the increase in weight of patients (see Section 2.15) the EAG ran two further scenarios (increasing the cost of pegzilarginase by 10% and by 20%). These analyses assume that more vials will be needed when the correct distribution of weight is used and has been triggered by the fact that when a dose of 0.14mg/kg is assumed with a fixed average weight (as in the company's base case) 5 vials are only used between the ages of [redacted] to [redacted] years. It is believed that a reasonable proportion of patients would have 5 vials if a distribution of weight was used and that this would be considerably larger than the proportion of patients who only required 3 vials.

2.7 Setting the distribution for peak ammonia level for patients treated with pegzilarginase to be halfway between the company's initial distribution and the EAG's scenario analysis

In its original base case, the company assumed that the distribution of peak ammonia levels when a hyperammonaemic crisis (HAC) occurred could be taken from observed data from PEACE (n=[redacted]) which implied [redacted]. As described in Section 4.5.2.11 of the EAG report, the EAG explored the impact of applied a continuity correction operationalised by splitting one additional data point across all four peak ammonia categories for both patients receiving pegzilarginase treatment and patients receiving IDM, which added 0.25 to all observed values. The company noted that in the DGD the committee "*requested a scenario in which the distribution of high levels of peak ammonia in the pegzilarginase arm is between the values used in the company's base case and EAG's scenario analysis*" and set the value for pegzilarginase-treated patients halfway between the company's initial base case and the EAG's scenario, whilst leaving the values for IDM as in the company's base case. This resulted in the average distributions for peak ammonia levels for IDM- and pegzilarginase-treated patients as shown in Table 6. As the analyses undertaken by the company appears aligned to the request made by the Appraisal Committee, the EAG is content with this change although notes that the uncertainty in probabilistic sensitivity analyses would be large due [redacted].

Table 6: Deterministic distribution of peak ammonia levels

Peak ammonia level	Individualised disease management treated patients	Pegzilarginase-treated patients
≤200 µmol/litre	[redacted]	[redacted]
>200-500 µmol/litre	[redacted]	[redacted]
>500-1000 µmol/litre	[redacted]	[redacted]
>1000 µmol/litre	[redacted]	[redacted]

2.8 Altering the methodology used to determine the utility of patient with no impairment in each GMFCS health state and the impact of cognitive impairments

In its original base case, the company assumed a predefined proportion of patients with normal/mild, moderate, and severe cognitive impairment within each GMFCS health state (Section 4.2.4.6 in the EAG report[3]). The DGD states that "*The committee considered that the company's approach to applying treatment-specific cognitive disutility for GMFCS health states 1 to 3 is uncertain. But it also recognised that this approach is supported by clinical expert advice and may be conservative. The committee concluded that it is appropriate to apply treatment-specific cognitive disutility for GMFCS-1 to GMFCS-3 health states.*" In its response to the DGD, the company revised its modelling approach stating that the new approach addressed limitations in the original model, in which cognitive decline

was solely determined by GMFCS health state and the model now reflected cognitive progression independently of motor deterioration.

Transitions between cognitive progression health states by treatment

In the revised model, three cognitive impact health states were established: 'None', 'Mild' and 'Moderate/Severe'. The company modelled cognitive transitions separately, using regression analysis of BOI study data for IDM (see Table 7). The company assumed "*nominal*" cognitive improvements for a period of 36-months, for pegzilarginase-treated patients with annual transitions from mild to none assumed to be 2%, and transitions from moderate/severe to mild assumed to be 1%. Patients receiving pegzilarginase were assumed to remain in the same cognitive health state after 36 months although patients receiving IDM continued to worsen from the None and Mild cognitive health states.

Table 7: Annual transitions between cognitive health states

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

GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; MLD: metachromatic leukodystrophy.

The company stated that "*Regression analyses from the European BOI study indicated that with time, cognitive score declines with IDM.*" However, the EAG highlights that the coefficient for age [redacted] ([redacted], 95% CI: [redacted] to [redacted]) and the analysis was based on a small sample size (n= 17). The EAG believes that any relationship between cognition score and age is highly uncertain with the data points shown in Figure 3 .

Figure 3: Regression analyses using baseline data for cognition in BOI study

Cognitive score range between 0-52 where 0 indicates no cognitive problems and 52 indicates most severe cognitive problems (N=17), The source for the assumed thresholds for mild, moderate and severe cognitive impairment were not reported by the company but are believed to be Olofsson *et al*.[10]

The company reported that transition probabilities for IDM were derived from a regression and generated the cognitive transition matrix shown in Table 7, however, no further details were provided regarding the regression model used, or any covariates that were included. In the absence of sufficient detail, the EAG considers that the company's regression-based approach to modelling cognitive transitions under IDM lacks transparency and cannot be robustly validated. In addition, given the small sample size for cognitive score ranges (0-10 n=7; 11-20 n=3; 21-52 n=7), reported in Olofsson *et al*.[10] and , the EAG does not have confidence that the model is appropriate.

Revised utility values based on cognitive impairment severity

In the company's initial submission cognitive impairment was grouped into three different categories: 'none/mild'; 'moderate'; and 'severe'. In the GDG response the company changed the categories to: none; mild; and moderate/severe stating that this was the categorisation in the BOI study – the EAG does not know whether the company had access to the individual patient data to maintain the previous grouping. The company also revised the utility values associated with cognitive impairment.

The utility for moderate/severe cognitive impairment was assumed to be the average of the previously used values for moderate and severe impairment. For example, in GMFCS-II, the previous utility value for none/mild impairment was [redacted], based on the BOI study (see EAG report of the 25th of July 2024[11] as the utility values changed from the main report as an error was identified) . The corresponding value for moderate impairment was [redacted] (calculated as [redacted] - 0.280) and for severe impairment was 0.034 ([redacted] - 0.570), using disutility values derived from an Institute for Clinical and Economic Review report[6] on MLD - note that the calculated disutilities from this report are conditional on GMFCS health state. The revised utility for the moderate/severe state was calculated to be the utility associated with mild or no cognitive impairment ([redacted]) minus the average disutility associated with a moderate impairment (0.280) and a severe impairment (0.570) which is 0.425. This results in an estimated utility for the moderate/severe state for patients in GMFCS-II of [redacted] which is ([redacted] – 0.425).

The company estimated the disutility of being in the mild cognitive state, as opposed to a none/mild combined state, by using data from the BOI study. These data suggested a disutility of [redacted] for mild impairment and a disutility of [redacted] for moderate/severe impairment which is a difference in utility of [redacted]. As an example of the company's calculations, in GMFCS II, for mild cognitive impairment the utility is [redacted] ([redacted] + [redacted]) which is the utility for moderate/severe patients in GMFCS-II plus the difference in disutility between moderate/severe cognitive impairment and mild cognitive impairment. The company did not state why it did not use the BOI study data for moderate/severe impairments.

The utility of patients with no cognitive impairment was calculated as the utility of moderate/severe impairment plus the disutility associated with moderate/severe impairment. As an example of the company's calculations, in GMFCS II, the utility for the no impairment is assumed to be [redacted] ([redacted] + [redacted]). The EAG comments that this introduces an inconsistency in that the approach uses disutilities for moderate/severe ([redacted] and [redacted] respectively – an average of [redacted]) estimated from the MLD report to calculate utility values for the moderate/severe health state but then uses disutility from the BOI study ([redacted]) to estimate the utility in the no impairment state. The EAG believes that this overestimates the utility in patients with no cognitive impairment, regardless of other limitations.

Figure 4 presents the utility values corresponding to each combination of cognitive impairment level and GMFCS health state. It also provides examples on how the original and new utility values were calculated. The revised utility values for the no cognitive impairment category are higher than the values originally submitted by the company. Notably, the utility value for GMFCS-I with no cognitive impairment is very high, at [redacted] If patients improved diet, see Section 2.9, [redacted].

Figure 4: The utility values used in the previous base case and the revised base case

GMFCS: Gross Motor Function Classification System

Example of calculation for original utilities

1) GMFCS-I for none/mild impairment: [redacted] (taken from BOI study)
2) GMFCS-I for moderate impairment: [redacted] (GMFCS-I none/mild value) - 0.241 (disutility estimated from MLD report) = [redacted]; GMFCS-I for severe impairment: [redacted] - 0.531 (disutility estimated from MLD report) = [redacted]

Example of calculation for new utilities

3) GMFCS-I for moderate/severe impairment: 0.5*([redacted]) (see example of calculation 2) = [redacted]
4) GMFCS-I for mild impairment: [redacted] (see example of calculation 3) + ([redacted] (the difference between the disutilities between the moderate/severe and mild groups from the BOI study) = [redacted]; GMFCS-I for no impairment: [redacted] (see example of calculation 3) + [redacted] (disutility in moderate/severe from the BOI study) = [redacted]

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. For example, as seen in Figure 5, patient within GMFCS-II, have a range of cognitive scores from [redacted], indicating that there are patients with severe cognitive impairment in GMFCS-II, but their EQ-5D-3L values have been used to generate a value for people with no or mild cognitive impairment.

Figure 5: Relationship between GMFCS health states and cognitive score (from the BOI study report, Figure 4)

GMFCS range between 1-5 where 1 indicates the best level. Cognitive score range between 0-52 where 0 indicates no cognitive problems and 52 indicates most severe cognitive problems (N=17)

Importantly, the disutilities associated with mild or moderate/severe health states used by the company are likely to be confounded because the GMFCS health state of the patient has not be considered. If there is a positive correlation between cognitive impairment and GMFCS health state, which is likely if both measures typically become more severe as patients age, then patients with more advanced cognitive impairment would also be more likely to have a more severe GMFCS health state. More severe GMFCS health states would also contribute to a lower EQ-5D-3L scores, which if not controlled for within a statistical analysis would overestimate the disutility associated with cognitive impairment states.

The EAG also highlights the EQ-5D-5L utility values reported by Olofsson *et al.,*[10] based on the same patient population. For individuals with no or mild cognitive impairment (score range 0–20), the mean utility was 0.845 for those in GMFCS–I and –II (SD = 0.161, n = 8) and 0.151 for those in GMFCS–III to –V (based on a single observation, n = 1; SD not applicable). For individuals with moderate to severe/extreme cognitive impairment (score range 21–52), the utility was 0.499 in GMFCS–I and –II (SD = 0.237, n = 5) and 0.029 in GMFCS–III to –V (SD = 0.001, n = 2). Despite the small sample sizes — particularly in higher GMFCS levels — these findings support the assumption that both functional status and cognitive impairment substantially impact utility although the disutility values (using the EQ-5D-5L) are [redacted] than that used by the company, being 0.346 for patients with moderate/severe cognitive impairment in GMFCS-I or -II, and 0.122 in patients with moderate/severe cognitive

impairment in GMFCS-III, IV, or -V. Whilst the EAG acknowledges both the use of EQ-5D-5L values rather EQ-5D-3L values, and the small sample size, the disutility is noticeably different, potentially as the correlation between worse cognitive health state and more severe GMFCS health states have been controlled for, to some extent, in the Olofsson *et al.*[10] study. The EAG also notes a potential contradiction in the company's position in terms of the high utility assumed for patients and the low assumed weight of patients; this is discussed in Section 2.15.

Given the limitations associated with the company's revised methodology and potential lack of face validity in the utility value assumed for patients with no cognitive impairment in GMFCS-I the EAG prefers an analysis using the method in the EAG's previous base case.

2.9 Increasing the proportion of patients who receive a utility gain due to an improved diet whilst on pegzilarginase treatment to 83.3%

In its original base case, the company assumed that 24.7% of patients would have utility gains due to pegzilarginase treatment and a more liberal diet. The value of 24.7% was calculated as the number of people who increased their dietary protein by more than 15% on IDM (18.2% of patients) subtracted from the proportion who achieved this with pegzilarginase treatment (42.9% of patients). The company has updated this value to 83.3% based on RWE from France,[9] stating that "*83.3% of pegzilarginase treated patients were able to increase their average daily amount of natural protein with a mean of +3.8 g/day (+20.6%) at 6 months (n=12), and +8.9 g/day (+44.9%) at 12 months (n=3)*". The EAG comments that the percentage of patients who increased protein intake by 15% or more (as used in the original submission) was not reported. From Figure 2 in the French RWE study,[9] it appears that [redacted] ([redacted]%) patients in the treatment-naïve group increased protein intake by more than 15%, over a follow up period of 12 months, suggesting that a value of 83.3% is too high.

The EAG also comments that the RWE data has not been adjusted to consider a placebo response, as happened in the company submission. If a placebo response in the RWE was at least as good as in PEACE (18.2% of patients increased protein intake by over 15%) then greater than 100% of patients would be receiving a benefit in the company's new value (as 83.3% + 18.2% = 101.5%). Without additional data on all patients within the RWE study, the EAG cannot provide a robust estimate of the true value of patients who could increase protein intake by more than 15%. The EAG provides the Appraisal Committee with a scenario analysis where the proportion with increased utility due to diet liberalisation is estimated to be [redacted], calculated as the percentage extracted from Figure 2 of the RWE paper ([redacted]), minus the proportion of patients who had a placebo response in PEACE (18.2%), A second scenario analysis has been undertaken using a value of 24.7%, as in the company's original base case.

2.10 Revising the time spent in each health state for patients on IDM

In the company's original base case, Gross Motor Function Classification System parts D and E (GMFM-DE) scores were used to model long-term progression for IDM (as detailed Section 4.2.4.3 in the EAG report[3]). The GMFM-DE cut-offs to transition between GMFCS health states in the company's base case were estimated as being halfway between the lower CI for the better health state and the upper CI for the worse health state. For example, the GMFM-DE score threshold for changing between GMFCS-I and GMFCS-II was assumed to be [redacted], (the midpoint of [redacted] and [redacted]). An annual reduction of 2.66 in the GMFM-DE score was assumed (Section 4.5.2.3 in the EAG report[3]). In its response to the DGD, the company updated the assumed annual decline in GMFM-DE score to 3.17, which assumes that patients will move linearly from the maximum GMFM-DE score of 111 to the minimum score of 0 over a 35-year period. No rationale was provided by the company for this assumption. The GMFM-DE cut-offs for GMFCS-I to -IV were then redefined "*to ensure that the average age* [within a health state provided by the Delphi panel] *occurs halfway through the time spent in each GMFCS health state*". A different approach was needed for GMFCS-V as the average age in GMFCS-IV is higher than in GMFCS-V as shown in Table 8. The company assumed that patients would leave GMFCS-IV at age 32 stating that this "*aligns with the consensus from clinicians that 90% of patients will be dead by age 32. Since clinicians noted during the Delphi panel that patients are likely to remain in GMFCS IV for an extended period, the Company considers the assumption, that patients progressing from GMFCS IV have an average age of 32 years, to be clinically plausible.*" The GMFM-DE cut-offs are provided in Table 8 and are shown graphically in Figure 6.

Table 8: Mean age for patients within GMFCS health states and estimated GMFM-DE cut-offs for those treated with IDM

Health state	Mean age (years) within health state	GMFM-DE
GMFCS-I	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]
GMFCS-III	[redacted]	[redacted]
GMFCS-IV	[redacted]	[redacted]
GMFCS-V	[redacted]	[redacted]

GMFCS: Gross Motor Function Classification System; GMFM-DE Gross Motor Function Classification System parts D and E; IDM: individualised disease management; MLD: metachromatic leukodystrophy.

Figure 6: Assumed linear relationship between age and GMFM-DE score with mean age distribution across GMFCS health states

The horizontal arrows reflect the estimated time spent within each health state, derived from GMFM-DE cut-offs and the fixed annual decline.
GMFCS: Gross Motor Function Classification System GMFM-DE; GMFM-DE: Gross Motor Function Classification System parts D and E

To estimate the duration spent in each GMFCS health states for patients treated with IDM, the company divided the GMFM-DE range for each state by the assumed annual decrement of 3.17. The estimated transition probabilities are presented in Table 9 for the revised company base case and the previous EAG base case. It is seen that the revised company's base case has a much faster progression through the earlier health states for patients on IDM than in its initial submission due to the small duration of time spent in GMFCS-I.

Table 9: GMFM-DE score cut-off and estimated progression probability for patients receiving IDM for patients receiving IDM

	Observed GMFM-DE score (n=22), mean (95% CI)	EAG's base-case			Company's new submission		
		Cut-off of GMFM-DE	Estimated time spent within each health state (years)	Transition probability per cycle	Cut-off of GMFM-DE	Estimated time spent within each health state (years)	Transition probability per cycle
GMFCS-I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GMFCS: Gross Motor Function Classification System; IDM: individualised disease management.

The EAG notes that the new methodology used by the company is reliant on a number of assumptions that are uncertain. These primarily include the clinicians estimate of average age within each GMFCS health states and also that there is a linear progression from the maximum GMFM-DE score of 111 to the minimum score of 0 over a 35-year period. The EAG also believes that the company should have used the averages ages agreed by the Delphi panel rather than GMFM-DE score ranges. Transition probabilities based on the average ages indicate a slower progression through GMFCS-II and -III, but quicker progression through GMFCS-IV. (Table 10)

Table 10: Transition probabilities for patients receiving IDM when using the average ages from the Delphi panel rather than the GMFCS-DE ranges

Transitioning from	Average age derived from the Delphi panel	Number of years to the next GMFCS health state	Transition probability per cycle
GMFCS-I	[redacted]	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]	[redacted]
GMFCS-III	[redacted]	[redacted]	[redacted]
GMFCS-IV	[redacted]	[redacted]	[redacted]

GMFCS: Gross Motor Function Classification System; IDM: individualised disease management.

The EAG believes that there is no clear reason to think that the new methodology is superior to that in the EAG base case which uses the lower 95% confidence interval (2.66 decrease of GMFM DE score per additional year of age) of the linear regression undertaken by the committee between GMFM DE score and age. Sensitivity analyses have been run where the transition probabilities from the EAG base case have been used, and where the company's revised method has been used, but the transition probabilities were calculated from the average ages agreed by the Delphi panel (Table 10).

2.11 Assuming that each year 5% of patients move from GMFCS-II and -III to GMFCS-V

In its original company model, there was a progression sequentially through the health states until a patient reached GMFCS-V or had died. In the company's response to the DGD, the company assumed that patients could move directly from GMFCS-II and GMFCS-III to GMFCS-V due to a severe HAC. At the Delphi panel, the company states that there was a "*consensus that 5-10% of patients progress from GMFCS II or GMFCS III to GMFCS V per year, based on clinical observations that patients may experience early disease progression from severe HACs in early childhood*" The company states that it conservatively used 5% (which represents approximately one sixth of those patients having a HAC on IDM).

The EAG has two key concerns with this approach. The first is that is assumed that transitions from GMFCS-II and GMFCS-III to GMFCS-V are impossible for patients treated with pegzilarginase despite a possibility that severe HACs can occur with this treatment, as shown in Table 6. The second is that the clinicians explicitly stated that movement from GMFCS-II and GMFCS-III to GMFCS-V would happen in "*early childhood*", yet this probability is modelled for all ages. The EAG has run a sensitivity analysis where transitions from GMFCS-II and -III to GMFCS-V are not assumed possible for patients aged 16 years or older, and that it is also possible for patients treated with pegzilarginase to transition between these health states up to 15 years of age. The relative risk of transition for pegzilarginase-treated compared to IDM-treatment patients was estimated by the EAG to be the product of the relative risk of a HAC after 24 weeks as used in the company's initial submission ([redacted]) and the assumed ratio that a HAC was of >500 µmol/litre ([redacted]) which is [redacted], meaning that the transitions from GMFCS-II and -III to GMFCS-V would be approximately [redacted] of the IDM value for pegzilarginase-treated patients.

2.12 Changing the standardised mortality rates for patients receiving IDM

In the company's original base, it was assumed that nearly all patients receiving IDM would die at, or before, 35 years of age with the model calibrated to obtain standardised mortality rates (SMRs) for patients treated with IDM. This was achieved by generating a multiplier for patients receiving IDM compared with pegzilarginase, assuming that SMRs by GMFCS health states for pegzilarginase could be generalised from MLD, but divided by 1.25 to account for a lower risk of toxitiy.[12] This resulted in a multiplier of 800 for IDM-treated patients compared with pegzilarginase-treated patients.

Table 11: The SMRs applied in different models

Health State	SMR (initial company submission)		SMR (EAG base case)		SMR (revised company base case)	
	IDM	Peg	IDM	Peg	IDM	Peg
GMFCS-I	928.0	1.16	232.0	1.16	[redacted]	[redacted]
GMFCS-II	1056.0	1.32	264.0	1.32	[redacted]	[redacted]
GMFCS-III	1440.0	1.80	360.0	1.80	[redacted]	[redacted]
GMFCS-IV	1440.0	1.80	360.0	1.80	[redacted]	[redacted]
GMFCS-V	6508.8	8.14	1627.2	8.14	[redacted]	[redacted]

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

The Appraisal Committee "*noted the lack of survival data from the clinical trials used to inform mortality in the economic model*" but "*concluded that the [EAG] scenario analysis in which nearly all people in the standard care arm die at age 50 is appropriate.*"

In its response to the DGD, the company did not use the EAG scenario analysis but attempted to improve the assumptions and values used in the model through the Delphi panel. The company states that the panel came to a consensus that:

- Diagnosis typically occurs at 5.1 years of age.
- That the distribution between GMFCS health state when patients receiving IDM die (excluding due to HACs) are: 5.3% (GMFCS-I), 6.1% (GMFCS-II), 13.9% (GMFCS-III), 32.3% (GMFCS-IV), and 42.3% (GMFCS- V).
- That 90% of patients receiving IDM are expected to die by age 32.

The EAG highlights that whether there was a consensus on each of these points is debatable, with: 4 out of 7 clinicians agreeing or strongly agreeing with age of diagnosis; with 3 out of 7 clinicians agreeing or strongly agreeing with the distribution between GMFCS health states at death (excluding death related to HACs) for patients receiving IDM; and with 1 out of 7 clinicians agreeing or strongly agreeing with the age at which 90% of patients receiving IDM are dead. The EAG believes that this uncertainty is increased when there are three components, in all of which, it is questionable that there has been a consensus reached.

The company recalibrated the SMRs using Delphi panel estimates on both the proportions of deaths within each GMFCS health state, and the age at which 90% of the population receiving IDM would have died, and the Committee's assumption that nearly all patients would have died by 50 years of age. The calibration was undertaken in the following manner. Firstly, all patients were assigned to GMFCS-I at baseline, with a starting age set of 5.1 years to reflect the estimated age at diagnosis. Secondly, a multiplication factor was applied to the age-matched general population SMRs so that at 50 years of

age, 99% of IDM-treated patients had died. Thirdly, individual multipliers for each health state were calibrated so that the distribution of deaths (excluding those due to HACs) across GMFCS states matched those from the Delphi panel. Finally, the SMR for GMFCS-V was recalibrated to ensure 90% mortality by 32 years of age; the company did not state why only the SMR in GMFCS-V was adjusted in this step, but the EAG believes that this is a constraint of the method (Goal Seek in Excel) used for calibration. The final SMRs applied in the base case are GMFCS-I ([redacted]), -II ([redacted]), -III ([redacted]), -IV ([redacted]), and -V ([redacted]). Additionally, a scenario analysis modelled 90% mortality by 32 years of age, consistent with Delphi panel feedback, using the same calibration method described above. In this scenario analysis the SMRs applied are GMFCS-I ([redacted]), -II ([redacted]), -III ([redacted]), -IV ([redacted]), and -V ([redacted]).

The EAG notes that the SMR assigned to GMFCS-V is markedly lower than that of GMFCS-IV (being approximately [redacted] the value). This appears counterintuitive, as GMFCS-V represents the most severe level of functional impairment, and a higher mortality risk would be expected relative to GMFCS-IV. This discrepancy raises concerns regarding face validity and the methodology of estimating the SMRs in each GMFCS health state. The EAG also highlights that if people receiving IDM can transition from the GMFCS-II and GMFCS-III health states to GMFCS-V (See Section 2.11) then this could result in a relatively large number of people surviving in GMFCS-V (which has high healthcare costs, low patient utility and high caregiver disutility thus favouring pegzilarginase).

The EAG also highlights that during the calibration process, the estimated SMRs were sensitive to the order in which GMFCS health states were calibrated, particularly for the SMR calibrated last (which was GMFCS-V in the company's revised model) with different sequences resulting in notably different SMR estimates. It may be the case that if the company had used a more complex method than Goal Seek, such as Solver, then further constraints could have been added to ensure that the SMRs increases as patient severity increases. The EAG further comments that SMRs have less of an impact than anticipated when the underlying general population mortality rate is low even when the SMR applied appears to be very high.

The EAG believes that there are many limitations in the company's new approach which include: the uncertainty in the Delphi panel estimates and the methodology associated with the calibration that forces the value of the SMR for GMFCS-V to be low.

The EAG has run an analysis where a common multiplier was applied to the SMRs for pegzilarginase at each GMFCS health state (see Table 12) in order that 10% of patients treated with IDM were alive at 32 years of age and 0.05% were alive at 50 years of age. For time reasons, the SMRs were calibrated while applying the other C1 scenario assumptions rather in isolation. In this analysis the SMRs applied are GMFCS-I (89), -II (101), -III (138), -IV (138), and -V (623). The EAG believes that the SMRs have

more face validity than those in the company's base case, although more people die in GMFCS-V than estimated by the Delphi panel as shown in Table 13. These extra deaths in GMFCS-V for IDM patients are likely favourable to pegzilarginase.

Table 12: SMRs applied in the company's revised base case and the EAG-preferred analysis

Health State	SMR (revised company base case)		EAG-preferred analysis	
	IDM	Peg	IDM	Peg
GMFCS-I	[redacted]	[redacted]	88.89	1.16
GMFCS-II	[redacted]	[redacted]	101.15	1.32
GMFCS-III	[redacted]	[redacted]	137.94	68.97
GMFCS-IV	[redacted]	[redacted]	137.94	68.97
GMFCS-V	[redacted]	[redacted]	623.47	311.74

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

Table 13: The proportion of deaths (excluding those due to HACs) in each GMFCS health state for those treated with IDM estimated by the Delphi panel and generated in the EAG's new analysis

Health State	EAG-preferred analysis	
	Delphi Panel	Value in EAG base case
GMFCS-I	5.3%	1.2%
GMFCS-II	6.1%	3.1%
GMFCS-III	13.9%	13.1%
GMFCS-IV	32.3%	11.9%
GMFCS-V	42.3%	70.7%

EAG: External Assessment Group; GMFCS: Gross Motor Function Classification System; IDM: individualised disease management.

2.13 Setting the SMR for pegzilarginase-treated patients to half that of IDM-treated patients for those in GMFCS-III to GMFCS-V

Having calibrated the SMRs for patients receiving IDM (see Section 2.12) the company "*acknowledged that, if the pegzilarginase standardised mortality rates remain unadjusted from the Company's original base case, patients treated with pegzilarginase show significantly improved overall survival due to updated time on treatment assumptions (See Section 11; implemented in line with feedback from the Delphi panel that no patients would discontinue treatment after one year of initiating pegzilarginase) compared to the Company's original base. Therefore, in the updated base case, the Company have conservatively set the pegzilarginase SMRs in GMFCS III-V to half that of those treated with IDM in the same GMFCS state. This reflects that patients treated with pegzilarginase in latter GMFCS states would have improved survival, but prevents survival returning to near general population norms. As noted by clinicians in the Delphi panel, patients treated with pegzilarginase in GMFCS I and II are likely to reach full or near-full health, therefore the Company considers it appropriate to maintain an*

SMR of 1.16 in GMFCS I and 1.32 in GMFCS II as in the Company's original base case." The new calibrated SMRs for patients treated with IDM are shown in Table 14.

Table 14: SMRs in the company's base case associated with GMFCS health state and treatment

Health State	SMR for patients treated with IDM in company's base case	SMR for patients treated with pegzilarginase in company's base case	SMR for patients treated with IDM in EAG sensitivity analysis	SMR for patients treated with pegzilarginase in EAG sensitivity analysis
GMFCS-I	[redacted]	[redacted]	88.89	44.45
GMFCS-II	[redacted]	[redacted]	101.15	50.58
GMFCS-III	[redacted]	[redacted]	137.94	68.97
GMFCS-IV	[redacted]	[redacted]	137.94	68.97
GMFCS-V	[redacted]	[redacted]	623.47	311.74

IDM: individualised disease management; SMR standardised mortality rate

The EAG notes the company's attempts to adjust what is considered to be overly long survival for pegzilarginase-treated patients but cannot determine if the changes made are conservative as the impact of pegzilarginase on overall survival are uncertain. The company did not attempt to ask clinicians at the Delphi panel the likely survival for patients with ARG1-D treated with pegzilarginase, maybe because this is so uncertain, so there are no robust data available to either the company or the EAG. The EAG highlights that by increasing the SMR in more severe GMFCS health states the cost-effectiveness of pegzilarginase is likely to improve as less time is spent in states with higher costs and with more impact on the utility of patients and caregivers. It also remains to be determined if clinicians would continue to provide pegzilarginase to patients in the most severe health states due to the high acquisition cost of the intervention. The EAG has run an analysis where all SMRs for pegzilarginase-treated patients are half that of IDM-treated patients to show the impact of applying the change to all GMFCS health states not just GMFCS-III to -V.

2.14 Correcting a minor error in the trace for pegzilarginase and IDM when applying cognitive disutilities

When preparing its response to the DGD, the company identified a minor error (occurring in both the pegzilarginase and IDM worksheets). This has been corrected, and in isolation, slightly increases the ICER. The EAG is content with this change.

2.15 Amending the ratio of weight between people with ARG1-D treated with pegzilarginase and the age-matched general population

In the company's previous base case it was assumed that patients with ARG1-D would weigh less than the average population due to the manifestation of the disease. The company assumed that patients under 16 years of age would weigh 91% of an age-matched population, whereas patients 16 years of age or older were assumed to weigh 77% of an age-matched population. In the DGD, the Appraisal Committee commented that "*scenario analyses using heavier weights are more plausible*", and that "*It considered that assuming adults would weigh 95% of the expected general population weight was the most appropriate scenario presented*".

The company disagreed with the Appraisal Committee and provided post-hoc analysis from PEACE that indicated that patients aged 13 years and over treated with pegzilarginase has "*a trend suggesting reducing weight compared to the general population after an initial rise following treatment initiation*" as shown in Figure 7. The average weight ratio was [redacted].

Figure 7: Weight of patients aged 13 years or older as a percentage of the general populations' weight according to time since starting pegzilarginase in PEACE

[redacted]

The values below each data point demonstrates the sample size.

However, for patients who may benefit earlier in their life from the advantages of pegzilarginase treatment (those 12 years or younger) the company states that "*their weight tends to slowly approach population norms.*" This is shown in Figure 8 where the average weight ratio was [redacted].

Figure 8: Weight of patients under 13 years as a percentage of the general populations' weight according to time since starting pegzilarginase in PEACE

The values below each data point demonstrates the sample size.

As anticipated in a rare disease, the patient numbers are low in both groups and the company decided to use the weight ratio of [redacted] within its model.

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 ([redacted]). 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 ([redacted]).

The EAG highlights the potential contradiction in the high utility for patients in less severe GMFCS states with no cognitive impairment (see Section 2.8) with the assumption relating to the low weight of patients. Contradictory positions include the fact that patients have a high underlying utility which is increased through benefits in diets, but that these do not gain weight with pegzilarginase treatment, as "*Given that the average age at baseline in the model is 13 years, patients will not start treatment early enough to benefit from growth improvements"* and that "*the increased protein intake associated with pegzilarginase would not alter muscle mass, as patients are unable to exercise due to spasticity*". The EAG highlights that patients who cannot exercise, or benefit from growth improvements, are unlikely to have the extremely high utility values assumed by the company in its base case and that

for patients who are treated at a young age may well benefit from growth improvements. The EAG has run sensitivity analysis (see Section 2.6) increasing the costs of pegzilarginase by 10% and 20%.

3. Additional analyses not related to changes made by the company

This sections describes additional analyses undertaken by the EAG that were not related to changes made by the company to the EAG base case. These include sensitivity analyses run by the EAG, that were not part of the original base case but that were preferred by the committee and also additional analyses that have been thought pertinent following the first Appraisal Committee meeting.

3.1 Exclusion of incremental QALYs associated with caregivers in calculating the QALY weight

In the company's original submission, the company included QALY losses associated with caregiver disutility in the QALY weight calculations. However, the appraisal committee concluded that *"it was appropriate to remove carer disutility from the QALY weighting calculation.*" The company did not remove the benefits associated with caregivers when calculating the weight for QALYs so this has been addressed in the EAG's analysis.

3.2 Alternative starting distribution by GMFCS health states

In the DGD, it is stated that *"The committee considered that the starting distributions from the European burden of illness survey is more representative of clinical practice in the NHS in England than the company's approach. It concluded that the starting distributions of people across each GMFCS health state informed by the European burden of illness survey was the most appropriate option."* This change was not made by the company, however, the EAG changed the starting distributions to those observed in the BOI study (see Table 15).

Table 15: Alternative starting distribution between GMFCS states

	Proportion of patients starting in GMFCS health state					**Source**
	I	**II**	**III**	**IV**	**V**	
Company's base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from the PEACE study, study 101A/102A, and BOI survey (n=[redacted])
Committee preferred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	BOI survey (n=[redacted])

3.3 Transition probabilities for pegzilarginase

Regarding the long-term progression for pegzilarginase, it is stated that "*The committee concluded that assuming people in the pegzilarginase arm remain in the same GMFCS health state after 3 years is appropriate for decision making, but this was associated with high levels of uncertainty."* in the DGD. Considering the large uncertainty, the EAG presents analyses relating to two scenarios: a) that after 3 years of treatment the risk of transition to the next worse GMFCS state is 10% of that associated with

IDM; b) that after 3 years of treatment the risk of transition to the next worse GMFCS state is 20% of that associated with IDM.

3.4 Potential underestimation of administration cost

According to the SmPC, following at 8 weeks of treatment, pegzilarginase may be self-administered or administered by a caregiver, provided that appropriate training in subcutaneous injection has been given. In the company's base case, it was assumed that during the first cycle (first 3 months), 100% of administrations would occur in a hospital setting, with 90% administered subcutaneously and 10% intravenously. In subsequent cycles, it was assumed that 90% of patients received home-based subcutaneous administration in long-term, while the remaining 10% continued to receive subcutaneous administration in a hospital setting. The NICE technical team requested to explore the uncertainty around the setting and route of administration. Therefore, the EAG ran two further scenarios which are presented in Table 16.

Table 16: Alternative scenario for long-term administration route

	Company's base case	EAG's scenario A	EAG's scenario B
Proportion of pegzilarginase administrations by route and setting			
IV in hospital	-	-	10%
SC in hospital	10%	20%	30%
SC at home	90%	80%	60%
Cost per cycle (£)	16.79	33.59	117.56

IV – intravenous injection; SC – subcutaneous.

3.5 The distribution of female

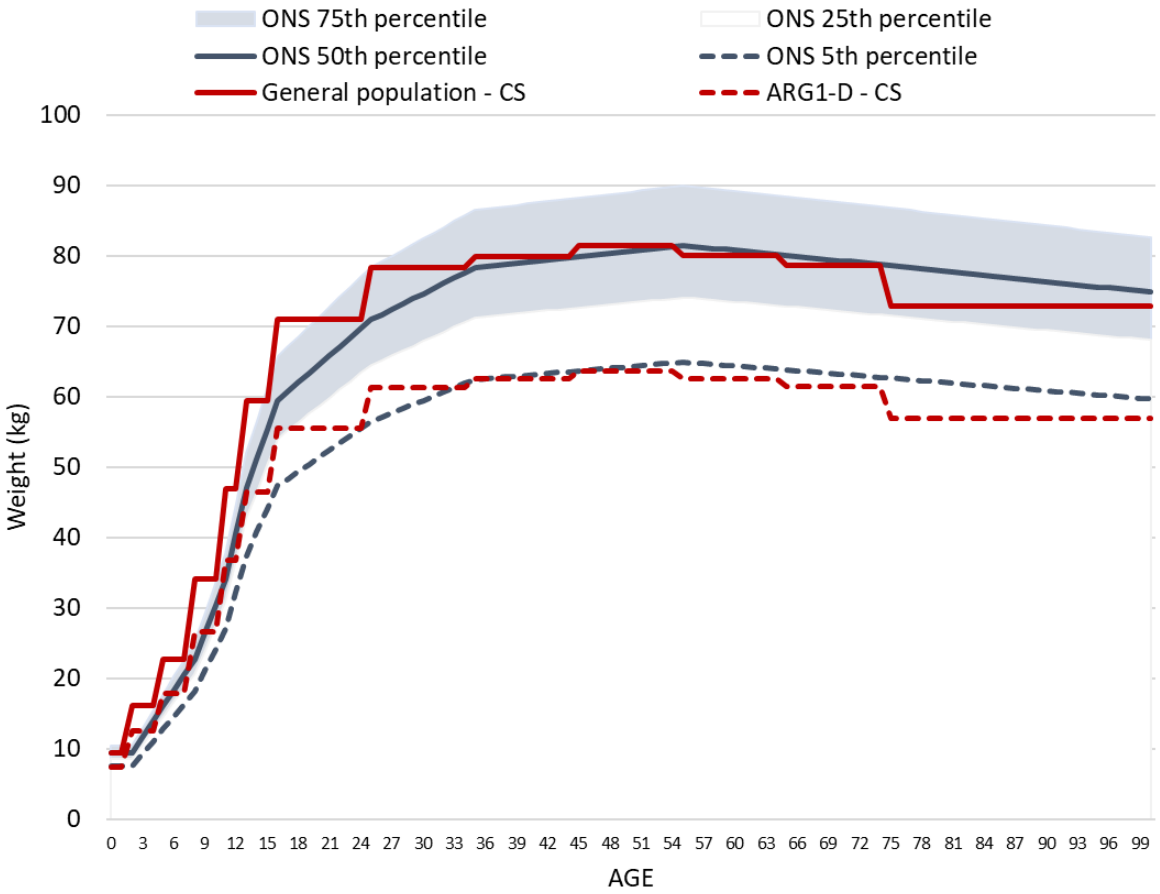
According to Bin Sawad *et al.*,[13] which is a systematic review related to epidemiology of arginase 1 deficiency, data from fifteen studies demonstrated an almost equal sex distribution, with females accounting for 49% of patients. This contrasts with the assumption in the company's base case where 56% of patients were female and could be important as pegzilarginase is a weight-based dose and on average males are heavier than females.

3.6 Estimation of the weight in the general population

For calculating dose, the company's base case use a weight data from the Health Survey for England 2019.[14] However, this had the disadvantage that weight was assumed constant between some age bands (3- or 10-year groups) rather than linearly changing An alternative weight dataset was provided by the NICE technical team, stated to be sourced from the Office for National Statistics (ONS). The dataset contains the following percentiles: 5th, 25th, 50th and 75th for individual years. The average weight by age are shown in Figure 9. The EAG notes that, although the weights used in the company's model were grouped into intervals rather than presented as continuous age-specific values, the overall trend was broadly consistent with the ONS data. For information, the estimated weights for patients with

ARG1-D used in the company's model is close to the 5th percentile of the general population weight distribution. A scenario analysis was undertaken by the EAG using age-specific 50th percentile weight data, as provided by the NICE technical team, although this may underestimate the average weight if there is a long tail in the distribution.

Figure 9: Comparison of age-based weights between Health Survey for England data and Office for National Statistics data



ARG1-D – arginase-1 deficiency; CS – company submission; ONS – office for national statistics.
This figure compares age-specific weight data from the general UK population (5th, 25th, 50th, and 75th percentiles, provided by the NICE technology team) with the weight used in the company's base case. The solid red line represents the general population weights applied in the company submission (CS), while the dashed red line shows the weights assumed for patients with ARG1-D. The shaded blue area represents the interquartile range (25th to 75th percentile) of ONS weight data, with the dark blue line indicating the 50th percentile.

4. Exploratory analyses undertaken by the EAG

4.1 Overview of the EAG's exploratory analyses

The EAG undertook exploratory analyses to address the key points identified within its critical appraisal of the company's response or after the DGD. Many issues raised are related to the use of alternative plausible assumptions rather than being points where the EAG fundamentally disagrees with the company's assumptions.

The EAG has provided an analysis where all C1 changes are made simultaneously, and where C2 and C3 changes are made independently to both the company's error-corrected base case, and to the analysis where all C1 changes have been simultaneously implemented. All scenario analyses were undertaken using the deterministic version of the model although probabilistic ICERs were also generated for all C1-combined analysis.

All analyses presented in this section reflect the PAS price of pegzilarginase and include the QALY weighting recommended within the NICE manual. The changes for each analysis are provided in Section 4.2 with the results are presented in Section 4.3. Table 17 summarises the changes made by the EAG and also whether these are categorised as C1, C2 or C3 changes.

Table 17: Summary of EAG's analyses based on the company's submitted model

	Changes
Analyses not related to the company changes to the EAG's base case model	
Calculation of weighted incremental QALYs	C1 – Exclusion of incremental QALYs associated with caregivers
Programming error related to caregiver QALY losses	C1 – Correction of this error
Starting distribution between GMFCS health states	C1 – Apply the GMFCS distributions informed by the European burden of illness survey
Percentage of female patients	C1 – Assume 50% of female
Long-term transition probabilities between GMFCS states for pegzilarginase after 3 years	C2 – Assume the risk of transition to the next worse GMFCS state is 10% of that associated with IDM; C2 – Assume the risk of transition to the next worse GMFCS state is 20% of that associated with IDM
Route of administration	C2 – Assume 20% of subcutaneous administrations occur in a hospital setting C3 – Assume 10% of intravenous and that 30% of subcutaneous administrations occur in a hospital setting
Weight of general population	C2 – Use the weight data for general population that was provided by the NICE technical team sourced from the Office of National Statistics
Analyses related to the company changes to the EAG's base case model (see Section 2)	
1. Compliance	None
2. Discontinuation	C1 – Loglogistic. C3 – Exponential at 2% per year
3. Costs of death	None

	Changes
4. Cost of diet medications	None
5. Caregiver disutility	C1 – Assume [redacted]% of families have more than one child with ARG1-D. C2 – Assume additional caregiver burden when there is more than one-child with ARG1-D is one-quarter that of the company's estimate, is one-half that of the company's estimate and three-quarters that of the company's estimate (three analyses). C2 – Revert to EAG scenario analysis for families with a single child with ARG1-D.
6. Average dose and drug wastage	C2 – Assume a dose of 16mg/kg per person. C2 – Assume no drug wastage and using a distribution of weight for patients. C2 – Assume increase in the cost of pegzilarginase by 10% C3 – Assume full drug wastage and using a distribution of weight for patients. C3 – Assume increase in the cost of pegzilarginase by 20%
7. Distribution of peak ammonia level during a HAC	None
8. Independent modelling of cognitive progression from the GMFCS states by treatment arm; revising baseline utility values and the disutility assumed from cognitive impairment	C1 – Revert to company's initial method for estimating baseline utility and disutility associated with cognitive impairment.
9. Percentage of patients with improved utility due to an improved diet	C1 – Using a value of [redacted]. C2 – Assuming a value of 24.7%
10. Revising the time spent in each GMFCS health state	C1 – Using transition probabilities to use the difference in average ages in each GMFCS health state rather than GMFM-DE ranges. C2 – Reverting to the transition probabilities between GMFCS states in the previous EAG base case.
11. Assuming that patients can transition from GMFCS-II or -III to GMFCS-V	C1 – Stopping all such transitions after 15 years of age; Using a relative risk for transition to GMFCS-V for pegzilarginase treated patients of [redacted]
12. Changing the SMRs for patients receiving IDM	C1 - Revert to the previous company's approach; assume that 10% of patients diagnosed at age 5.1 in GMFCS I remain alive at age 32
13. Changing the SMRs for patients receiving pegzilarginase	C2 – As in Table 14, where SMR for pegzilarginase is half of that for IDM
14. Correcting a minor error in the trace for pegzilarginase and IDM when applying cognitive disutilities	None
15. Amending the ratio of weight between people with ARG1-D treated with pegzilarginase and the age-matched general population	C2 – Using a weight ratio of 0.900

Grouped into 3 categories: C1 - Likely to be more appropriate than the company's value, C2 - unclear of whether it is more appropriate than the company's value, and C3 – Not likely to be appropriate, but potentially informative to the Appraisal Committee as putting a bound on the ICER.
GMFCS: Gross Motor Function Classification System

4.2 EAG's exploratory analyses by categories

The following changes were made to the company's base case to from the company's base case.

Category C1:

C1-1. Removing QALY losses for carers when calculating the QALY weight used to calculate the weighted ICER (see Section 3.1)

C1-2. Correction of a programming error (see Section 2.5)

C1-3. Using the distribution for starting GMFCS state from the BOI study (see Section 3.2)

C1-4. Assuming 50% of patients are female (see Section 3.5)

C1-5. Applying a log-logistic model for the distribution of treatment discontinuation (see Section 2.2)

C1-6. Assuming [redacted] of families have more than one child with ARG1-D (see Section 2.3)

C1-7. Reverting to the company's original method for estimating disutility from cognitive impairment (see Section 2.8)

C1-8. Updating the proportion of patients with utility gains from improved diet to [redacted] (see Section 2.9)

C1-9. Using transition probabilities derived from the difference in average ages in each GMFCS health state (see Section 2.10)

C1-10. Transitions from GMFCS-II/III to GMFCS-V stopped after age 16; applied relative risk for transitions to GMFCS-V for pegzilarginase-treated patients. (see Section 2.11)

C1-11. Applying recalibrated SMRs using the original method, assuming 10% of patients diagnosed at age 5.1 in GMFCS-I remain alive at 32 years of age (see Section 2.12)

The following EAG's additional sensitivity analyses were undertaken using both the company's base case, and the analysis where all C1 changes have been simultaneously implemented.

Category C2:

C2-1. Using the proportion of patients with utility gains from improved diet to 24.7% (see Section 2.9)

C2-2. Applying caregiver burden for families with multiple children at 25% of the company's estimate (see Section 2.5)

C2-3. Applying caregiver burden for families with multiple children at 50% of the company's estimate (see Section 2.5)

C2-4. Applying caregiver burden for families with multiple children at 75% of the company's estimate (see Section 2.5)

C2-5. Reverting to EAG scenario for families with a single child with ARG1-D (see Section 2.5)

C2-6. Assuming a fixed dose of 16 mg/kg per person (see Section 2.6)

C2-7. Assuming no drug wastage and applying a weight distribution for patients (see Section 2.6)

C2-8. Reverting to the transition probabilities between GMFCS states in the previous EAG base case (see Section 2.10)

C2-9. Assuming a weight ratio of 0.900 for dosing calculations (see Section 2.15)

C2-10. Applying SMRs for pegzilarginase-treated patients equal to half of those used for IDM (see Section 2.13)

C2-11. Assuming a 10% increase in pegzilarginase cost to explore higher drug costs due to uncertainties in the distribution of weight (see Section 2.6)

C2-12. Assuming the risk of transition to the next worse GMFCS state is 10% of that associated with IDM (see Section 3.3)

C2-13. Assuming the risk of transition to the next worse GMFCS state is 20% of that associated with IDM (see Section 3.3)

C2-14. Assuming that after month 3, that 20% of subcutaneous administrations occur in a hospital setting (see Section 3.4)

C2-15. Using the weight data from the ONS provided by the NICE technical team (see Section 3.6)

Category C3:

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

C3-2. Assuming full drug wastage; applying a weight distribution for patients (see Section 2.6)

C3-3. Applying the SMRs when assuming that 10% of patients diagnosed at age of 13 years with the distribution of GMFCS health states remain alive at 32 years of age (see Section 2.12)

C3-4. Assuming a 20% increase in pegzilarginase cost to explore higher drug costs due to uncertainties in the distribution of weight (see Section 2.6)

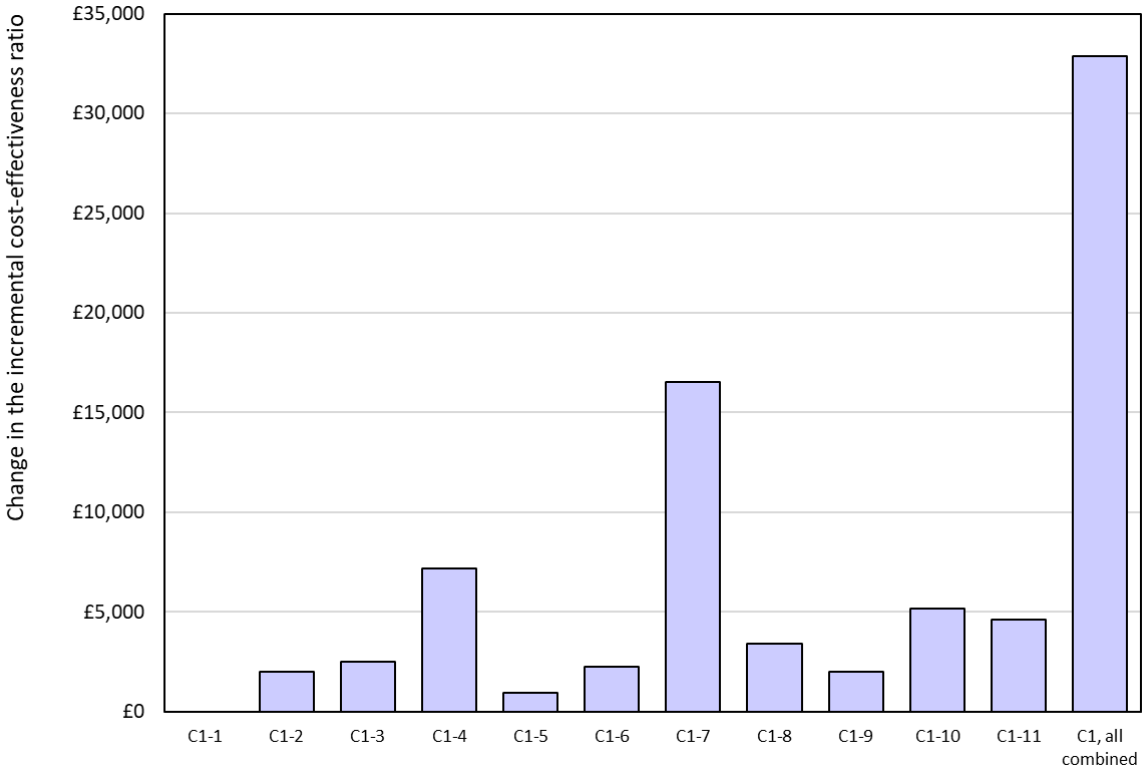
C3-5. Assuming that after month 3, that 10% of doses are intravenous and that 30% of subcutaneous administrations occur in a hospital setting (see Section 3.4)

4.3 Results of the EAG's exploratory analyses

Figure 10 illustrates the impact of individual scenario analyses (C1-1 to C1-11) and their combined effect on the ICER. Among individual scenarios, C1-7 (reverting to the company's original method for estimating disutility from cognitive impairment) had the most pronounced impact, increasing the ICER by £16,552. Other scenarios with moderate impact, include stopping the possibility of moving from GMFCS-II or -III to GMFCS V after 15 years of age for IDM-treated patients, and allowing this transition for pegzilarginase patients aged 15 years and below (C1-10, £5175), and reverting to the calibrated SMRs used in the EAG's base case (C1-11, £4638)

The combined scenario (C1, all combined) resulted in the increase in ICER of £32,870, indicating a substantial cumulative effect when all assumptions are applied simultaneously. The detailed results of the EAG's C1 analyses are provided in Table 18 (deterministic) and Table 19 (probabilistic).

Figure 10: The change in ICER associated with each change made the company to the EAG base case



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

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

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

C1-4. Assuming 50% of patients are female

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

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

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

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

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

C1-10. Transitions from GMFCS-II/III to GMFCS-V stopped after 15 years of age; applied relative risk for transitions to GMFCS-V in pegzilarginase-treated patients

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

Table 18: EAG exploratory analysis results, deterministic

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
The company's base case									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£88,595	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-1. Removing QALY losses for carers when calculating the QALY weight									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£88,595	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-2. Correcting programming errors									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,615	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-3. Applying the starting GMFCS distributions informed by the European burden of illness survey									
Pegzilarginase	54.75	[redacted]	[redacted]	42.95	[redacted]	[redacted]	[redacted]	£91,086	[redacted]
IDM	11.79	[redacted]	[redacted]						
C1-4. Assuming 50% of the cohort is female									
Pegzilarginase	55.92	[redacted]	[redacted]	44.65	[redacted]	[redacted]	[redacted]	£95,754	[redacted]
IDM	11.27	[redacted]	[redacted]						
C1-5. Applying a log-logistic model for the distribution of treatment discontinuation									
Pegzilarginase	50.66	[redacted]	[redacted]	39.16	[redacted]	[redacted]	[redacted]	£89,547	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-6. Assuming [redacted] of families have more than one child with ARG1-D									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,830	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-7. Reverting to the company's original method for estimating disutility from cognitive impairment									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£105,148	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-8. Updating the proportion of patients with utility gains from improved diet to [redacted]									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£92,019	[redacted]
IDM	11.50	[redacted]	[redacted]						
C1-9. Using transition probabilities derived from the difference in average ages in each GMFCS health state									
Pegzilarginase	56.25	[redacted]	[redacted]	43.76	[redacted]	[redacted]	[redacted]	£90,602	[redacted]
IDM	12.49	[redacted]	[redacted]						

C1-10. Transitions from GMFCS-II/III to GMFCS-V stopped after 15 years of age; applied relative risk for transitions to GMFCS-V in pegzilarginase-treated patients.									
Pegzilarginase	56.08	[redacted]	[redacted]	45.54	[redacted]	[redacted]	[redacted]	£93,770	[redacted]
IDM	10.53	[redacted]	[redacted]						
C1-11. Applying recalibrated SMRs using the original method, assuming 10% of patients diagnosed at 5.1 years of age in GMFCS-I remain alive at 32 years of age									
Pegzilarginase	56.86	[redacted]	[redacted]	45.57	[redacted]	[redacted]	[redacted]	£93,233	[redacted]
IDM	11.29	[redacted]	[redacted]						
C1 base case, all C1 changes combined									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£121,465	[redacted]
IDM	12.19	[redacted]	[redacted]						

* Undiscounted ** Calculated using the undiscounted QALY gains (not shown in the table)
CI: confidence interval; EA: exploratory analysis; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Classification System; IDM: Individualised disease management. LYG: life year gained; QALY: quality-adjusted life year

Table 19: EAG exploratory analysis results, probabilistic

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight,** mean (range)
							Unweighted	Weighted	
The company's base case, probabilistic									
Pegzilarginase	55.97	[redacted]	[redacted]	44.30	[redacted]	[redacted]	[redacted]	£93,063	[redacted] ([redacted]88[redacted])
IDM	11.66	[redacted]	[redacted]						
C1 base case, all combined, probabilistic									
Pegzilarginase	49.91	[redacted]	[redacted]	37.48	[redacted]	[redacted]	[redacted]	£124,327	[redacted] ([redacted])
IDM	12.43	[redacted]	[redacted]						

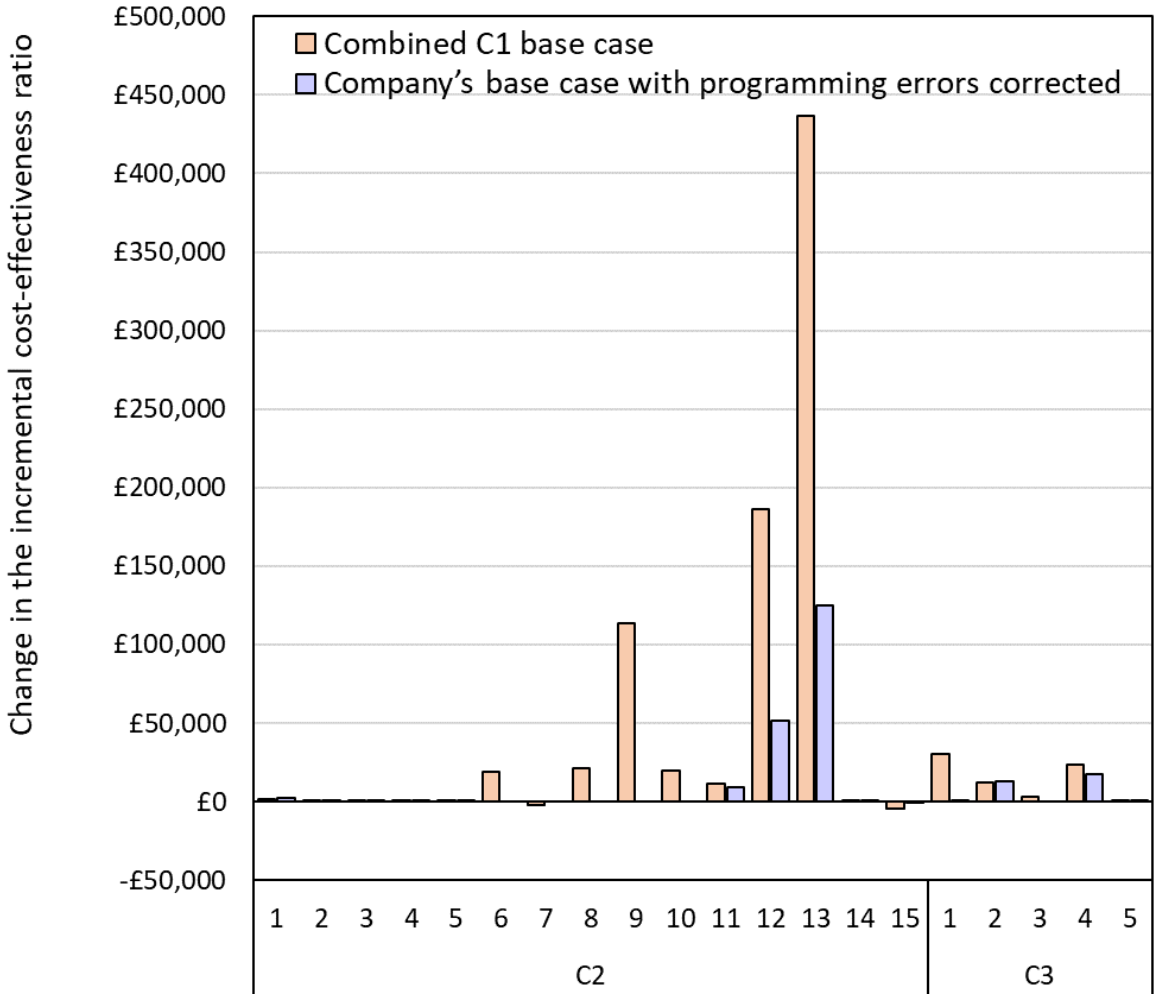
* Undiscounted ** Calculated using the undiscounted QALY gains (not shown in the table)
GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Classification System; IDM: Individualised disease management. LYG: life year gained; QALY: quality-adjusted life year

Figure 11 presents the change in ICER resulting from scenario analyses C2-1 to C3-5. Each scenario is evaluated against both the C1 base case (shown in orange) and the company's base case with programming errors corrected (shown in purple).

C2-13 and C2-12 (having 10% or 20% of the risk of long-term progression associated with IDM for pegzilarginase), leads to the largest increase in ICER—approximately £180,000–£430,000 above the C1 base case, indicating large sensitivity to assumptions related to the long-term GMFCS progression for pegzilarginase-treated patients. The EAG highlights that there are little data on this aspect. Other scenarios, such as C2-6 (assuming 16 mg/kg dosing), C2-8 (reverting to the transition probabilities between GMFCS states in the previous EAG base case), C2-9 (halving all SMRs for pegzilarginase), C2-10 (a weight ratio of 0.900 for patients with ARG1-D), C3-1 (2% annual treatment discontinuation), C3-2 (full drug wastage assuming a weight distribution), C2-11 and C3-4 (additional pegzilarginase costs to take into consideration the distribution of weight) also produce substantial increases in ICER (in the range of £11,000–£113,000 compared with the C1 base case), highlighting the sensitivity of the model to assumptions around dosing, survival, and transition probabilities. In contrast, C2-1 to C2-5, 2-7 and C2-14, result in minimal changes to the ICER, indicating these factors (caregiver QALY losses and dietary-related utility gain) have a relatively limited impact on ICER.

The detailed results of sensitivity analyses based on C2 and C3 are presented in Table 20 and Table 21. As C3-3 incorporates changes that are already included within C1-8, it was not included in Table 21, which presents comparisons against the company's submitted base case.

Figure 11: The change in ICER associated with C2 and C3, compared with combined C1s and the company's submission



C2-1. Assuming the proportion of patients with utility gains from improved diet to be 24.7%
C2-2. Applying caregiver burden for families with multiple children at 25% of the company's estimate
C2-3. Applying caregiver burden for families with multiple children at 50% of the company's estimate
C2-4. Applying caregiver burden for families with multiple children at 75% of the company's estimate
C2-5. Reverting to the previous EAG scenario for families with a single child with ARG1-D
C2-6. Assuming a fixed dose of 16 mg/kg per person
C2-7. Assuming no drug wastage and applying a weight distribution for patients
C2-8. Reverting to the transition probabilities between GMFCS states used in the previous EAG base case
C2-9. Applying SMRs for pegzilarginase-treated patients that are half that used for IDM
C2-10. Assuming a weight ratio of 0.900 for dosing calculations
C2-11. Assuming a 10% increase in pegzilarginase cost due to uncertainties in the distribution of weight
C2-12. Assuming after 3 years that the risk of transition to the next worse GMFCS state is 10% of that associated with IDM
C2-13. Assuming after 3 years that the risk of transition to the next worse GMFCS state is 20% of that associated with IDM
C2-14. Assuming that 20% of subcutaneous administrations occur in a hospital setting
C2-15. Using the weight data, provided by the NICE technical team from the Office for National Statistics
C3-1. Assuming an exponential distribution for treatment discontinuation (2% per year)
C3-2. Assuming full drug wastage and applying a weight distribution for patients
C3-3. Applying the SMRs assuming that 10% of patients diagnosed at age of 13 years with the distribution of GMFCS health states remain alive at age 32
C3-4. Assuming a 20% increase in pegzilarginase cost due to uncertainty in the distribution of weight
C3-5. Assuming 10% of intravenous and 30% of subcutaneous administrations occur in a hospital setting

CS: company submission; ICER: incremental cost-effectiveness ratio

Table 20: EAG sensitivity analyses, starting from the EAG's C1 analysis, deterministic

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
C1, all combined									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£121,465	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-1. Using the proportion of patients with utility gains from improved diet to 24.7%									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£123,109	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-2. Applying caregiver burden for families with multiple children at 25% of the company's estimate									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£122,012	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-3. Applying caregiver burden for families with multiple children at 50% of the company's estimate									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£121,829	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-4. Applying caregiver burden for families with multiple children at 75% of the company's estimate									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£121,647	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-5. Reverting to EAG scenario for families with a single child with ARG1-D									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£122,195	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-6. Assuming a fixed dose of 16 mg/kg per person									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£140,596	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-7. Assuming no drug wastage and applying a weight distribution for patients									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£119,367	[redacted]

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
IDM	12.19	[redacted]	[redacted]						
C2-8. Reverting the transition probabilities to the previous EAG base case									
Pegzilarginase	50.21	[redacted]	[redacted]	36.27	[redacted]	[redacted]	[redacted]	£142,647	[redacted]
IDM	13.94	[redacted]	[redacted]						
C2-9. Applying SMRs for pegzilarginase-treated patients equal to half of those used for IDM									
Pegzilarginase	23.93	[redacted]	[redacted]	11.74	[redacted]	[redacted]	[redacted]	£234,953	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-10. Assuming a weight ratio of 0.900 for dosing calculations									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£141,287	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-11. +10% for pegzilarginase cost due to uncertainties in the distribution of weight									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£133,325	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-12. Assuming the risk of transition to the next worse GMFCS state is 10% of that associated with IDM									
Pegzilarginase	36.06	[redacted]	[redacted]	23.87	[redacted]	[redacted]	[redacted]	£308,095	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-13. Assuming the risk of transition to the next worse GMFCS state is 20% of that associated with IDM									
Pegzilarginase	29.18	[redacted]	[redacted]	16.99	[redacted]	[redacted]	[redacted]	£558,402	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-14. Assuming 20% of subcutaneous administrations occur in a hospital setting									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£121,498	[redacted]
IDM	12.19	[redacted]	[redacted]						
C2-15. Using the weight data, provided by the NICE technical team									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£117,054	[redacted]

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
IDM	12.19	[redacted]	[redacted]						
C3-1. Assuming an exponential distribution for treatment discontinuation at 2% annually									
Pegzilarginase	37.00	[redacted]	[redacted]	24.81	[redacted]	[redacted]	[redacted]	£151,934	[redacted]
IDM	12.19	[redacted]	[redacted]						
C3-2. Assuming full drug wastage; applying a weight distribution for patients									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£133,527	[redacted]
IDM	12.19	[redacted]	[redacted]						
C3-3. Applying the SMRs assuming that 10% of patients diagnosed at age of 13 years with the distribution of GMFCS health states remain alive at age 32									
Pegzilarginase	48.72	[redacted]	[redacted]	39.50	[redacted]	[redacted]	[redacted]	£124,436	[redacted]
IDM	9.22	[redacted]	[redacted]					-	
C3-4. +20% for pegzilarginase cost due to uncertainties in the distribution of weight									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£145,185	[redacted]
IDM	12.19	[redacted]	[redacted]						
C3-5. Assuming 10% of intravenous and 30% of subcutaneous administrations occur in a hospital setting									
Pegzilarginase	49.92	[redacted]	[redacted]	37.74	[redacted]	[redacted]	[redacted]	£121,660	[redacted]
IDM	12.19	[redacted]	[redacted]						

*Undiscounted ** Calculated using the undiscounted QALY gains (not shown in the table)
GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Classification System; IDM: Individualised disease management. LYG: life year gained; SA: sensitivity analysis; QALY: quality-adjusted life year

Table 21: EAG sensitivity analyses, starting from the company's base case, deterministic

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
The company's base case, revised to correct programming errors									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,615	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-1. Using the proportion of patients with utility gains from improved diet to 24.7%									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£93,005	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-2. Applying caregiver burden for families with multiple children at 25% of the company's estimate									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£91,134	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-3. Applying caregiver burden for families with multiple children at 50% of the company's estimate									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,960	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-4. Applying caregiver burden for families with multiple children at 75% of the company's estimate									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,787	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-5. Reverting to EAG scenario for families with a single child with ARG1-D									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£91,308	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-6. Assuming a fixed dose of 16 mg/kg per person									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£110,254	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-7. Assuming no drug wastage and applying a weight distribution for patients									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£92,712	[redacted]
IDM	11.50	[redacted]	[redacted]						

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
C2-8. Reverting the transition probabilities to the previous EAG base case									
Pegzilarginase	56.44	[redacted]	[redacted]	41.77	[redacted]	[redacted]	[redacted]	£96,681	[redacted]
IDM	14.67	[redacted]	[redacted]						
C2-9. Applying SMRs for pegzilarginase-treated patients equal to half of those used for IDM									
Pegzilarginase	27.03	[redacted]	[redacted]	15.53	[redacted]	[redacted]	[redacted]	£111,025	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-10. Assuming a weight ratio of 0.900 for dosing calculations									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£110,747	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-11. +10% for pegzilarginase cost due to uncertainties in the distribution of weight									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£99,590	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-12. Assuming the risk of transition to the next worse GMFCS state is 10% of that associated with IDM									
Pegzilarginase	33.23	[redacted]	[redacted]	21.73	[redacted]	[redacted]	[redacted]	£142,124	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-13. Assuming the risk of transition to the next worse GMFCS state is 20% of that associated with IDM									
Pegzilarginase	24.88	[redacted]	[redacted]	13.38	[redacted]	[redacted]	[redacted]	£215,825	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-14. Assuming 20% of subcutaneous administrations occur in a hospital setting									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,640	[redacted]
IDM	11.50	[redacted]	[redacted]						
C2-15. Using the weight data, provided by the NICE technical team									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,037	[redacted]
IDM	11.50	[redacted]	[redacted]						

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weight**
							Unweighted	Weighted	
C3-1. Assuming an exponential distribution for treatment discontinuation at 2% annually									
Pegzilarginase	36.99	[redacted]	[redacted]	25.50	[redacted]	[redacted]	[redacted]	£91,116	[redacted]
IDM	11.50	[redacted]	[redacted]						
C3-2. Assuming full drug wastage; applying a weight distribution for patients									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£103,926	[redacted]
IDM	11.50	[redacted]	[redacted]						
C3-3. Applying the SMRs assuming that 10% of patients diagnosed at age of 13 years with the distribution of GMFCS health states remain alive at age 32									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,615	[redacted]
IDM	11.50	[redacted]	[redacted]						
C3-4. +20% for pegzilarginase cost due to uncertainties in the distribution of weight									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£108,565	[redacted]
IDM	11.50	[redacted]	[redacted]						
C3-5. Assuming 10% of intravenous and 30% of subcutaneous administrations occur in a hospital setting									
Pegzilarginase	56.16	[redacted]	[redacted]	44.66	[redacted]	[redacted]	[redacted]	£90,769	[redacted]
IDM	11.50	[redacted]	[redacted]						

*Undiscounted ** Calculated using the undiscounted QALY gains (not shown in the table)
GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Classification System; IDM: Individualised disease management. LYG: life year gained; SA: sensitivity analysis; QALY: quality-adjusted life year

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