Highly Specialised Technology

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission from Immedica:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Metabolic Support UK

4. **Expert personal perspectives** from:
   a. Arunabha Ghosh – Clinical expert, nominated by Metabolic Support UK
   b. Reena Sharma - Clinical expert, nominated by Immedica
   c. Zafar Aslam – Patient expert, nominated by Metabolic Support UK
   d. [redacted] – patient expert nominated by Metabolic Support
   e. Ayesha Ali – NHS England commissioning expert

5. **External Assessment Report** prepared by ScHARR

6. **External Assessment Report – factual accuracy check**

7. **External Assessment Report additional analysis**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Company evidence submission

March 2024

File name	Version	Contains confidential information	Date
ID4029 Pegzilarginase i. Company Evidence Submission [CON]_08.08.24	**2.0**	**Yes**	**08/08/2024**

Contents

Tables and figures

Tables

Tables in Appendices

Figures

Figures in Appendices

Abbreviations

Abbreviation	Definition
2MWT	2-Minute Walk Test
6MWT	6-Minute Walk Test
AE	Adverse event
ARG1	Arginase 1
ARG1-D	Arginase 1 deficiency
ARGA	Argininic acid
BIMDG	British Inherited Metabolic Disease Group
BoI	Burden of illness
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CEAC	Cost-effectiveness acceptability curve
CP	Cerebral palsy
CSR	Clinical study report
EAA	Essential amino acid
E-IMD	European Registry and Network for Intoxication type Metabolic Diseases
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQol-5 Dimension-5 Levels
EQ-VAS	EuroQol-Visual Analogue Score
FAS	Full Analysis Set
FSIQ	Full-scale IQ
GAA	Guanidinoacetic acid
GC	Guanidino compound
GMFCS	Gross Motor Function Classification System
GMFM-D	Gross Motor Function Measure, Part D
GMFM-E	Gross Motor Function Measure, Part E
GVA	Alpha-keto-δ-guanidinovaleric acid
HAC	Hyperammonaemic crisis
HCRU	Healthcare resource utilisation
HRQoL	Health-related quality of life
HRG	Healthcare resource group
ICER	Incremental cost-effectiveness ratio
IDM	Individualised disease management
IV	Intravenous

LOCF	Last observation carried forward
LS	Least squares
LTE	Long-term extension
LY	Life year
MAS	Modified Ashworth Scale
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MLD	Metachromatic leukodystrophy
MMRM	Mixed effect model repeated measures
NAArg	Alpha-N-acetylarginine
NHB	Net-health benefit
OS	Overall survival
pArg	Plasma arginine
PedsQL	Paediatric Quality of Life Inventory
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SAE	Serious adverse event
SC	Subcutaneous
SF-36	36-Item Short Form Health Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
TEAE	Treatment-emergent adverse event
UCD	Urea cycle disorder
UCDC	Urea Cycle Disorders Consortium
VABS-II	Vinelands Adaptive Behaviour Scale, Second Edition
WAIS-V	Wechsler Adult Intelligence Scale, Fourth Edition
WISC-V	Wechsler Intelligence Scale for Children, Fifth Edition
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition
WRS	Wilcoxon rank sum
X-ALD	X-linked adrenoleukodystrophy
ZBI-12	Zarit Burden Interview Short: 12 items

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's current Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation, namely, for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older. Pegzilarginase is intended for chronic management of patients with ARG1-D in conjunction with individualised disease management (IDM) such as dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers (1).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with arginase 1 deficiency (ARG1-D) aged 2 years and older	Patients with ARG1-D aged 2 years and older	N/A
Intervention	Pegzilarginase	Pegzilarginase	N/A
Comparator(s)	Established clinical management without pegzilarginase (including dietary protein restriction, essential amino acid supplementation and/or the use of ammonia scavengers).	Individualised disease management (including dietary protein restriction, essential amino acid supplementation and/or the use of nitrogen scavengers).	Immedica proposes to use the term 'individualised disease management' as opposed to 'established clinical management without pegzilarginase' to better align with the terminology used to define standard of care in the published literature and UK clinical practice, as well as the terminology used in the PEACE trial.
Outcomes	The outcomes to be considered include: • Plasma arginine concentration • Level of ornithine and guanidino compounds • Mobility • Adaptive behaviour • Neurocognitive function • Adverse effects of treatment • Health-related quality of life	The outcomes to be considered include: • Plasma arginine concentration • Level of ornithine and guanidino compounds • Mobility • Adaptive behaviour • Neurocognitive function • Adverse effects of treatment • Health-related quality of life	N/A
Impact of the technology beyond direct health benefits,	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs	Pegzilarginase can be administered via intravenous (IV) infusion or subcutaneous injection (SC) by a healthcare professional	N/A

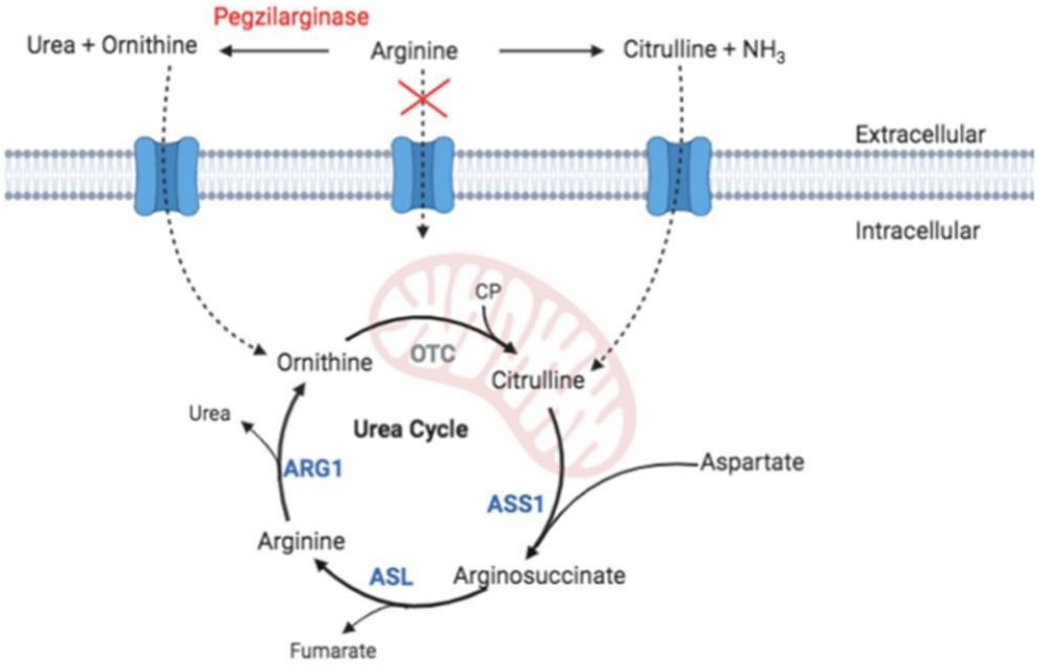
and on the delivery of the specialised service	(savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits of to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	in an outpatient setting upon initiation of treatment. After eight weeks, and if deemed appropriate by a healthcare professional, SC home administration by the patient or caregiver may be considered (1). Flexibility with regards to the mode and setting of pegzilarginase administration will allow for treatment to be tailored according to the requirements of the patient and/or caregiver. Furthermore, for patients and/or caregivers who are deemed able to do so, self-administration of pegzilarginase can minimise disruption to day-to-day routines through avoiding hospital attendance, thereby improving patient and caregiver satisfaction.	

Key: NHS: National Health Service; N/A: not applicable.

B.1.2 Description of the technology being evaluated

Pegzilarginase is a modified, cobalt-substituted, pegylated recombinant form of the human enzyme arginase 1 (ARG1). Compared to the native enzyme, pegzilarginase demonstrates enhanced stability, more potent catalytic activity, and an extended half-life, and represents the first potential enzyme therapy for patients with ARG1-D (2). Pegzilarginase substitutes for the deficient ARG1 enzyme and provides an alternative pathway for the metabolism of the amino acid arginine into ornithine and urea, thereby lowering blood arginine levels. This normalises blood arginine levels in patients with ARG1-D and prevents hyperargininaemia (Figure 1) (3, 4).

Figure 1: Pegzilarginase mechanism of action



Key: ARG1: arginase 1; ASL: argininosuccinate lyase; ASS: argininosuccinate synthase; CP: carbamoyl phosphate; NH_3: ammonia; OTC: ornithine transcarbamylase.
Source: Adapted from Grimes *et al*. (2021) (4).

On July 14th 2016, pegzilarginase was granted orphan designation by the European Medicines Agency (EMA) (EU/3/16/1701) due to the seriousness of ARG1-D, the lack of licensed treatment options, and the rarity of the condition (5). On December 15th 2023, the European Commission granted marketing authorisation of pegzilarginase, under exceptional circumstances, for the treatment of ARG1-D in patients aged two years and older (6). In the UK, the MHRA granted marketing authorisation of

pegzilarginase on December 20th 2023 for the treatment of ARG1-D in patients aged 2 years and older. Orphan designation was also granted (1).

Table 2 provides an overview of the technology being evaluated. The Summary of Product Characteristics (SmPC) is included in Appendix C1.1.

Table 2: Technology being evaluated

UK approved name and brand name	Pegzilarginase (Loargys®)
Mechanism of action	Pegzilarginase is intended to substitute for the deficient human arginase 1 enzyme activity in patients with ARG1-D. Pegzilarginase has been shown to rapidly and sustainably reduce plasma arginine and convert it to urea and ornithine (1).
Marketing authorisation/CE mark status	Pegzilarginase received a marketing authorisation under exceptional circumstances on December 15th 2023 (EU/1/23/1774) (6). Pegzilarginase received marketing authorisation from the MHRA on December 20th 2023 (PLGB 53487/0007). Orphan designation was also granted (1).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pegzilarginase is indicated for the treatment of ARG1-D, also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older. Pegzilarginase is intended for chronic management of patients with ARG1-D in conjunction with individualised disease management (IDM) such as dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers (1).
Method of administration and dosage	The treatment should be administered by intravenous (IV) infusion or subcutaneous (SC) injection in conjunction with IDM. Pegzilarginase is available in 3mL single-use vials, containing 0.4mL of 5mg/mL for injection/infusion. The recommended initial dose of pegzilarginase administered IV is 0.1mg/kg/week. The dose of pegzilarginase may be increased or decreased in 0.05mg/kg increments to achieve therapeutic goals. Doses above 0.2mg/kg/week have not been studied in clinical trials in ARG1-D. If appropriate, SC administration by the patient or caregiver may be considered after at least 8 weeks of treatment, once a stable maintenance dose has been established and the risk of hypersensitivity reactions

	is assessed as low. Before self-administration, the patient or caregiver should be adequately trained.
Additional tests or investigations	Pegzilarginase will interfere with routine laboratory analysis, resulting in erroneous low measurements due to post-collection degradation of arginine. During clinical studies, nor-NOHA tubes were used to inhibit residual pegzilarginase activity and stabilise arginine in plasma samples. Tubes of nor-NOHA will be available upon commercialisation of pegzilarginase. Beyond this, no additional tests or investigations are anticipated beyond what is already performed in clinical practice to identify patients eligible to receive pegzilarginase.
List price and average cost of a course of treatment	List price: £4,690 per vial of 2 mg pegzilarginase for solution for injection/infusion Pegzilarginase is intended for chronic management of patients with ARG1-D. The recommended dose of Loargys® is 0.1mg/kg per week, with ≥ 1 vial per administration required (52 administrations per year).
Patient access scheme (if applicable)	A patient access scheme (PAS) has been approved by PASLU for NHSE&I. This PAS involved a simple [redacted] discount from list price. The confidential net price is [redacted] per vial of 2 mg pegzilarginase

Key: ARG1-D: arginase 1 deficiency; IDM: individualised disease management; IV: intravenous; MHRA: Medicines and Healthcare products Regulatory Agency; SC: subcutaneous.

B.1.3 Health condition and position of the technology in the treatment pathway

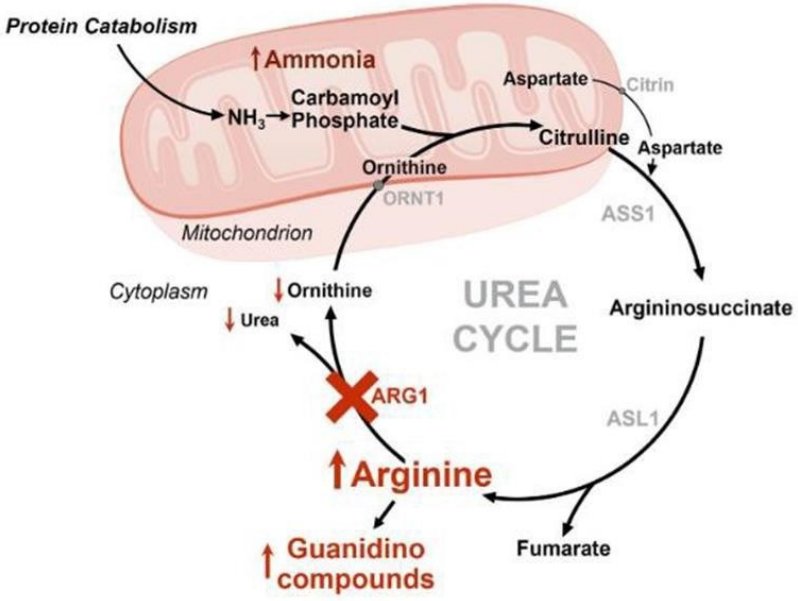
B.1.3.1. Disease overview

ARG1-D, also known as hyperargininaemia, is an ultra-rare, inherited, debilitating, progressive, neurotoxic, metabolic disease characterised by marked increases in arginine and its metabolites, with increased morbidity, substantial reductions in health-related quality of life (HRQoL), and premature mortality (7-9). It is an autosomal recessive disease caused by a deficiency in the ARG1 enzyme, which is active in the urea cycle (10).

The role of the urea cycle is to detoxify waste nitrogen by producing urea from ammonia. The cycle consists of five consecutive enzymatic reactions distributed between the mitochondria and the cytosol, as well as two transporters mediating the transport of urea cycle intermediates between mitochondria and cytosol. The final enzyme reaction within the urea cycle is by ARG1 hydrolysis of arginine to ornithine

and urea (Figure 2). Urea can thereby be excreted by the kidneys, whereas ornithine is returned to the mitochondria to continue the cycle (11). All patients with ARG1-D have a defective ARG1 enzyme with decreased or non-existent activity that leads to the accumulation of arginine and its metabolites, namely guanidino compounds (GCs), in the body approximately 50-fold higher than normal levels (Figure 2) (12). Persistently elevated levels of arginine and its metabolites are believed to be key contributors to disease manifestation and progression for patients with ARG1-D (see Section B.1.3.1.1) (13).

Figure 2: Metabolic effects of ARG1-D

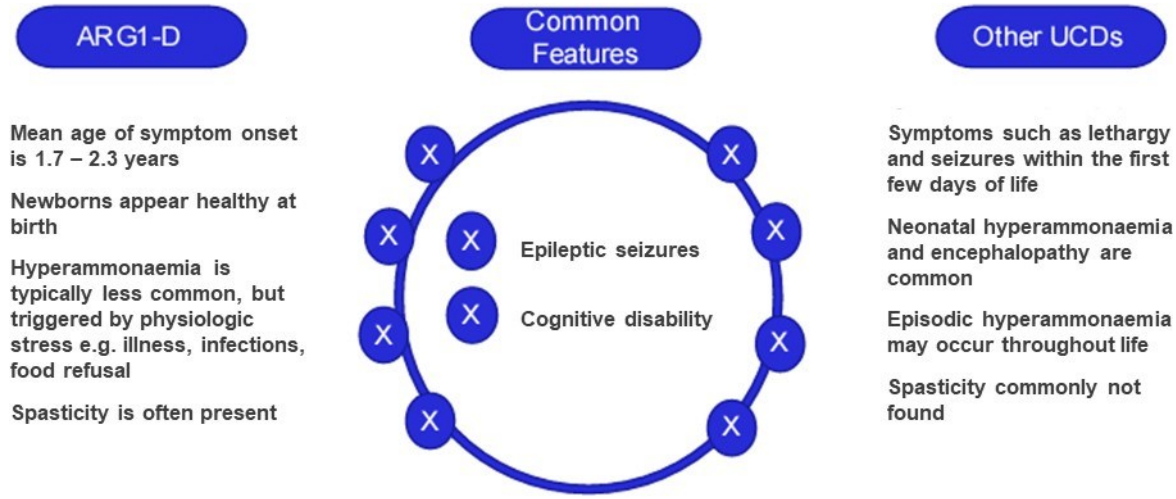


Key: ARG1: arginase 1; ASL: argininosuccinate lyase; ASS: argininosuccinate synthase; NH_3: ammonia; ORNT: ornithine translocase.
Source: Diaz *et al.* (2023) (13).

Although ARG1-D has overlapping features with the other urea cycle disorders (UCDs), it has its own distinct characteristics and manifestations (Figure 3) (11, 14, 15). The common phenotype of ARG1-D involves insidious onset with manifestations developing in the first one to five years of life, which worsen progressively over time at variable rates (14, 16-18). The clinical profile of ARG1-D includes spastic paraparesis, progressive neurological and motor deterioration affecting mobility, growth and developmental delays, cognitive delays, seizures, and the potential for early mortality (9, 10, 19). Patients with ARG1-D exhibit lower-limb spasticity which worsens in severity and impact over time. As a result, these patients may initially

stumble and appear clumsy, develop gait abnormalities, and mobility impairments, and eventually lose the ability to walk independently (16). Based on this clinical profile, ARG1-D is uniquely recognised among UCDs as a clinical mimic of cerebral palsy (CP) and hereditary spastic paraplegia, hence misdiagnosis is common due to similarities in clinical presentation (20, 21).

Figure 3: Characteristics and manifestations of ARG1-D versus other UCDs



Key: ARG1-D: arginase 1 deficiency; UCD: urea cycle disorder.
Source: Adapted from FDA Patient-led Listening Session for the ARG1-D Community (22).

ARG1-D is one of the least common UCDs, accounting for approximately 3.5% of all UCD cases (23). It is an ultra-rare disease that has an estimated prevalence of 0.58 per million live births in the UK, in accordance with the most recent literature (24). When applying the population prevalence rate from Catsburg *et al*. (2022) to the total population in England of 56.5 million people (25), a cohort of approximately 33 patients with ARG1-D is estimated. However, [redacted] (26). The discrepancy between the two figures could arise due to patient death before a diagnosis of ARG1-D could be made, and/or that some patients may be misdiagnosed (20, 21, 26). Of the assumed total patients in England, clinical experts agreed that approximately [redacted] of prevalent patients are paediatric (<18 years of age) (26). An estimate based on newborn screening of other UCDs suggests an

incidence of 1 in 950,000 births, which, with a 2022 birthrate of 605,479 live babies in England and Wales in 2022, correlates to one newborn in England and Wales biennially (27, 28).

B.1.3.1.1. Disease pathogenesis

Markedly elevated plasma arginine (pArg) is the most readily apparent feature of ARG1-D (13). In a systematic review of case reports by Bin Sawad *et al*. (2022), 81.5% of ARG1-D patients with information available were reported to have elevated pArg levels (29), highlighting that elevated pArg level is the single most common manifestation in all patients. Clinical recognition of the importance of pArg levels in ARG1-D is also reflected in current trans-European management guidelines for UCDs (15).

A clear clinical and pathophysiologic profile of ARG1-D has been formulated as more case reports/case series have been published in the literature, which demonstrate a strikingly uniform picture of raised pArg in the first years of life followed by an increase in disease severity and extent as the patient journey progresses (11, 14, 18, 30). High pArg, whether as the primary driver or proximal causal component of downstream toxicity, is believed to be the key driver of global developmental delay, progressive intellectual disability, seizures and, unique to ARG1-D compared to other UCD disorders, progressive spasticity, which develop early in childhood and progresses over time (31, 32). The neurotoxic effects of persistently high pArg and its metabolites (GCs) in ARG1-D and a mechanistic role in the development and progression of neurologic manifestations have long been speculated and are supported by both anecdotal and empirical evidence (9, 11, 33, 34).

Results from the Urea Cycle Disorders Consortium (UCDC) Longitudinal Study suggest a role of arginine in the development and progression of ARG1-D manifestations. The study testing included age-appropriate measures of intelligence and global functioning verbal abilities, visual performance, motor skills, and memory. The study found that cumulative arginine exposure was correlated with the deterioration in select neuropsychological outcomes in patients with ARG1-D. Patients with ARG1-D were at greater risk for low full-scale IQ (FSIQ) and poor performance in all of the aforementioned age-appropriate measures. Global functioning and memory

deficits were more tightly associated with pArg than other biochemical markers, while higher pArg level was also significantly correlated with a worse motor skills score (32).

Furthermore, patients very rarely, if ever, achieve adequate arginine control with the current IDM approach. Despite this, case reports from the literature further support that lowering arginine is associated with slower disease progression and/or disease improvement (31, 35-40). In patients exposed to sustained high levels of arginine due to a delayed disease diagnosis, the subsequent lowering of pArg with severe dietary restrictions was demonstrated to lead to improvements in disease manifestations (35, 37, 40). In adolescent siblings with established neuromotor and neurocognitive manifestations of ARG1-D, the lowering of pArg with a chemically defined diet resulted in clinical improvement – spasticity was lessened, mobility improved, independent feeding and toilet training were regained, and language improved (36, 37). In addition, in a severely affected paediatric case unresponsive to IDM approaches, lowering of pArg using an exchange blood transfusion to enhance extra-hepatic arginase activity resulted in an improvement in clinical status, including a reduction in spasticity (41).

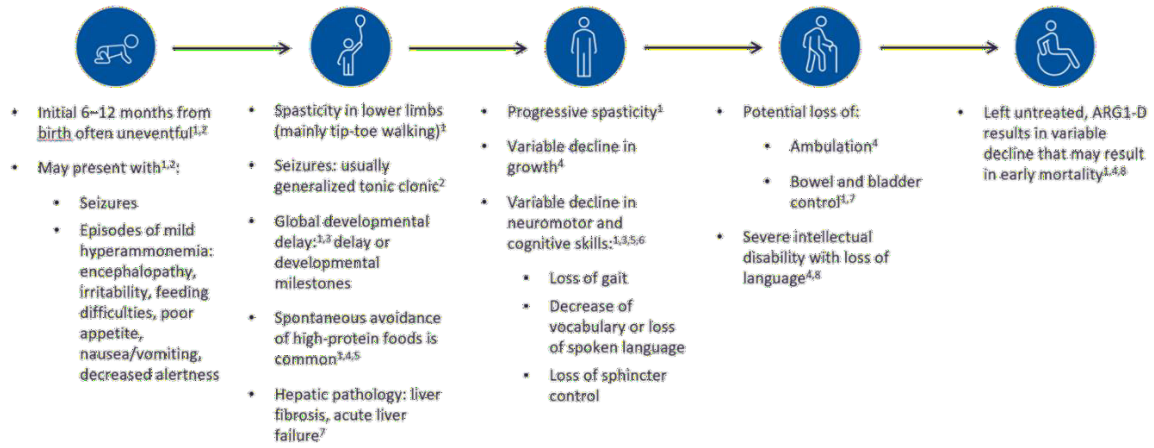
Taken together, the literature findings provide confirmatory evidence of the importance of arginine with its subsequent metabolite accumulation as the key driver of the disease manifestations of ARG1-D and illustrate the effectiveness of reducing pArg to reverse neurologic damage, through enzyme administration or hepatic expression of ARG1, for functional recovery of oligodendrocytes to improve central nervous system abnormalities.

B.1.3.1.2. Clinical burden

a. Morbidity related to ARG1-D

ARG1-D is associated with the development of a variety of progressive and debilitating manifestations. Initial disease manifestations often consist of clumsiness, tripping, falling, and diminished growth. The disease is progressive and leads to a gradual loss of developmental milestones and spasticity (Figure 4) (42). Some patients may display persistent or intermittent episodes of irritability, nausea, poor appetite, vomiting, and lethargy that require symptomatic treatment (33).

Figure 4: The progressive impact of persistently high arginine

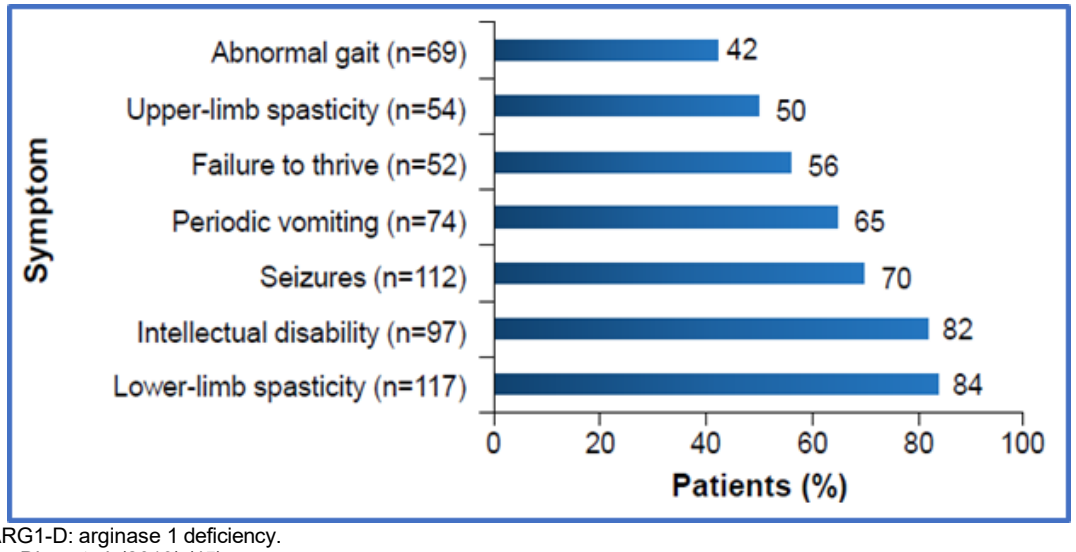


Key: ARG1-D: arginase 1 deficiency.
Sources: [1]Carvalho *et al*. (2012) (14); [2]Scaglia *et al*. (2006) (42); [3]Wong *et al*. (1993) (10); [4]Crombez *et al*. (2005) (33); [5]Cai *et al*. (2018) (43); [6]Bakhiet *et al*. (2018) (17); [7]Schlune *et al*. (2015) (11); [8]Prasad *et al*. (1997) (21).

A systematic literature review (SLR) of epidemiology, methods of diagnosis and clinical management of patients with ARG1-D by Bin Sawad *et al*. (2022) reported the proportion of patients with various manifestations of disease, suggesting that of patients receiving IDM, 84.8% had intellectual disability, 81.3% had spasticity, 70.7% had motor deficits, 60% experienced seizures, 49% had developmental delays, 13% had adaptive behaviour issues, and 7% had impaired balance or ataxia. These studies indicate a significant impact on patients' lives and support the notion that current IDM does not successfully normalise arginine levels (44).

Furthermore, a systematic review of case reports by Bin Sawad *et al.* (2022), which included 157 unique patients from 111 publications, reported a multitude of clinical manifestations of ARG1-D, including developmental delays, intellectual disability, motor deficits (including spasticity and impaired mobility), and seizures. Motor deficits, including spasticity, cognitive impairment, and presence of seizures were the most commonly reported clinical manifestations of patients with ARG1-D (>50% of cases), followed by developmental delay (37%), impaired mobility/gait (38%), vomiting (30%), somatic growth delay (22%), spastic quadriplegia (16%), microcephaly (15%), and hepatomegaly (11%). Progressive spasticity and failure to thrive were reported for <10% of patients (29). A similar analysis conducted by Diaz *et al*. (2019) examined 140 unique case reports of patients with ARG1-D and reported lower-limb spasticity as the most commonly reported ARG1-D manifestation, closely followed by intellectual disability (Figure 5) (45).

Figure 5: Commonly reported disease manifestations of ARG1-D



Key: ARG1-D: arginase 1 deficiency.
Source: Diaz *et al*. (2019) (45).

With regards to symptom onset, developmental delays are typically the earliest observed clinical manifestation of ARG1-D, followed by intellectual disabilities, seizures, and motor deficits (Figure 5). Clinical manifestations typically appear by the age of 1-3 years among case reports detailing age of onset (29, 45). The mean age of symptom onset in two studies including UK-based ARG1-D patients, namely the European burden of illness (BoI) study (IMM-PEG-001) conducted by Immedica (46), which is elaborated in further detail in the following narrative, and a real-world UK-based study by Keshavan *et al*. (2022) (30), was 3.7 years and 3.3 years, respectively.

To further understand the clinical and economic burden of ARG1-D in Europe, a BoI study in an ARG1-D cohort, in the form of a patient survey, was conducted across the UK, France, Spain, and Portugal, between June 2023 and August 2023. The study population comprised patients diagnosed with ARG1-D (n=21) and their caregivers (n=16). This report is referred to as the European BoI study, providing data on a heterogenous cohort of ARG1-D patients observed in clinical practice.

Since ARG1-D is an ultra-orphan disease, the study included all patients and their caregivers who visited participating clinics during the period defined above. Of the 21 patients included in the study, nearly one third (29%) were from the UK (6 of 21 patients). The median age of all ARG1-D patients was 14 years (range: 0 – 49), slightly lower than the median age at last follow-up calculated in a real-world cohort of UK ARG1-D patients by Keshavan *et al*. (2022) (16 years; range: 12 – 28) (n=6) (30),

while 76% of patients were female. Overall, 71% of patients (15 of 21 patients) reported limited mobility and/or cognitive deficiency, whereof 73% (11 of 15 patients) reported both, despite standard treatment. In addition, 57% patients with ARG1-D (12 of 21 patients) reported spasticity of the lower limbs, which is slightly lower than the reported figure of 65% in a systematic review of case reports by Bin Sawad *et al*. (2022) (29). Furthermore, 29% of patients (6 of 21 patients) reported experiencing seizures (46), which falls just outside the 30-50% prevalence estimate quoted by UK clinical experts in consultation with Immedica (47). Table 3 outlines the prevalence of manifestations of ARG1-D amongst sampled European patients.

Table 3: Disease and symptoms reported in the European BoI study

Variable	Proportion (%) of patients if not other stated	n
Mobility and cognitive ability		
Limited mobility only	10	2
Cognitive deficiency only	10	2
Both	52	11
None	24	5
Do not know	5	1
Mean (SD) age at first sign of limited mobility	9.2 (12.6)	13
Mean (SD) age at first sign of cognitive deficiency	5.0 (3.5)	13
Spasticity		
Lower limbs	57	12
Upper limbs	0	0
Both lower and upper limbs	5	1
No	38	8
Experienced seizures		
Yes	29	6
No	62	13
Do not know	10	2
Taking anti-epileptic medication to control seizures (n=20)		
Yes	20	4
No	75	15
Do not know	5	1
Missing	--	1
Other symptoms[a]		
Yes	33	7*
No	62	13
Do not know	5	1
Other long-term illness or disability[b]		
Yes	19	4**
No	81	17

Key: BoI: burden of illness; SD: standard deviation.
Notes: Number of patients = 21.
[a]For example, vomiting, confusion, and dizziness.
[b]For example, hypertension, type 2 diabetes, low body weight/eating disorder.

Source: Table 4, A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers (46).

In order to manage the manifestations of ARG1-D, patients are placed on low-protein, arginine-restricted diets, often supplemented with essential amino acids (EAAs), with the aim of reducing pArg levels below <200 µM (15, 30). A cross-sectional study by Adam *et al*. (2012) reported that 75% of ARG1-D patients, including all patients below the age of 16 years, were prescribed EAA supplements as part of their dietary management in the UK (48). The strict low protein diet is extremely restrictive and is often unpalatable for patients; low adherence is frequently reported in the literature (30, 33, 42, 49). Furthermore, even for those who adhere to strict dietary intervention, mean arginine levels persist well above the target range, in part because a substantial proportion of arginine comes from endogenous sources (50, 51). As a result, patients continue to show little or no clinical improvement after the onset of disease manifestations despite intervention, resulting in the development of significant neurodisability (14, 30).

Some of the most common ARG1-D-related abnormalities reported in the literature are elaborated below.

i. Developmental delay

Developmental delay is typically the earliest clinical manifestation observed in patients with ARG1-D (29). Between 1-3 years of age, linear growth slows, and the majority of affected children demonstrate growth reduction, slowing cognition, and developmental regression, which persists if the disease is left untreated (10). Elevated pArg, whether as the primary driver or proximal causal component of downstream toxicity, is associated with the onset of global developmental delay (52, 53). The role of elevated pArg in the pathogenesis of ARG1-D has been described previously in Section B.1.3.1.1.

The impairment of neurodevelopmental milestones can affect the ability of patients to use verbal language. In a retrospective evaluation of 16 patients with ARG1-D in Brazil by Carvalho *et al*. (2012), three patients with severe mental retardation never developed spoken language. The ability to speak for the remainder of the cohort was limited, with patients only able to speak sentences or report facts. Two patients lost

the ability to elaborate spoken language at 7 and 10 years of age, highlighting the severe neurological deterioration associated with the disease (14).

Furthermore, variation in cognitive abilities was observed in a European BoI study of ARG1-D patients. Across 13 cognitive dimensions, approximately 30-40% of ARG1-D patients reported some or moderate problems with cognitive abilities, while 30% reported either severe problems or no ability. The most severe problems were related for reading and writing, play and leisure, stressful situations and dimensions related to the ability to learn, think, and solve problems (46). A clear correlation between cognitive score and Gross Motor Function Classification System (GMFCS) Level (see Section B.1.3.1.2.a.iv), was not identified, although these findings could be considered to be inconclusive given the limited sample of patients enrolled in the study.

Feeding difficulties can develop in early childhood, leading to inadequate nutrition and consequently, some patients may require supplemental feeding. An SLR conducted by Bin Sawad *et al*. (2022) reported that 25% of patients with ARG1-D required tube feeding, albeit this finding is restricted to a single study (44, 48). Mechanical feeding problems and unsafe swallow were cited as primary reasons for tube feeding amongst patients with UCDs, including ARG1-D (48). Literature estimates were aligned with that of UK clinical experts, who suggested that up to 20% of patients may require supplementary feeding through a percutaneous endoscopic gastronomy or nasogastric tube (47).

ii. Intellectual disability

Intellectual disability is a commonly reported manifestation amongst patients with ARG1-D. The degree of intellectual disability amongst patients with ARG1-D is heterogenous, with 39% of patients reported to have moderate or severe intellectual disability in a review of case reports conducted by Diaz *et al*. (2019) (45). According to the literature, the onset of intellectual disability typically occurs beyond 3 years of age, where previously normal cognitive development slows or stops, causing the patient to lose developmental milestones (10, 54). Deterioration in neuropsychological outcomes has been shown to correlate with cumulative arginine exposure (32).

A recent analysis of the UCDC Longitudinal Study, a longitudinal investigation of the natural history, morbidity, and mortality in patients with UCDs, reported that 67% of enrolled ARG1-D patients aged ≥3 years (8 of 12 patients) had intellectual disabilities, with a mean FSIQ of 65, which is below the population mean of 100 for all age groups. As a result, patients' school performance and educational achievement can be negatively impacted (32). As patients progress to adulthood, intellectual disability has profound impacts on the ability of patients to live independently. In an earlier report on the UCDC Longitudinal Study by Waisbren *et al*. (2016), four adult patients with ARG1-D (50%) were unable to live independently. The remaining 50% who were able to live independently suffered from significant memory and motor deficits (54).

Patients with ARG1-D may also experience behavioural problems, including hyperactivity, inability to obey commands, lack of concentration, and diminished recent memory (14, 16, 17, 54). In a patient-led listening session for the ARG1-D community facilitated by the US Food and Drug Administration (FDA), several caregivers referred to short attention span, hyperactivity, high distractibility, poor impulse control, cognitive impairment, outbursts, fear, and anger amongst ARG1-D patients receiving caregiving (22).

iii. Seizures

The neurotoxic effects of GCs, which increase in the plasma and cerebrospinal fluid as a result of elevated pArg, may contribute to the susceptibility of seizures amongst patients with ARG1-D (16, 21, 31, 55).

In UK practice, clinical experts consulted by Immedica estimated 30-50% of patients with ARG1-D experience seizures (47). This estimate aligns closely with the results obtained from the European BoI study, whereof 29% of patients (6 of 21 patients) reported experiencing seizures at the time of data collection (46). However, in the literature, the reported prevalence is much higher, with seizures reported in 60-75% of patients with ARG1-D, with generalised tonic-clonic seizures the most reported seizure type (18, 45, 56). In a retrospective study of 19 ARG1-D patients by Huemer *et al*. (2016), 63% of patients (12 of 19 patients) had experienced seizures at most recent follow-up (mean age: 15.4 years, range: 0.9 - 44.7 years), with 75% of these

patients experiencing generalised tonic-clonic seizures (18). Discrepancies in the data can be owed to small sample sizes attributed to the orphan nature of the disease.

iv. Motor deficits

Neuromotor complications are a hallmark feature of ARG1-D (10, 34). Patients typically present with some form of lower-limb spasticity, such as hyperreflexia, clonus, toe walking and other gait abnormalities, between 1-5 years of age (45). The lower-limb spasticity typically seen in early childhood impairs mobility and balance, eventually leading to a complete loss in ambulation and loss of bowel and bladder control (10). The progressive worsening of mobility impairment causes patients to become dependent on wheelchairs, orthoses, and other mobility devices, which can be required at an early age (35, 36). In the European BoI study, 43% of patients (9 of 21 patients) required mobility aids or devices, whereof 78% (7 of 9 patients) reported using a wheelchair. The use of mobility aids or devices began at a mean age of 12 years, while walking stabilators were used from a mean age of 8 years (46).

Several observational studies report the progressive nature of spasticity in patients with ARG1-D (14, 18, 30). In a UK-based retrospective review of patient medical records by Keshavan *et al*. (2022), all patients with diagnosed ARG1-D developed significant motor deficits. Four of six ARG1-D patients developed spastic diplegia, with the remainder developing spastic quadriplegia (30). Furthermore, in a retrospective evaluation of 16 patients with ARG1-D in Brazil, all patients demonstrated a worsening of spastic paraplegia over time, with 94% of patients (15 of 16 patients) unable to ambulate as a consequence (14).

In the European BoI study, movement abilities were assessed according to the Gross Motor Function Classification System (GMFCS). The GMFCS assigns gross motor function capabilities based on movements such as sitting, walking, and use of mobility devices with five categories ranging from I (most functional) to V (transported in wheelchair in all settings) (see Figure 6 for GMFCS categories for patients aged 6-12 years of age) (57). Among the 16 patients who responded to the survey, 50% were categorised as Level I. The remaining eight patients were distributed between Level II (31%), Level IV (13%), and Level V (6%) (46). At present, the published literature does not report on the distribution of ARG1-D patients according to GMFCS classification.

Figure 6: GMFCS categorisation

Key: GMFCS: Gross Motor Function Classification System.
Notes: GMFCS categories for patients aged 6-12 years of age.
Source: Palisano *et al.* (2008) (57).

b. Other clinical symptoms related to ARG1-D

i. Hyperammonaemia

Although symptomatic hyperammonaemia and hyperammonaemic crises (HACs) are comparatively less common and less severe in ARG1-D compared to other UCDs, they are still a well-known manifestation of ARG1-D. (10, 15). HACs may be preceded by reported illness, non-compliance with diet, non-compliance with medication, and major life events (such as surgery, accidents, school stress, etc.) (58). In the pivotal PEACE study, HACs were defined as ammonia levels ≥100 µM requiring acute care or hospitalisation (59).

In an analysis of [redacted] ARG1-D patients in the UCDC registry, [redacted] of patients ([redacted] of [redacted] patients) had HACs reported either as part of their medical history or after study enrolment, with each patient averaging [redacted] HACs (range:[redacted]) (60).

As depicted in Figure 7, a relationship between arginine and ammonia levels has been observed in some patients with ARG1-D, with markedly elevated pArg typically coinciding with peak ammonia levels and metabolic decompensation events (30). [redacted]

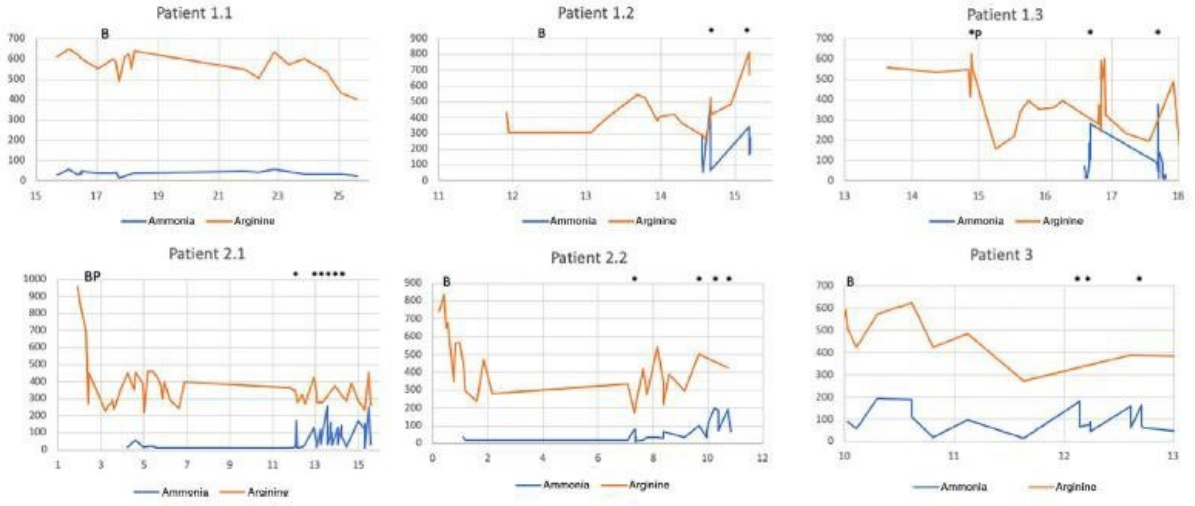
[redacted]

[redacted], confirmed that a correlation between pArg and ammonia levels is observed amongst their patient cohort, with elevated levels of pArg believed to be the triggering factor for HACs and metabolic decompensation (personal communication).

Hyperammonaemia, in the context of metabolic decompensations, remains a key driver of mortality for patients with ARG1-D, as confirmed by [redacted] and an additional UK clinical expert consulted by Immedica (47), with the risk of mortality increasing according to peak plasma ammonia levels. In a study by Enns *et al*. (2007), which observed HACs in patients with UCDs, peak ammonia levels of ≤200 µM, >200-500 µM, >500-1,000 µM, and >1,000 µM were associated with survival rates of 98%, 99%, 84%, and 47%, respectively (61). Few publications report on the peak ammonium levels of ARG1-D patients at death. Amongst the cohort of deceased ARG1-D patients who died following HACs identified in the literature, peak ammonium levels ranged from 345 – 1,897 µM (21, 30).

Further information on the mortality associated with ARG1-D can be found in Section B.1.3.1.2.c.

Figure 7: Arginine and ammonia levels (µM) followed up over time (age/years)



Notes: For Patients 2.1 and 2.2, there were no data points between the ages of 7–12 years and 2–7 years, respectively, as they had been lost to follow-up. In all patients, arginine levels were above the target of 200 µM virtually throughout follow-up. B: regular sodium benzoate commenced P: regular sodium phenylbutyrate commenced *: Metabolic decompensation
Source: Keshavan *et al*. (2022) (30).

ii. Growth deficiency

Patients with ARG1-D show a failure to thrive and a persistent low growth rate that leads to a short stature. Despite interventions to aid with nutrient uptake, failure to thrive is common in ARG1-D patients, with Diaz *et al*. (2019) reporting a prevalence of 56% in an analysis of 140 unique case reports (Figure 5) (45). Studies conducted by Carvalho *et al*. (2012) and Prasad *et* al. (1997) report that 81% of patients with ARG1-D demonstrate growth restriction (14, 21), and patients may never subsequently reach adult height (62). Microcephaly is also a common manifestation reported in the published literature (29).

iii. Eating disorders

Dietary habits and eating patterns in patients with ARG1-D are infrequently reported in the literature. In the European BoI study, 19% of patients had a long-term illness or disability, including low body weight/eating disorder (46). Among patients with UCDs, protein aversion, food refusal, frequent vomiting, and poor appetite are frequently reported (63). Amongst 44 patients with UCDs prescribed tube feeds in a cross-sectional study by Adam *et al*. (2012), which included three patients with ARG1-D, inadequate energy intake (25%), poor quality diet (23%), and food refusal (21%) were highlighted as the primary reasons for tube feeding (48).

c. Mortality

The morbidity associated with ARG1-D increases the risk of early mortality for patients (29, 45). Very few patients are described in the literature who survive far into adulthood. While data on the prognosis of ARG1-D is not readily available in a large cohort of patients, life expectancy is estimated to be 35 years, which is below half the average life expectancy of the general population in the UK (females: 82.9 years; males: 79.0 years) (2, 30, 59, 64). A study by Keshavan *et al*. (2022) and the clinical studies of pegzilarginase did not enrol any patients above the age of 32 years (2, 30, 59). It is acknowledged that occasionally, patients may live beyond 35 years; Schlune *et al*. (2015) describe two deceased patients aged 45 and 47 years, with a third patient aged 42 years still alive at the last study visit in 2013 (11), while one patient surveyed in the European BoI study was aged 49 years (46). However, such cases are believed to be extremely rare.

The specific factors driving early mortality in ARG1-D are not yet clear; precipitating events in the literature are diverse and the end stages of the disease remain to be fully characterised (13). As described in Section B.1.3.1.2.b.i, hyperammonaemia in the context of metabolic decompensations, remains a key driver of mortality for patients with ARG1-D (47). Seizures, liver failure, sepsis, and chest infection due to immobility or other related cause were also highlighted as primary causes of mortality by [redacted] and [redacted] (personal communication).

Despite this, the potential for early mortality is frequently reported in patients with ARG1-D in the published literature. A literature review by Diaz *et al*. (2019), which analysed 140 case reports of patients with ARG1-D, identified 20 patients who had died at the time of publication, with a median age at time of death of 17 years (45). Where information was reported, causes of death included respiratory complications (n=6), liver complications (n=4), metabolic complications (n=2), and hyperammonaemia (n=1). In addition, an SLR of published case reports conducted by Bin Sawad *et al*. (2022) identified 16 deceased patients, with a median age at death of 5.7 years. The reported causes of death include cardiac arrest, cerebral oedema, pneumonia/respiratory complications and/or sepsis (29).

B.1.3.1.3. Humanistic burden

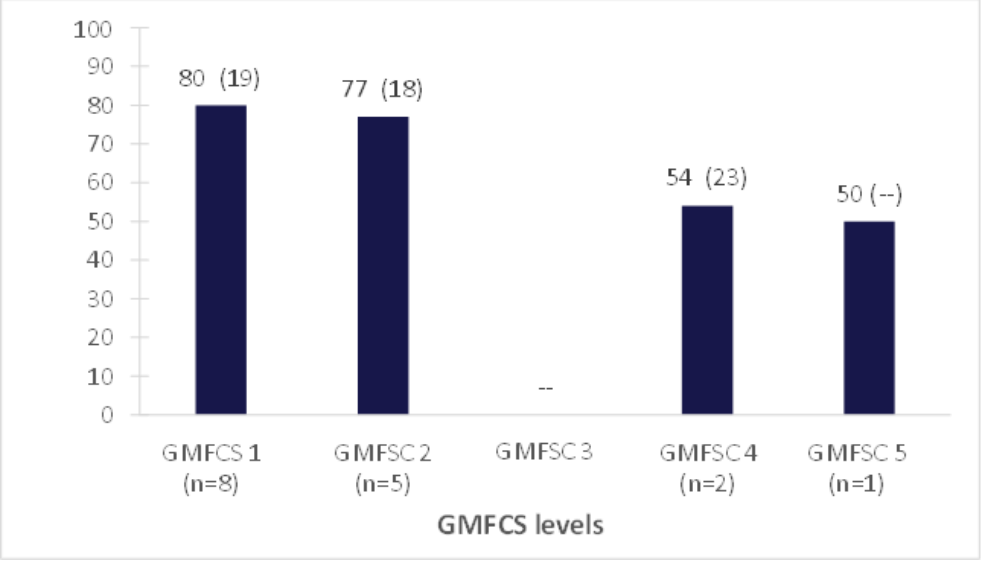
As outlined in B.1.3.1.2.a, the clinical symptoms of ARG1-D result in functional disability and can impair activities of daily living for patients with the condition (32). Due to learning difficulties, many paediatric patients don't attend mainstream education and often require specialist schooling. The European BoI study reported that 43% of sampled patients had received/did receive specialised education (46). For those who remain in mainstream schooling, additional educational input is required (30). Post-education, cognitive deficits can limit the ability of the patient to find and maintain employment (26). Of the nine patients aged ≥16 years of age in the survey, none were employed, highlighting the substantial loss of productivity associated with adult ARG1-D patients (46).

The adherence to a strict protein-restricted diet, which forms a fundamental part of IDM in ARG1-D, is cited as one of the most difficult aspects of managing the condition for patients and caregivers (22). Although the specific impact in ARG1-D has not yet

been quantified, studies in other metabolic diseases report that the HRQoL for patients and caregivers is affected by dietary restrictions, even to a higher extent than taking medications (65-67).

At present, studies in ARG1-D are limited to clinical symptoms and disease-specific assessments. No study has investigated the longitudinal impact of ARG1-D on patient HRQoL (29). In the European BoI study, the burden of ARG1-D on HRQoL was measured cross-sectionally using the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire. Most ARG1-D patients experienced problems with the ability to conduct daily activities (69%), mobility (62%), and pain/discomfort (56%). The mean (standard deviation [SD]) HRQoL score reported on the EuroQol-Visual Analogue Scale (EQ-VAS) was 72 (19), and 0.498 (0.352) when reported by the van Hout crosswalk tariff (68); similar scores have been recorded in patients with multiple sclerosis (69, 70), another disabling disease associated with spasticity. Both the EQ-5D-5L and EQ-VAS scores for ARG1-D were also highly correlated with GMFCS level (Figure 8) (46).

Figure 8: Mean EQ-VAS score for ARG1-D patients by GMFCS level



Key: EQ-VAS: EuroQoL-Visual Analogue Scale; GMFCS: Gross Motor Function Classification System; SD: standard deviation.
Source: Figure 10, A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers (46).

As a result of functional disability and impairment of activities of daily living from an early age, patients often require substantial levels of assistance in their home by professional caregivers and/or family members (46). In the European BoI study, professional caregiving was provided for 29% of patients (6 of 21 patients) enrolled

ARG1-D patients. With regards to family caregiving, eight caregivers for patients with ARG1-D reported providing care for an average of 24 hours a week, with other family members also contributing to an additional 25 hours of care throughout the week. Assistance with daily activities (38%) and transportation (38%) were the most common types of assistance provided, whilst aid with personal care and household activities were also reported. The level of assistance provided to patients also has a profound impact on the productivity of caregivers; 50% of caregivers surveyed (8 of 16 caregivers) were unemployed, with 33% (3 of 9 caregivers) stopping work due to caregiving. Of the caregivers who were employed, 57% (4 of 7 caregivers) had to reduce work hours in order to be a caregiver (46).

The impact of assistance provision and loss of productivity for caregivers of ARG1-D patients has not previously been reported in the literature (29). The European BoI study reported that most ARG1-D caregivers experienced problems with anxiety/depression (50%), pain/discomfort (50%), and the ability to conduct daily activities (44%), albeit the number of observations were small (46).

Furthermore, the European BoI study also collected information on caregiver burden using the Zarit Burden Interview Short: 12 items (ZBI-12) questionnaire (46). The ZBI-12 score ranges from 0-48, with a higher score representing a greater caregiver burden (71). Amongst the 16 caregivers involved in the study, a mean score of 12.3 was reported, indicating a mild to moderate burden (72), falling between published ZBI-12 scores for caregivers of patients with cancer (mean: 10.2) and dementia (mean: 14.2) (73, 74). Results indicated a higher caregiver burden for patients with greater mobility limitations, with caregivers of patients with GMFCS levels I and II demonstrating a lower ZBI-12 score (11.3 and 11.5 respectively) compared to those caring for ARG1-D patients with a GMFCS score of IV and V (16.0 and 16.5 respectively) (46).

B.1.3.1.4. Societal and economic burden

Despite a lack of data, it is evident that the management of ARG1-D is associated with significant healthcare resource use (HCRU). In the published literature, HCRU for patients with ARG1-D is based on a single study from the US (75). A retrospective, observational analysis of claims data by Bin Sawad *et al*. (2022) found that HCRU was

twice as high for patients with ARG1-D in terms of emergency room visits, 1.5 times higher for performing laboratory tests, and patients required hospitalisation three times more often, compared to those without the disease (75).

Substantial HCRU for ARG1-D patients was confirmed in the European BoI study (Table 4). Over a 12-month period, six ARG1-D patients (29%) reported having visited the emergency department, with five of these patients reporting having been hospitalised for an average of eight days. ARG1-D patients were treated by multiple healthcare professionals, with metabolic specialists (70%), dieticians (52%), neurologists (43%), and physiotherapists (38%) amongst the most frequently visited specialists (46).

Table 4: Healthcare resource use associated with managing ARG1-D

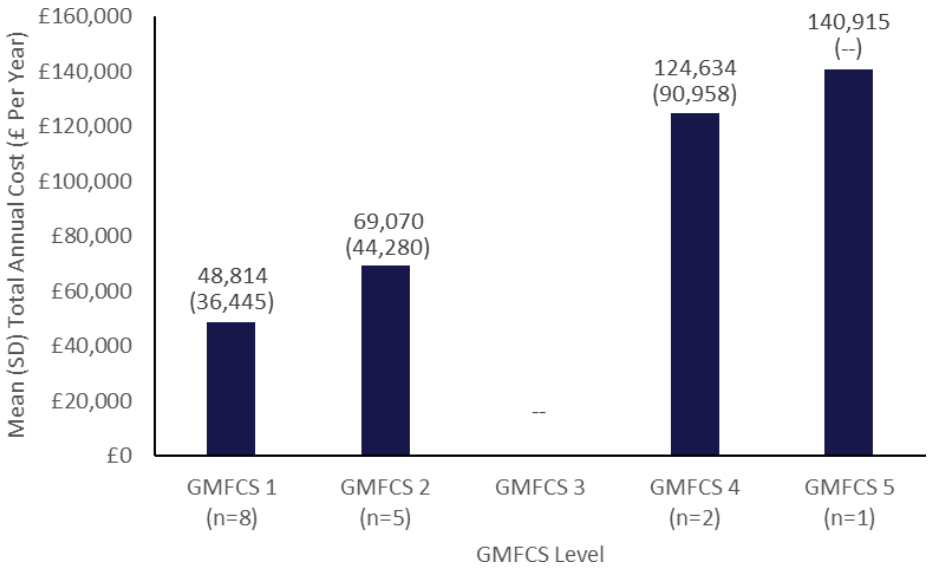
Variable	Proportion (%) of patients	n	Mean (SD) number of visits among those with any visits	Missing values in the mean calculation
Visited emergency department at the hospital, n=21				
Yes	29	6	1.8 (0.75)	
No	71	15		
Been hospitalised				
Yes	29	6		
No	71	15		
No. of hospitalisation n=6				
1	67	4		
2	17	1		
3	17	1		
No. of hospitals days, n=6	--	6	7.7 (6)	
Visited health care staff, n=21		6		
Neurologist	43	9	1.4 (0.8)	2
Paediatrician	14	3	2.3 (2.1)	
Metabolic specialist	70	13	4.2 (3.5)	
Geneticist	0	0	0	
General practitioner/paediatrician	5	1	3 (--)	
Nurse	21	4	22.8 (34.3)	
Physiotherapist/ Rehabilitation specialist	38	8	26.3 (31.0)	1
Occupational therapist	14	3	20.0 (21.2)	1
Psychologist	24	5	13.4 (20.7)	
Dietician	52	11	5.3 (4.2)	1
Speech therapist	10	2	18.0 (24.0)	
Other*	14	3	17.7 (16.2)	

Treatment with botulinum toxin, yes, n=21	52	11	10.1	3
Surgical treatment for muscle stiffness, yes, n=21	0	0	0	

Key: BoI: burden of illness; SD: standard deviation.
Notes: Number of patients = 21.
*For example, endocrinology, haematology, orthopaedics.
Source: Table 8, A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers (46).

Furthermore, the cohort of ARG1-D patients and caregivers who participated in the European BoI study experienced a substantial economic burden as a result of the condition. The mean (SD) annual total cost per patient was calculated at £67,096 (£53,225), driven primarily by indirect costs (production loss) to both patients and caregivers (46%). The cost burden associated with ARG1-D is also driven by GMFCS level, with an increase in healthcare costs associated with disease progression as measured by GMFCS level (Figure 9) (46).

Figure 9: Mean (SD) total annual cost stratified by GMFCS levels (£ per year)



Key: GMFCS: Gross Motor Function Classification System; SD: standard deviation.
Notes: Costs were calculated from a societal perspective. Total annual costs included direct medical costs (healthcare, medications, and diet), direct non-medical costs (professional caregiving, family caregiving, wheelchair, and special schooling), and indirect costs (production loss for patient and caregiver).
Source: Table 16, A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers (46).

B.1.3.2. Clinical care pathway

Neither the National Institute for Health and Care Excellence (NICE) nor NHS England provide guidance on the treatment of ARG1-D in the UK (26), while the British Inherited Metabolic Disease Group (BIMDG) only provide guidelines on the emergency

management of UCDs, including ARG1-D, and do not provide details of ongoing treatment (76). As such, the clinical care pathway for ARG1-D patients in England, depicted in Figure 10, was developed based on feedback from discussions with UK clinical experts (26). Available guidelines are summarised in the Section B.1.3.2.1 and Section B.1.3.2.2.

In England, a diagnosis of ARG1-D can be readily made with routinely available assessment of red blood cell arginase level, pArg assessment, or genetic analysis (15). Genetic testing is routinely used to confirm diagnosis of ARG1-D, as supported by structured clinical interviews conducted by Immedica. Screening for ARG1-D is not part of the NHS newborn screening programme (26).

Despite the multiple and straightforward means of diagnosis, delays in diagnosis or misdiagnosis still occur. This is likely due to the heterogenous nature of the symptomatology overlapping with other developmental conditions, such as CP and hereditary spastic paraplegia, and lack of awareness among healthcare professionals (14, 43, 77). In a UK-based retrospective review of patient medical records by Keshavan *et al*. (2022), a mean delay in diagnosis of 6.1 (0.0 – 11.5) years was reported (n=6) (30). In the European BoI study, the time to ARG1-D diagnosis for three patients after initial misdiagnosis ranged from 1-13 years (46). Delays in diagnosis can lead to disease progression and the deterioration of clinical outcomes (17, 18, 46).

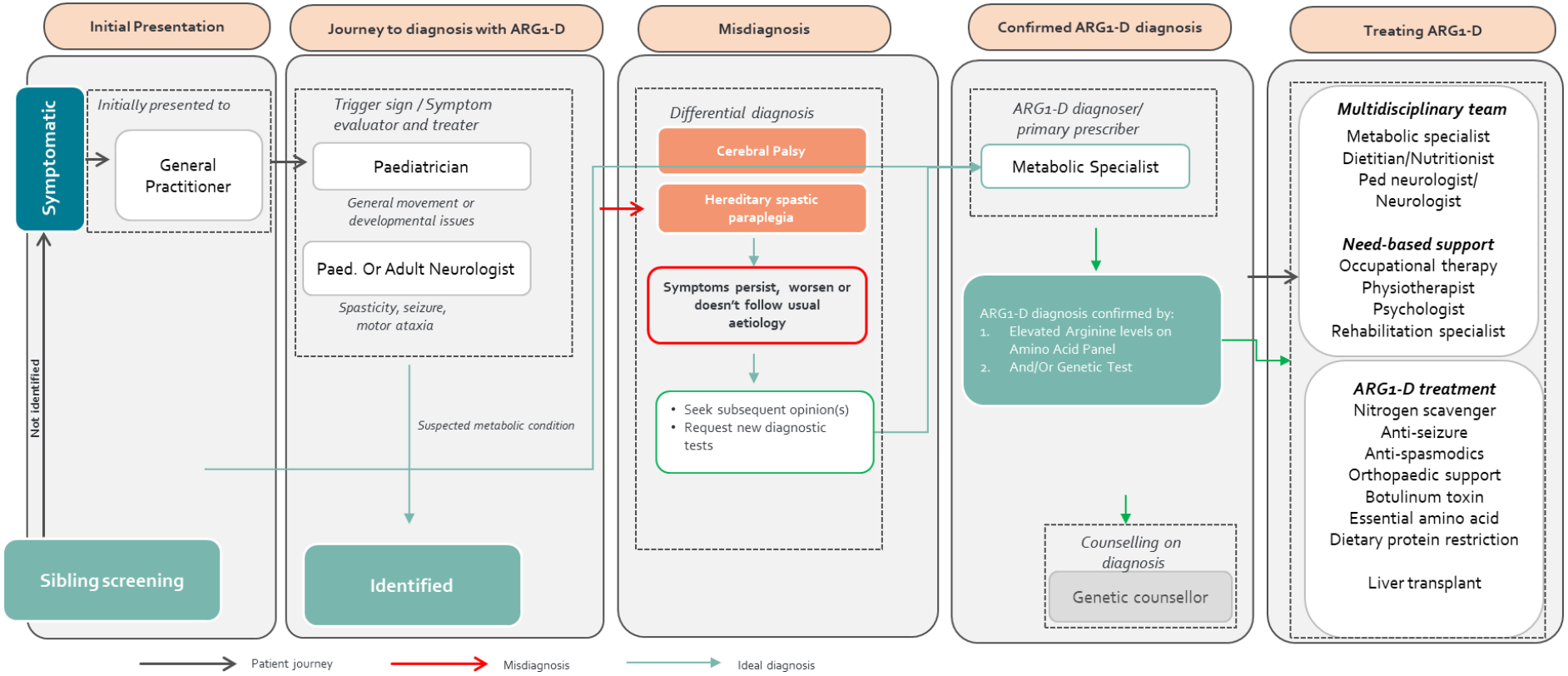
There are no licensed treatments specifically targeting pArg for patients with ARG1-D. IDM for ARG1-D is based on case reports and limited clinical studies and does not address the issue of endogenous arginine production (15, 78, 79). IDM consists of dietary protein restriction, supplemented with EAAs, to manage high arginine levels, and nitrogen scavengers to prevent HACs that are less commonly associated with ARG1-D compared to other UCDs (26, 44).

With continued disease progression, an increasing variety of supportive pharmacological therapies are required to mitigate some of the effects of the disease, including the control of seizures, reduction of spasticity, and improvement in nutritional status (26). In addition, these patients may require surgical procedures to address complications, including contractures related to long-term spasticity (30), or treatment

with botulinum toxin, which may be used to treat spasticity (26). In rare cases, ARG1-D is treated by liver transplantation (29).

Consequently, given the heterogenous nature of ARG1-D, the approach to patient management is highly individualised and requires support from a multidisciplinary team of specialists, including metabolic specialists, paediatricians, dieticians, and neurologists (26).

Figure 10: Current clinical care pathway for ARG1-D patients in England



Key: ARG1-D: arginase 1 deficiency.
Sources: ARG1-D modified Delphi: Stage 1 Report (26).

B.1.3.2.1. BIMDG formulary

Guidance issued by the BIMDG is intended for the emergency management of UCDs only. Management decisions are based on the clinical status of the patient. If there is clinical suspicion of hyperammonaemia, or the plasma ammonia level is significantly elevated, the patient is treated with intravenous fluids. For patients with ARG1-D, the intravenous fluid contains sodium benzoate and sodium phenylbutyrate solutions, and is provided at a rate of 2mls/kg/hour (76).

No guidance is provided on how to reduce arginine levels in ARG1-D (76).

B.1.3.2.2. Guidelines for the diagnosis and management of ARG1-D

Häberle *et al*. (2019) provide a trans-European consensus clinical practice guideline for the diagnosis and management of UCDs, with recommendations on ARG1-D limited to a small sub-section (15). Key recommendations are summarised below:

- Adherence to a strict protein restriction is suggested to reduce pArg levels as low as possible and <200 μM (15)
- EAA supplementation is required in patients with ARG1-D, providing an overall adequate EAA intake from natural foods and supplements. Given the severe natural protein restriction necessary for patients with ARG1-D, up to 50% of the protein supply may be offered as EAA (15)
- Nitrogen scavengers, including sodium benzoate, sodium phenylbutyrate, or sodium phenylacetate, and glycerol phenylbutyrate are recommended to prevent the occurrence of HACs (15)
- Liver transplantation should be considered for patients with severe UCDs without sufficient response to standard treatment, poor quality of life, without neurological damage and while in a stable metabolic condition (15)

B.1.3.2.3. Unmet needs with current treatment

Current international guidelines for ARG1-D focus on the reduction of pArg to levels of <200 μM and ideally to within normal range (defined as ≥40 - ≤115 μM) as the

primary treatment goal (15, 80). However, there are no pharmacologic agents known to effectively reduce arginine levels in patients with ARG1-D. Current management approaches for ARG1-D include individualised combinations of protein restriction to reduce arginine, EAA supplementation, and concomitant medications to manage other clinical symptoms such as nitrogen scavengers to help control ammonia levels. Dietary modifications can produce modest reductions in pArg levels but reducing pArg to the guideline recommended level of <200 μM is very rarely, if ever, achieved via dietary restriction alone as arginine flux is largely dependent on whole body protein turnover and is minimally affected by dietary intake (29, 81). In addition, treatment is difficult to adhere to, does not account for endogenous protein catabolism, may be initiated after irreversible neurological damage and may therefore not offer an effective treatment for all patients. Around 25% of patients still suffer from severe mental deficits and loss of ambulation despite dietary/drug intervention (7).

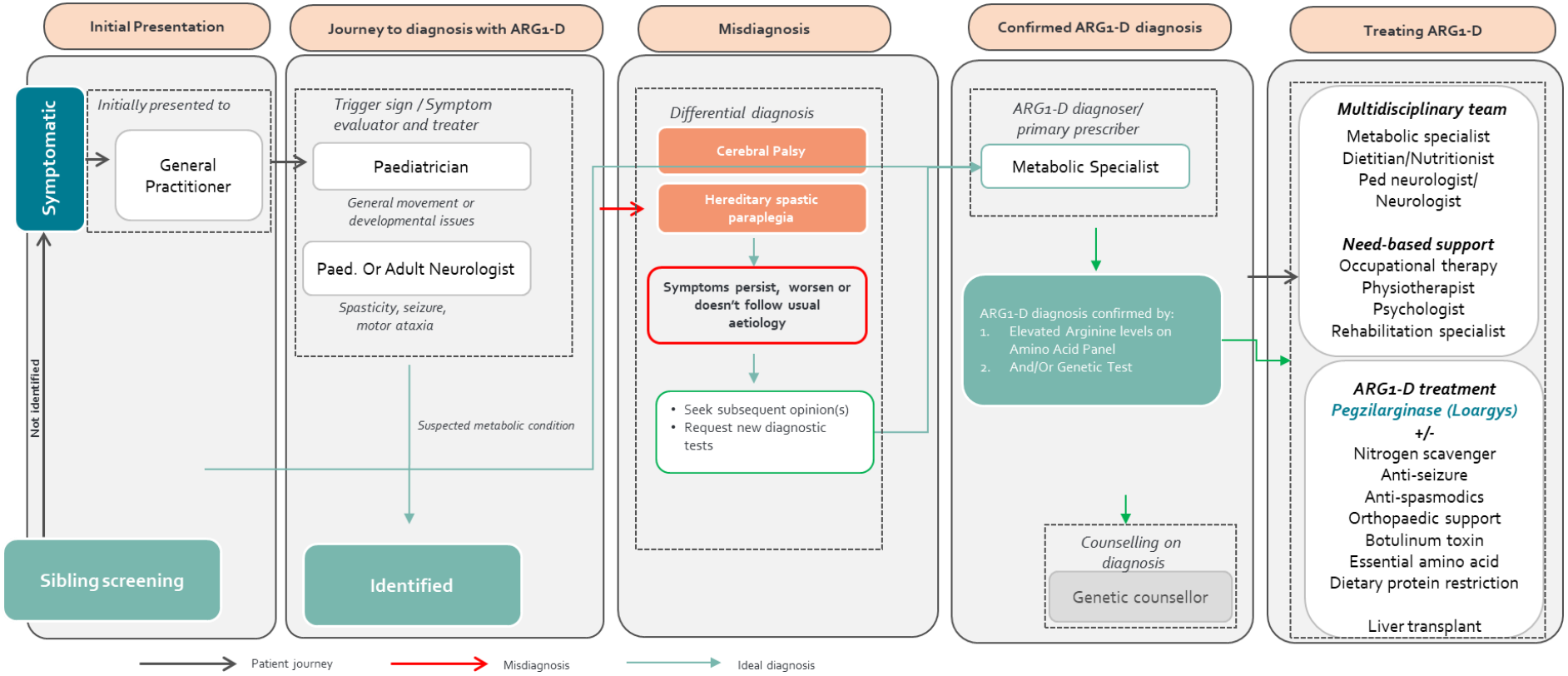
Liver transplantation has been reported to achieve disease normalisation in some patients (82, 83); however, transplantation is only available to only a small fraction of patients, carries a significant risk of morbidity and mortality, and does not reverse disease progression that has already taken place (29).

Considering the above, a substantial unmet need remains for a treatment option that can lower and maintain pArg levels to treatment guidelines or within normal range and offer the opportunity for normal neurocognitive and neuromotor development through minimising patients to the neurotoxic effects of elevated arginine and its metabolites.

B.1.3.2.4. Proposed positioning of pegzilarginase

Pegzilarginase is positioned for the treatment of ARG1-D, also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older. Pegzilarginase is intended for chronic management of patients with ARG1-D in conjunction with IDM such as dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers. The proposed positioning of pegzilarginase within the current clinical care pathway in England is displayed schematically below in Figure 11.

Figure 11: Proposed positioning of pegzilarginase in the ARG1-D treatment pathway



Key: ARG1-D: arginase 1 deficiency.
Sources: ARG1-Deficiency modified Delphi: Stage 1 Report (26).

B.1.4 Equality considerations

In the UK, ARG1-D predominantly affects individuals from ethnic minority backgrounds. [redacted] (personal communication). In addition, all patients analysed in a UK-retrospective review of patient medical records by Keshavan *et al*., (2022) were of Somali or Pakistani ethnicity (30), supporting the notion that a large majority, if not all, ARG1-D patients in the UK are from an ethnic minority background.

Due to the autosomal recessive inheritance of ARG1-D, the birth and population prevalence of the condition is highest in countries with high consanguinity. Estimates of country-specific birth and population prevalence are highest amongst countries in the Middle East, including Qatar, Kuwait, United Arab Emirates, and Saudi Arabia. By contrast, countries with predominantly homogenous white European populations and very low consanguinity have the lowest birth and population prevalence of ARG1-D (24). In systematic literature review of case reports conducted by Bin Sawad *et al* (2022), 50 of 157 identified patients (32%) were born of consanguineous parents (29, 44). Consanguinity was also observed in two of three families with ARG1-D patients included in the aforementioned UK-based study by Keshavan *et al*., (2022) (30).

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify all the clinical evidence relevant to the technology being appraised.

See Appendix D1.3 for full details of the process and methods used to identify and select the clinical evidence relevant to pegzilarginase for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older.

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified three trials that provide direct evidence on the efficacy and safety of pegzilarginase for the treatment of ARG1-D in patients aged 2 years and older:

- **CAEB1102-300A (hereafter referred to as PEACE)**: a Phase 3, randomised study consisting of a 24-week double-blind, placebo-controlled period followed by an open-label, long-term extension (LTE) period to evaluate the efficacy and safety of IV and SC pegzilarginase (up to 150 weeks planned duration) (Table 5)

- **CAEB1102-102A (hereafter referred to as Study 102A)**: a Phase 2, open-label, LTE study to evaluate the long-term safety, tolerability, and efficacy of IV pegzilarginase in patients with ARG1-D who completed Part 2 of CAEB1102-101A (Table 5)

- **CAEB1102-101A (hereafter referred to as Study 101A)**: a Phase 1/2 open-label, two-part (Part 1 [single ascending dose escalation] and Part 2 [repeated dosing] study in patients with ARG1-D to investigate the safety, pharmacokinetics, and pharmacodynamics of IV pegzilarginase (Table 5)

PEACE was a Phase 3, randomised study consisting of a 24-week, double-blind, placebo-controlled period followed by an open-label LTE period to evaluate the efficacy and safety of IV and SC pegzilarginase in 32 paediatric and adult patients with

ARG1-D. The primary source of data underpinning this submission is available from the PEACE clinical study report (CSR), which describes the final analyses for the double-blind period of the study and LTE data up to 150 weeks, with the last patient's last visit on February 1st 2023 (84). To date, five records relating to final data from the double-blind period and interim LTE data are available in the public domain, including one publication (59), three conference abstracts (85-87), and one oral presentation (88).

Final data from the double-blind period and interim data for the LTE (up to LTE Week 24) was recently published by Sanchez Russo *et al*. (2024) in *eClinicalMedicine* (59), and provides the most-recent source of publicly available long-term data from PEACE, with a data cut-off date of March 24th 2022. Where possible, published data from Sanchez Russo *et al*. (2024) will be used to underpin the narrative on clinical effectiveness for the 24-week, double-blind period of the study. Furthermore, the most-recent patient-level analyses of pegzilarginase effect on plasma arginine and clinical response in the LTE up to LTE Week 120 was recently shared with the EMA as part of mandatory post-authorisation measures for the marketing authorisation under exceptional circumstances (23, 89). As a result, this data is used to underpin the narrative on responder analysis and composite clinical outcome in Section B.2.6.1.2.g. Besides this, the PEACE CSR forms the primary source underpinning the narrative on clinical effectiveness for the LTE.

Supporting clinical evidence of the efficacy and safety of pegzilarginase is available from Study 102A, a Phase 2, open-label LTE study to evaluate the long-term safety, tolerability, and efficacy of IV and SC pegzilarginase for up to four years in patients who had previously participated in the parent study, Study 101A. Study 102A was completed on December 15th 2022, with the CSR providing follow-up data for the efficacy and safety of pegzilarginase up to 262 weeks. The SLR identified six records relating to Study 101A/102A in the public domain including one publication (2), four conference abstracts (90-93), and one oral presentation (94).

Interim data for the first 12 weeks of the open-label LTE Study 102 were published in the *Journal of Inherited Metabolic Disease* (2), while limited results from Study 102A have also been presented in the EMA EPAR (through Week 120) (23). Where

possible, information sourced from the public domain will be used to supplement results from the CSR, which forms the primary source of data underpinning Study 102A. Of note, the most-recent patient-level analyses of pegzilarginase effect on plasma arginine and clinical response in the LTE up to Week 190 was recently shared with the EMA as part of mandatory post-authorisation measures for the marketing authorisation under exceptional circumstances (23, 89). As a result, this data is used to underpin the narrative on composite responder analysis in Section B.2.6.2.6.

Study 101A was a Phase 1/2 open-label, uncontrolled dose-finding study in 16 paediatric and adult patients with ARG1-D. In Part 1, single IV doses were individually titrated every two weeks to an arginine target level of <200 µM, followed by Part 2, where treatment was continued as weekly IV dosing for seven weeks. Study 101A was completed on February 28th 2019, and the CSR provides the primary source of data underpinning the study narrative. Results from Study 101A were published in the *Journal of Inherited Metabolic Disease*, which is used to supplement the narrative on Study 101A where appropriate (2).

Study 101A was an uncontrolled dose-finding study and was not designed to measure the efficacy of pegzilarginase, however, given the ultra-orphan nature of ARG1-D, the study has been included as appropriate in the submission. For the sake of brevity, we report the study methodology for Study 102A, with details on Study 101A supplemented in Sections B.2.3 and B.2.4. Details of the clinical effectiveness and safety data for Study 101A have been included in Appendix P.

Table 5: Clinical effectiveness evidence: PEACE, Study 102A, and Study 101A

Study	CAEB1102-300A (PEACE) (NCT03921541)	CAEB1102-102A (NCT03378531)	CAEB1102-101A (NCT02488044)
Study design	A Randomised, Double-blind, Placebo-controlled Phase 3 Study of the Efficacy and Safety of Pegzilarginase in Children and Adults With Arginase 1 Deficiency	A Phase 2 Open-label, Multicentre Extension Study to Evaluate the Long-Term Safety, Tolerability and Effects of Intravenous AEB1102 in Patients With Arginase I Deficiency Who Previously Received	A Phase 1/2 Open-label Study in Patients with Arginase I Deficiency to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous AEB1102

		Treatment in Study CAEB1102-101A.	
Population	Patients aged 2 years and older with ARG1-D	Patients aged 2 years and older with ARG1-D	Patients aged 2 years and older with ARG1-D
Intervention(s)	Pegzilarginase plus IDM	Pegzilarginase plus IDM	Pegzilarginase plus IDM
Comparator(s)	Placebo plus IDM	None (Study 102A is a single-arm study)	None (Study 101A is a single-arm study)
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	Yes
Rationale if study not used in model	*Not applicable. PEACE presents the pivotal, regulatory, clinical evidence in support of pegzilarginase in ARG1-D.*	*Not applicable. Study 102A provides long-term efficacy and safety data in support of pegzilarginase in ARG1-D.*	*Not applicable. Data used for the statistical model of the relationship between GMFCS and GMFM*
Reported outcomes specified in the decision problem	• Plasma arginine concentration • Level of ornithine and guanidino compounds • **Mobility** • Adaptive behaviour • **Neurocognitive function** • Adverse effects of treatment • **Health-related quality of life**	• Plasma arginine concentration • Level of ornithine and guanidino compounds • **Mobility** • Adaptive behaviour • **Neurocognitive function** • Adverse effects of treatment • **Health-related quality of life**	• Plasma arginine concentration • Level of ornithine and guanidino compounds • **Mobility** • Adaptive behaviour • **Neurocognitive function** • Adverse effects of treatment • **Health-related quality of life**
All other reported outcomes	Not applicable	Not applicable	Not applicable

Key: ARG1-D: arginase 1 deficiency; IDM: individualised disease management.
Notes: Outcomes used in the economic model are highlighted in bold.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. PEACE

B.2.3.1.1. Trial methodology

Table 6: Summary of study methodology for CAEB1102-300A (PEACE)

Study	**CAEB1102-300A (PEACE) (NCT03921541)**
Location	This study is being conducted at 19 sites across seven countries: United States (9 sites), United Kingdom (4 sites), France (2 sites), Austria (1 site), Canada (1 site), Germany (1 site), and Italy (1 site)
Study design	A randomised, double-blind, placebo-controlled Phase 3 study of the efficacy and safety of pegzilarginase when added to IDM in children and adults with ARG1-D
Key eligibility criteria for participants	**Inclusion criteria:** • Documented ARG1-D diagnosis (through elevated plasma arginine (pArg), pathogenic variants in *ARG1*, and/or erythrocyte ARG1 activity) • pArg ≥250 µM (mean of all screening values) • Male and female patients aged ≥2 years of age on the date of informed consent/assent • Impairment on any secondary functional mobility assessment (see Table 8, Section B.2.3.1.3) **Exclusion criteria:** • Symptomatic hyperammonaemia (ammonia ≥100 µM requiring acute care or hospitalisation) • Extreme mobility deficit (i.e., unable to complete mobility assessments) • Other medical conditions or comorbidities that would preclude study compliance (e.g., severe intellectual disability) • Patients with ongoing or planned initiation of treatment with botulinum toxin containing regimens during the blinded portion of the study, or surgical or botulinum toxin treatment for spasticity-related complications within 16 weeks before first pegzilarginase dose • Participation in previous interventional study with pegzilarginase • Prior liver or haemopoietic transplant procedure

Settings and locations where the data were collected	• In the double-blind period, treatment and all study procedures were performed on outpatient visits to the study site • If appropriate, in the opinion of the investigator in consultation with the sponsor, patients were permitted to be administered study treatment and have laboratory samples taken outside of the study site by appropriately qualified and trained home healthcare personnel
Study periods and trial drugs	The study consisted of the following study periods: 1. A screening period of 3-4 weeks to collect all necessary information to ensure the patients met study eligibility criteria and to establish baseline pArg data, collect prescribed diet data, and determine adherence to prescribed diet using a diet diary 2. A randomised, double-blind period of 24 weeks 3. An open-label LTE period of up to approximately 150 weeks in which all patients received pegzilarginase. The first eight weeks of treatment previously administered during the double-blind period were to remain blinded to ensure that study data relating to the randomised period was collected prior to unblinding Eligible patients were randomised in a 2:1 ratio to receive weekly IV infusions of pegzilarginase plus IDM or placebo plus IDM during the 24-week double-blind treatment period.
Prior and concomitant medication	Patients were required to maintain dietary protein intake levels that were consistent with their baseline levels that were consistent with baseline levels for the entire duration of the randomised, double-blind period and the eight-week blinded period of the LTE period of the study.
Primary efficacy endpoint	• Change from baseline in pArg after 24 weeks of study treatment
Secondary outcomes used in the model/specified in the scope	Key secondary outcomes: • Mean change from baseline at Week 24 in the 2-Minute Walk Test (2MWT) • Mean change from baseline at Week 24 in the Gross Motor Function Measure-88, Part E (GMFM-E) Other secondary outcomes: • Change from baseline in ornithine and guanidino compounds after 24 weeks of study treatment • Mean change from baseline at Week 24 in the GMFM-88, Part D (GMFM-D) • Mean change from baseline at Week 24 in the VABS-II • Adverse events Tertiary outcomes specified in the scope: • Responder analysis and composite clinical outcomes • Neurocognitive function (BSID-III and Wechsler intelligence batteries)

	• Improvement of spasticity (Modified Ashworth Scale) • Health-related quality of life (PedsQL, SF-36, and ZBI-12)
Pre-planned subgroups	• Age • Sex • Region • GMFCS classification

Key: ARG1-D: arginase 1 deficiency; BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; EAA: essential amino acid; GMFCS: Gross Motor Function Classification System; GMFM-D: Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88, Part E; IDM: individualized disease management; IV: intravenous; PedsQL: Paediatric Quality of Life Inventory; SC: subcutaneous; SF-36: 36-Item Short Form Health Survey; VABS-II: Vineland Adaptive Behaviour Scale, Second Edition; ZBI-12: Short-Form Zarit Burden Interview.
Sources: Sanchez Russo *et al.* (2024) (59); PEACE CSR (84).

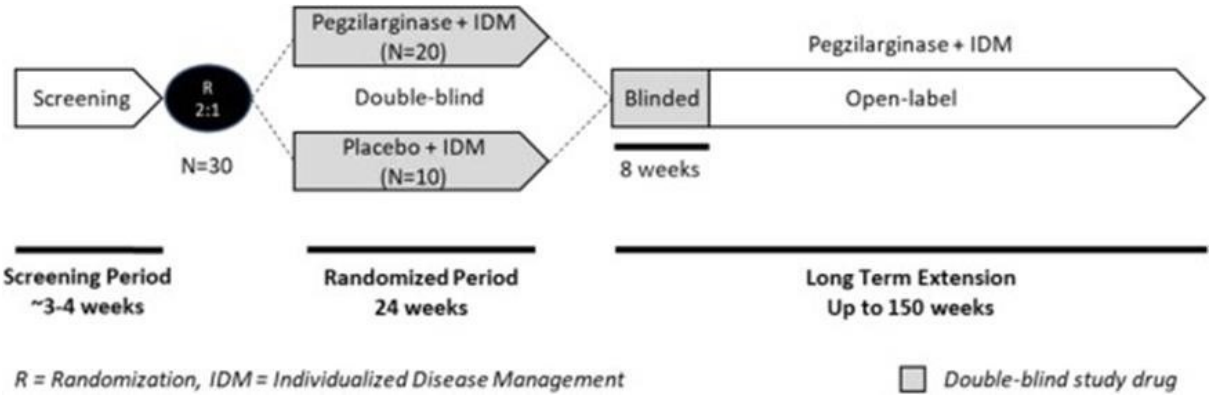
B.2.3.1.2. Trial design

PEACE is a Phase 3, randomized study consisting of a 24-week, double-blind, placebo-controlled period followed by an open-label, LTE period to evaluate the efficacy and safety of IV and SC pegzilarginase in conjunction with IDM in patients aged 2 years and older with ARG1-D (59, 84).

Approximately 30 patients with ARG1-D were to be assessed to evaluate the efficacy and safety of pegzilarginase, with change in pArg from baseline after 24 weeks of study treatment (end of the double-blind period) as the primary endpoint (84).

As described in Table 6, and depicted below in Figure 12, the study consisted of the following stages: a screening period of 3-4 weeks, a randomised, double-blind, placebo-controlled period of 24 weeks, and an open-label LTE period of up to approximately 150 weeks in which all patients received active pegzilarginase (59, 84).

Figure 12: Study schema for PEACE



Source: Supplementary Information, Sanchez Russo *et* al. (2024) (59); Figure 1, PEACE CSR (84).

Patients were randomly assigned to a treatment group following completion of all screening assessments and confirmation of study eligibility in a 2:1 ratio to receive weekly IV infusions of pegzilarginase plus IDM or placebo plus IDM during the 24-week double-blind treatment period. Randomisation was stratified by the severity of prior history of hyperammonaemia to minimise potential bias from treatment group imbalance (59, 84).

Overall, 32 patients were enrolled and randomised in a 2:1 ratio to either pegzilarginase (n=21) or placebo (n=11) (59). Thirty-one of 32 randomised patients completed the 24-week double-blind period and continued onto the LTE portion of the study (59, 84). All 31 patients who continued onto the LTE portion of the study completed the study, with the last patient's final visit occurring on February 1st 2023 (84).

B.2.3.1.3. Eligibility criteria

The key inclusion and exclusion criteria for PEACE are described below in Table 7.

Table 7: Key eligibility criteria for PEACE

Key inclusion criteria	Key exclusion criteria
• A current diagnosis of ARG1-D including one of the following: elevated plasma arginine (pArg) levels, a mutation analysis that resulted in a pathogenic variant, or reduced RBC arginase activity • Average of all measured values of pArg during the screening period prior to randomisation visit (Visit 1, Study Day 1) is ≥ 250 µmol/L • Male and female patients aged ≥ 2 years of age on the date of informed consent/assent • Patient was able to complete a key secondary/secondary assessment and had a baseline deficit in at least one component as defined in Table 8 • Have received documented confirmation from the investigator and/or dietician that the patient can maintain their diet in accordance with	• Hyperammonaemic episode (defined as an event in which a subject has an ammonia level ≥100 µM with one or more symptoms related to hyperammonaemia requiring hospitalisation or emergency room management) within the 6 weeks before the first dose of study drug is administered • Extreme mobility deficit, defined as either inability to be assessed on the GFAQ or a score of 1 on the GFAQ • Other medical conditions or comorbidities that, in the opinion of the Investigator would interfere with study compliance or data interpretation (e.g., severe intellectual disability precluding required study assessments) • Patient is being treated with botulinum toxin-containing regimens or plans to initiate such regimens during the double-blind or blinded follow-up

dietary information presented in the protocol (i.e., can maintain the current level of protein consumption, including natural protein and EAA supplementation) • Patients receiving nitrogen scavenger therapy, anti-epileptic drugs, and/or medications for spasticity (e.g., baclofen) must be on a stable dose of the medication for at least 4 weeks prior to randomisation, and be willing to remain on a stable dose during the blinded portions of the study	portions of the study of the study or received surgical or botulinum-toxin treatment for spasticity-related complications within the last 16 weeks prior to the first dose of study treatment in this study • Participation in previous interventional study with pegzilarginase • Previous liver haematopoietic transplant procedure

Key: ARG1-D: arginase 1 deficiency; EAA: essential amino acid; GFAQ: Gillette Functional Assessment Questionnaire.
Sources: Sanchez Russo *et* al. (2024) (59); Section 9.3, PEACE CSR (84)

Given the importance of demonstrating clinically relevant treatment effects, in addition to reducing pArg levels in the PEACE study, enrollment was limited to patients with a measurable deficit in at least one of the ARG1-D manifestation(s) considered for the key secondary/other secondary endpoints: 2-Minute Walk Test (2MWT) or Gross Motor Function Measure-88, Part D (GMFM-D) or Gross Motor Function Measure-88, Part E (GMFM-E) (59, 84). Baseline deficits for the key secondary/other secondary endpoints are described in Table 8.

Table 8: Definition of baseline deficits for key secondary/other secondary endpoints

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

Key: 2MWT: 2-Minute Walk Test; GMFM: Gross Motor Function Measure.
Notes: *Definition of baseline deficit is calculated from the NIH toolbox motor domain dataset (2-Minute Walk Endurance Test). **Definition of baseline deficit from Oeffinger *et al*. (2008) (95).

For a full list of eligibility criteria, please refer to the PEACE CSR (84).

B.2.3.1.4. Settings and locations where data were collected

PEACE was conducted at a total of 19 study sites across seven countries: US (9 sites), UK (4 sites), France (2 sites), Austria (1 site), Canada (1 site), Germany (1 site), and Italy (1 site). All treatment and study procedures occurred on an outpatient basis at the study site (59, 84).

If appropriate, in the opinion of the investigator in consultation with the study sponsor, patients were permitted to be administered study treatment and have laboratory samples taken outside of the study site by appropriately qualified and trained home healthcare personnel (59, 84).

All site personnel involved in the study, including patients, families, caregivers, investigators, expert assessors of relevant endpoints, and all sponsor and contract personnel were blinded to the patient's randomised treatment assignment to minimise potential biases of safety and clinical outcomes (59, 84).

B.2.3.1.5. Trial drugs and concomitant medications

a. Pegzilarginase

In PEACE, the study drug was pegzilarginase. This was supplied as a liquid formulation in 10 mL single-use glass vials containing 5 mL of formulated drug product at a concentration of 1 mg/mL, or 5 mL of formulated drug product at 5 mg/mL. Patients initially randomised to the pegzilarginase treatment group received an initial dose of 0.10 mg/kg per week. In the LTE, patients initially randomized to pegzilarginase continued their optimized dose from the double-blind period, and those initially randomised to placebo transitioned to 0.10 mg/kg pegzilarginase with dose modifications permitted as appropriate.

Patients could be switched to SC administration at any point after the first eight weeks of the LTE. After the fourth SC dose, injections could be administered at the study site or at home by a qualified health care professional (59, 84).

b. Placebo

The comparator arm in the PEACE study was placebo. Placebo was supplied in a 10 mL single-use vial containing 5 mL of vehicle. The placebo infusion was volume-adjusted to match the volume of a hypothetical pegzilarginase infusion. Placebo was administered by IV infusion at the study site by the site investigator when the patient was attending a study centre visit during the randomised, double-blind period of the study, prior to the transition to the pegzilarginase treatment arm (59, 84).

c. Concomitant medications

All eligible patients had stable IDM plans, as demonstrated during the initial screening phase prior to study participation, including the amount of prescribed protein and the amount of prescribed EAAs with or without the use of a prescribed dose of nitrogen scavenger medication. Patients were required to have a stable, consistent diet for the entire duration of the blinded periods of the study (24-week randomization period and the first eight weeks of the LTE period). Study sites were instructed to minimize changes to within 15% of baseline for patients dietary protein intake to keep diet stable as much as possible throughout the study (59, 84).

Patients receiving ammonia scavenging therapy must have been willing to remain on a stable dose during the blinded portions of the study (59, 84).

d. Restricted medication

The use of botulinum toxin was prohibited until after patients completed the end of the blinded period. If necessary for the patient to utilise botulinum toxin during the LTE period, it was to be discussed with the sponsor prior to administration (84).

In addition, it was recommended that patients not undergo surgical procedures (e.g., tendon release) for correction of disease-related abnormalities during the double-blinded period of the study (84).

B.2.3.1.6. Outcomes in the economic model or specified in the scope, including primary outcome

The primary efficacy endpoint of PEACE was change from baseline in pArg concentration after 24 weeks of treatment (59, 84). As highlighted previously in Section B.1.3.1.1, pArg is mechanistically related to the primary disorder, is the single most common manifestation in all patients, and is believed to be the key driver of clinical manifestations of ARG1-D.

Additional secondary endpoints used to evaluate the magnitude, onset, and duration of changes in pArg levels included:

- Proportion of patients with pArg levels below target guidance (<200 µM) after 24 weeks of study treatment
- Proportion of patients with pArg levels within the normal range (≥40 µM to ≤115 µM) after 24 weeks of study treatment
- Change from baseline in ornithine and GCs after 24 weeks of study treatment

Other secondary and tertiary outcome measures that were used to evaluate the clinical benefit of pegzilarginase, per domain, are summarised in Table 9.

Table 9: Clinical outcome assessments in PEACE by domain

Domain Assessed	Test Name	Study Endpoint	Age Range*
Locomotion / Mobility / Endurance	2-Minute Walk Test (2MWT)	Mean change from baseline at Week 24 in the 2MWT	3 to 85
Motor Function	Gross Motor Function Measure-88, Part D (GMFM-D)	Mean change from baseline at Week 24 in the GMFM-D	≥5 months
	Gross Motor Function Measure-88, Part E (GMFM-E)	Mean change from baseline at Week 24 in the GMFM-E	≥5 months
	Modified Ashworth Scale (MAS)	Mean change from baselines at Week 24 in the MAS	All ages
Adaptive Behaviour	Vineland Adaptive Behaviour Scale,	Mean change from baseline at Week 24 in the VABS-II	All ages

	2nd Edition (VABS-II)		
Neurocognition and Memory	Bayley Scales of Infant Development, Third Edition (BSID-III)*	Mean change from baseline at Week 24 in the BSID-III	2 to 3.5 years
	Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV)	Mean change from baseline at Week 24 in the WPPSI-IV	2.5 to 7.6 years
	Wechsler Intelligence Scale for Children V (WISC-V)	Mean change from baseline at Week 24 in the WISC-V	6 to 16 years
	Wechsler Adult Intelligence Scale IV (WAIS-IV)	Mean change from baseline at Week 24 in the WAIS-IV	16 years and older
HRQoL	Pediatric Quality of Life Inventory (PedsQL)	Mean change from baseline at Week 24 in the PedsQL	2 to 18 years
	36-Item Short Form Health Survey (SF-36)	Mean change from baseline at Week 24 in the SF-36	≥19 years
Caregiver QoL	12-Item Short Form Zarit Burden Interview (ZBI-12)	Mean change from baseline at Week 24 in the ZBI-12	Completed by Caregiver; All ages

Key: HRQoL: health-related quality of life; QoL: quality of life.
Notes: *A patient who completed a baseline assessment continued with that assessment during follow-up, even if they were out of this age range for the test during follow-up.
Source: PEACE CSR (84).

Safety evaluations used to assess the safety of pegzilarginase monitored the frequency and nature of AEs, based on the assessment of clinical events, growth assessments, physical examination (including neurological examination), vital signs, electrocardiograms, electroencephalograms, and laboratory tests (59, 84).

B.2.3.1.7. Patient datasets

Analyses for both efficacy and safety endpoints were performed using the Full Analysis Set (FAS). The FAS comprised all patients who were randomised and received at least one dose of blinded study treatment (59, 84).

Of the 44 patients who were screened and consented to take part in PEACE, 32 were considered eligible and were randomised in 2:1 ratio to either the pegzilarginase arm (n=21) or the placebo group (n=11). All 32 patients received at least one dose of

blinded study treatment and were included in the FAS. Thirty-one of 32 patients completed the double-blind period of PEACE and continued onto the LTE portion of the study; one patient in the pegzilarginase group discontinued at Week 6 of the double-blind stage of the study for personal reasons. All 31 patients who enrolled onto the LTE portion of the study completed the study (Table 10) (59, 84).

Table 10: Patient disposition (PEACE)

Analysis Set, n (%)	Pegzilarginase (n=21)	Placebo (n=11)	Total (n=32)
Consented Set	-	-	44
Screen failures	-	-	12
Randomised Set	21 (100)	11 (100)	32 (100)
Full Analysis Set	21 (100)	11 (100)	32 (100)
Completed double-blind period[a]	20 (95.2)	11 (100)	31 (96.9)
Completed double-blind period and enrolled in LTE[b]	20 (95.2)	11 (100)	31 (96.9)
Completed LTE	20 (95.2)[c]	11 (100)	31 (96.9)

Notes: Percentages were based on the total number of subjects randomized in each treatment group. Consented Set included all patients who signed an informed consent form. Randomized Set included all patients in the Consented Set who were randomized to a blinded study treatment. Full Analysis Set included all patients who were randomised and received at least one dose of blinded study treatment.
[a]Completers were defined as patients who did not discontinue from study prior to LTE and therefore completed the 24-week double-blind randomisation period.
[b]All 31 patients who completed the double-blind period continued on to the LTE portion of the study. In the LTE, patients initially randomised to placebo transitioned to 0.1mg/kg pegzilarginase with dose modifications permitted as appropriate.
[c]One patient completed dosing but did not attend the final follow-up visit and was reported as discontinued (reason: family bereavement).
Sources: Sanchez Russo *et al*. (2024) (59); Table 11, PEACE CSR (84).

B.2.3.1.8. Baseline characteristics

Table 11 presents the key baseline characteristics for the PEACE FAS. With a few exceptions (slightly younger age, lower pArg levels, and less moderate/severe spasticity among patients randomised to pegzilarginase vs placebo), characteristics were generally comparable across treatment groups (59, 84).

For the 32 patients enrolled in the PEACE FAS, the median (range) age of patients at enrolment was 10.5 years (range: 2 to 29 years), which was lower than the median age of patients enrolled onto the European BoI study (14 years [range: 0 – 49 years)) and those included in the UK-based study by Keshavan *et al*. (2022) (16.0 years [range: 12 – 28 years) (30, 46).Only three patients (9.4%) in the FAS were aged ≥18.0 years (aged [redacted] and [redacted] years), further reiterating that patients with ARG1-D are

subjected to early mortality, and very few patients survive into adulthood beyond 35 years of age (see Section B.1.3.1.2.c).

Despite IDM, median baseline pArg levels, based on data obtained from medical records prior to enrolment, was 398.2 µM, which is approximately 3.5-fold the upper limit of normal (115 µM) (80), and twice the recommended treatment goal of <200 µM specified in clinical guidelines (15). Historical median pArg levels were lower in the pegzilarginase group compared to the placebo group (84).

In addition, the majority of patients (56.2%) in the PEACE FAS had gross motor functional impairment of GMFCS Level ≥II (59, 84), a proportion similar to that reported in the European BoI study (50.0%), which included six ARG1-D patients from the UK (46).

Table 11: Patient demographics and baseline characteristics (PEACE; FAS)

	Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Age at enrollment (years)			
n	21	11	32
Mean (SD)	9.6 (6.16)	12.9 (6.77)	10.7 (6.47)
Median	8.0	12.0	10.5
Min, Max	2, 28	5, 29	2, 29
Age categories (years), n (%)			
2 - <6	5 (23.8)	1 (9.1)	6 (18.8)
6 - <12	8 (38.1)	4 (36.4)	12 (37.5)
12 - <18	7 (33.3)	4 (36.4)	11 (34.4)
≥18	1 (4.8)	2 (18.2)	3 (9.4)
Sex, n (%)			
Female	9 (42.9)	4 (36.4)	13 (40.6)
Male	12 (57.1)	7 (63.6)	19 (59.4)
Race, n (%)			
Asian	3 (14.3)	3 (27.3)	6 (18.8)
Black/African American	0	2 (18.2)	2 (6.3)
White	10 (47.6)	4 (36.4)	14 (43.8)
Other	6 (28.6)	0	6 (18.8)
Multiple Race	1 (4.8)	1 (9.1)	2 (6.3)
Missing	1 (4.8)	1 (9.1)	2 (6.3)
Age at onset of manifestations, years			
n	11	10	21
Mean (SD)	1.6 (2.5)	2.5 (2.0)	1.9 (2.4)
Median	1.0	2.0	1.0
Min, Max	1, 10	0, 7	0, 10
Age at diagnosis, years			
n	17	9	26

Mean (SD)	2.8 (4.1)	4.2 (3.1)	3.3 (3.8)
Median	0.7	4.6	2.6
Min, Max	0, 15	0, 11	0, 15
Historical pArg, µM[a]			
n	19	11	30
Mean (SD)	365.4 (93.7)	471.7 (79.9)	402.0 (101.8)
Median	368.2	483.7	398.2
Min, Max	202, 572	294, 573	202, 573
Level of spasticity, n (%)			
Any	13 (61.9)	8 (72.7)	21 (65.5)
Lower-limb	13 (61.9)	8 (72.7)	21 (65.6)
Upper-limb	1 (4.8)	3 (27.3)	4 (12.5)
Moderate to severe	6 (28.6)	6 (54.5)	12 (37.5)
History of seizures, n (%)			
Yes	7 (33.3)	4 (36.4)	11 (34.4)
No	14 (66.7)	7 (63.6)	21 (65.6)
History of hyperammonaemia, n (%)			
Yes	12 (57.1)	6 (54.5)	18 (56.3)
No	9 (42.9)	5 (45.5)	14 (43.8)
GMFCS level at baseline, n (%)[b]			
I	9 (42.9)	5 (45.5)	14 (43.8)
II	9 (42.9)	4 (36.4)	13 (40.6)
III	0	0	0
IV	3 (14.3)	2 (18.2)	5 (15.6)
V	0	0	0
Baseline GMFM-E score, points[c]			
n	21	11	31
Mean (SD)	48.3 (19.93)	46.5 (24.56)	47.7 (21.25)
Median	53.0	56.0	54.0
Min, Max	5, 71	0, 72	0, 72
Baseline 2MWT, metres[d]			
n	20	11	31
Mean (SD)	109.0 (55.76)	99.9 (49.00)	105.8 (52.82)
Median	122.0	102.0	118.0
Min, Max	2, 202	0, 171	0, 202
Baseline GMFM-D score, points[e]			
n	21	11	31
Mean (SD)	28.0 (9.6)	29.5 (12.4)	28.5 (10.4)
Median	30.0	33.0	32.0
Min, Max	1, 38	0, 39	0, 39

Key: 2MWT: 2-Minute Walk Test; FAS: full analysis set; GMFCS: Gross Motor Function Classification System; GMFM-D: Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88 Part E; Max: maximum; Min: minimum; pArg: plasma arginine; SD: standard deviation.

Notes: Percentages are based on the total number of patients in the FAS.

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

[b]No patients at GMFCS Level V were enrolled due to inability to complete functional mobility assessments.

[c]Baseline GMFM-E was assessed in 10 of 11 patients in the placebo group; one patient was not assessed at baseline because of severe disability and wheelchair dependence.

[d]Baseline 2MWT was assessed in 20 of 21 patients in the pegzilarginase group; one patient was not assessed at baseline due to young age.

[e]Excludes one patient (placebo) with missing baseline value.

Sources: Table 1, Sanchez Russo *et* al. (2024) (59); Table 14 & Table 15, PEACE CSR (84).

B.2.3.2. Study 101A/102A

B.2.3.2.1. Trial methodology

Table 12: Summary of study methodology for Study 101A/102A

Study	CAEB1102-101A (NCT02488044)	CAEB1102-102A (NCT03378531)
Location	Study 101A was conducted at 9 sites in the United States (6 sites), United Kingdom (1 site), Portugal (1 site), and Canada (1 site).	Study 102A was conducted at 8 sites in the United States (5 sites), United Kingdom (1 site), Portugal (1 site), and Canada (1 site).
Study design	An open-label, multicentre study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in patients with ARG1-D	An open-label, multicentre study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in patients with ARG1-D
Key eligibility criteria for participants	**Inclusion criteria:** • Patient ≥2 years old with baseline plasma arginine (pArg) levels >200 µM. • Diagnosis confirmed by the presence of pathogenic variants in the *ARG1* gene or deficiency in red blood cell enzyme activity. **Exclusion criteria:** • Recent hyperammonaemic episode requiring hospitalisation or active infection requiring treatment • History of hypersensitivity to polyethylene glycol • Any comorbid condition or laboratory abnormality that could interfere with study participation or interpretation	As per Study 101A. For participation in Study 102A, patients were also required to complete Study 101A without experiencing any clinically significant adverse event or other unmanageable drug toxicity that would preclude continued dosing
Settings and locations where the data were collected	• Treatment and all study procedures were performed on an outpatient basis	• Treatment and all study procedures were performed on outpatient visits to the study sit for the initial 12 doses of IV pegzilarginase. • After the initial 12 IV doses, patients were dosed outside of the clinical research unit by home health care professionals if considered safe and appropriate. After 24 weeks, patients could be switched to SC weekly dosing.

		• In cases where patients were dosed outside of the study site, home health care professionals were responsible for performing the dosing and conducting the protocol-required safety and efficacy assessments and procedures. In instances where this was not appropriate, patients continued to attend outpatient visits for treatment and all study procedures.
Study periods and trial drugs	Study 101A was an open-label study conducted in two parts. In Part 1, patients received single ascending doses of IV pegzilarginase at two-week intervals. In Part 2, patients received eight weekly repeat doses of IV pegzilarginase. All patients received at least one dose of pegzilarginase.	Study 102A was an open-label, long-term extension study conducted for up to four years in patients with ARG1-D who had previously completed participation in Study 101A. All patients received at least one dose of pegzilarginase.
Prior and concomitant medication	Individualised disease management prior to the study was maintained and remained unchanged during the trial.	As per Study 101A
Primary efficacy endpoint	• Frequency of adverse events	As per Study 101A
Secondary outcomes used in the model/specified in the scope	• Change from baseline in pArg levels • Change from baseline in ornithine and guanidino compounds • Change from baseline in the 6-Minute Walk Test (2MWT) • Mean change from baseline at Week 24 in the Gross Motor Function Measure-88, Part E (GMFM-E) • Change from baseline in the GMFM-88, Part D (GMFM-D) • Change from baseline in Modified Ashworth Scale (MAS) Exploratory outcomes specified in the scope	As per Study 101A

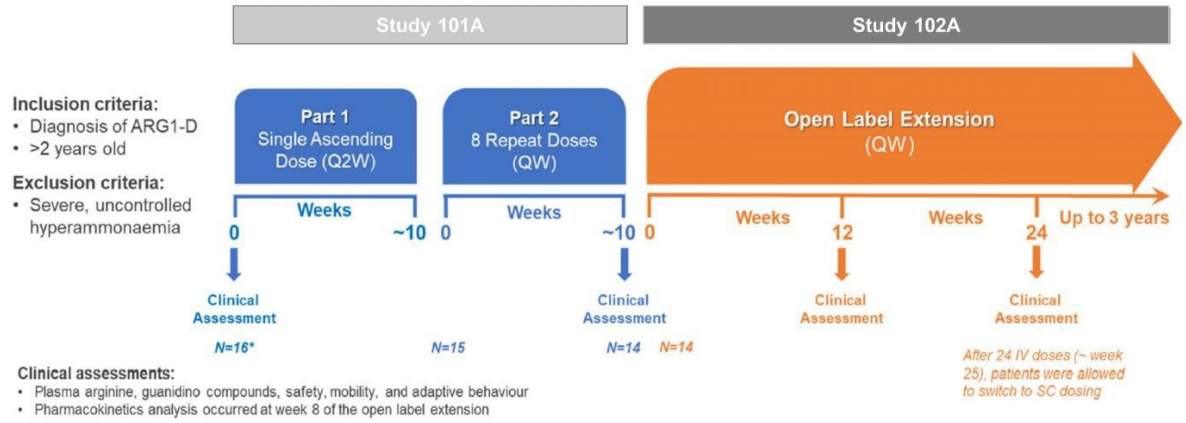
	• Composite responder analysis • Neurocognitive function (BSID-III and Wechsler intelligence batteries • Health-related quality of life (PROMIS, PedsQL, ZBI-12)	
Pre-planned subgroups	None	As per Study 101A

Key: ARG1-D: arginase 1 deficiency; BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; IV: intravenous; pArg: plasma arginine; PedsQL: Paediatric Quality of Life Inventory; PROMIS: Patient Reported Outcomes Measurement Information System; SC: subcutaneous; ZBI-12: Short-Form Zarit Burden Interview (ZBI-12).

B.2.3.2.2. Trial design

Study 102A is an open-label, multicentre extension study to evaluate the long-term safety, tolerability and effects of weekly IV and SC pegzilarginase for up to four years in patients aged 2 years and older with ARG1-D previously enrolled in the parent study, Study 101A (96). The study design for the parent study, Study 101A, and the LTE, Study 102A, is depicted below in Figure 13.

Figure 13: Study schema for Study 101A/Study 102A



Key: ARG1-D: arginase 1 deficiency.
Notes: *Two patients withdrew for personal reasons.
Source: Adapted from Figure 1, Diaz *et al*. (2021) (2).

Study 101A was a Phase 1/2, open-label dose-finding study in 16 adult and paediatric patients with ARG1-D. The study was conducted in two parts. In Part 1, patients received single ascending doses of IV pegzilarginase at 2-week intervals. The pre-defined doses were escalated until stopping rules were met for each patient in Part 1. In Part 2, patients received 8 weekly repeat doses of IV pegzilarginase and started with a dose chosen based on dose response from Part 1 of the study. After completion of Study 101A, patents were eligible to enrol in Study 102A to evaluate the long-term

effects of pegzilarginase. In Study 102A, patients resumed treatment with weekly administration of pegzilarginase at a dose selected based on Study 101A data (2, 97). Overall, 14 patients completed Study 101A and enrolled onto Study 102A. At the termination of Study 102A (December 15th 2022), 13 patients completed the study (96).

The primary objective of Study 102A was to evaluate the long-term safety and tolerability of IV and SC pegzilarginase, with long-term clinical effectiveness on sustained pArg reduction, GCs, and improvement or stabilisation of neuromotor manifestations evaluated as secondary endpoints. Long-term clinical effectiveness on neurocognitive, developmental, and HRQoL outcomes was investigated as an exploratory outcome in the study (96).

B.2.3.2.3. Eligibility criteria

Briefly, eligible patients for Study 101A were ≥2 years old with baseline pArg levels >200 µM. Diagnosis was confirmed by the presence of pathogenic variants in the ARG1 gene or deficiency in red blood cell enzyme activity. Exclusion criteria included recent HACs requiring hospitalization or active infection requiring treatment; history of hypersensitivity to polyethylene glycol; or any comorbid condition or laboratory abnormality that could interfere with study participation or interpretation (2, 97).

All patients who completed Study 101A were eligible for participate in Study 102A. Further details on the key inclusion and exclusion criteria for Study 102A are described below in Table 13 (96).

Table 13: Key eligibility criteria for Study 102A

Key inclusion criteria	Key exclusion criteria
• Completed participation in Study 101A without experiencing any clinically significant AE or other unmanageable drug toxicity that precluded continued dosing • A current diagnosis of ARG1-D as documented in medical records, which must include one of the following: elevated plasma arginine levels, a mutation analysis that resulted in a	• Had transfusion of ≥2 units of RBCs within 60 days before enrolment • Had an active infection requiring systemic treatment • Had a known infection with human immunodeficiency virus, hepatitis B, or hepatitis C. • Had unstable hyperammonaemia requiring hospitalisation within the 14 days before enrolment

pathogenic variant, or reduced RBC arginase activity. • Male and female patients aged ≥ 2 years of age on the date of informed consent/assent • Adequate organ function as follows: o Bone marrow: haemoglobin ≥10 g/dL; white blood cell count >3.0 x 10^9/L; platelet count o Hepatic (bilirubin): total bilirubin ≤2.0 x the upper limit of normal (ULN) o Hepatic (transaminases): either aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x ULN or ALT and/or AST >3.0 x ULN but both ≤5.0 x ULN, and in the opinion of the investigator, related to ARG1-D. o Renal: serum creatinine <1.5 x ULN	• Had a history of sensitivity to polyethylene glycol or any other component of the study drug formulation

Key: AE: adverse event; ARG1-D: arginase 1 deficiency; RBC: red blood cell.
Source: Diaz *et* al. (2021) (2); Section 9.3, Study 102A CSR (96)

For a full list of eligibility criteria, please refer to the Study 102A CSR (96).

B.2.3.2.4. Settings and locations where the data were collected

In Study 101A, a total of nine centres enrolled at least one patient. These centres were concentrated primarily in the US, which contributed six study centres, with the UK, Portugal and Canada each contributing a single study site (97). Five US study sites from Study 101A enrolled patients in Study 102A; one study site failed to enrol any patients (96).

All doses in Study 101A, and the first 24 doses of pegzilarginase in Study 102A, were administered IV, with the initial 12 doses in Study 102A administered weekly in the clinical research unit (CRU) (96, 97). After the initial 12 doses, patients were dosed IV outside the CRU (i.e., by home health care professionals) if considered safe and appropriate to do so. After 24 weeks of IV dosing, patients were switched to SC dosing if it was considered safe and appropriate for the patient. If patients were switched to the SC dosing route, the first four SC doses were given at the study site. Subsequent SC injections were administered outside of the study site by appropriately trained home health care personnel if considered safe and appropriate (96). In Study 102A,

76.9% of patients (10 of 13 patients) received SC administration by home healthcare (23, 96).

In cases where patients were dosed outside of the study site in Study 102A, appropriately qualified and trained home health care personnel were responsible for performing the dosing and conducting the protocol-required safety and efficacy assessments and procedures. In instances where this was not appropriate, patients were required to attend visits at the study site (96).

B.2.3.2.5. Trial drugs and concomitant medications

a. Pegzilarginase

In both Study 101A and Study 102A, the study drug was pegzilarginase. Pegzilarginase was supplied as a liquid formulation in 10 mL single-use glass vials containing 5 mL of formulated drug product at a concentration of 1 mg/mL (96, 97).

The pegzilarginase dose level and frequency in Study 102A initially matched the dose and regimen the patient last received at the end of Study 101A. Patients received weekly IV pegzilarginase for the first 24 weeks of Study 102A, with the SC dosing route investigated as an option post 24-weeks if considered safe by the investigator (see Figure 13, Section B.2.3.2.2). In total, all eligible patients (13 of 14 patients) opted to have SC pegzilarginase (see Section B.2.10.2) (23, 96).

b. Concomitant medication

Patients who experienced a mild or moderate hypersensitivity reaction or an infusion reaction during or after the first injection of pegzilarginase received prophylaxis prior to subsequent injections (96, 97).

As necessary, patients were able to receive supportive care including blood products, transfusions, antibiotics, nitrogen scavengers, pain medications, and replacement hormonal therapies (e.g., insulin, thyroid hormone, oestrogen/progesterone) (96, 97).

c. Restricted medication

Patients were prohibited from receiving other investigational therapies or other enzyme replacement therapy while participating in the study (96, 97).

B.2.3.2.6. Outcomes used in the economic model or specified in the scope, including primary outcome

The long-term safety and tolerability of IV or SC pegzilarginase was the primary outcome measured in Study 101A and Study 102A. Safety outcomes assessed throughout the study included AEs, vital signs, electrocardiograms, concomitant medications, physical examinations, and clinical laboratory tests (96, 97).

The magnitude, onset, and duration of changes in pArg levels and GCs, as well as clinical response, were assessed using multiple neuromotor, neurocognitive, and HRQoL measures (Table 14). Efficacy outcomes were measured through a series of secondary and exploratory outcomes in Study 102A, while Study 101A only measures the efficacy of pegzilarginase as an exploratory objective.

Table 14: Clinical outcome assessments in Study 101A/Study 102A by domain

Domain Assessed	Test Name	Age Range[a]
Locomotion / Mobility / Endurance	6-Minute Walk Test (6MWT)	3 to 85
Motor Function	Gross Motor Function Measure-66, Part D (GMFM-D)	≥5 months
	Gross Motor Function Measure-66, Part E (GMFM-E)	≥5 months
	Modified Ashworth Scale (MAS)	All ages
Adaptive Behaviour	Vineland Adaptive Behaviour Scale, 2nd Edition (VABS-II)[b]	All ages
Neurocognition and Memory	Bayley Scales of Infant Development, Third Edition (BSID-III)[c]	2 to 3.5 years
	Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV)	2.5 to 7.6 years
	Wechsler Intelligence Scale for Children V (WISC-V)[c]	6 to 16 years

	Wechsler Adult Intelligence Scale IV (WAIS-IV)[d]	16 years and older
HRQoL	Pediatric Quality of Life Inventory (PedsQL)	2 to 18 years
	36-Item Short Form Health Survey (SF-36)	≥19 years
	Patient-Reported Outcomes Measurement Information System (PROMIS)	All ages
Caregiver QoL	12-Item Short Form Zarit Burden Interview (ZBI-12)	Completed by Caregiver; All ages

Key: HRQoL: health-related quality of life; QoL: quality of life.
Notes:
[a]A patient who completed a baseline assessment continued with that assessment during follow-up, even if they were out of this age range for the test during follow-up.
[b]Adaptive behavior was assessed via the Adaptive Behavior Assessment System, Third Edition (ABAS-III) until Protocol Amendment 1.1, after which it was assessed via the VABS-II.
[c]The BSID-III was not used in the study because there were no subjects enrolled in that age group (ie, younger than 3.5 years old).
[d]The WAIS-IV, WISC-V, and ZBI-12 assessments were added in Protocol Amendment 1.1.
Source: Study 101A CSR (97), Study 102A CSR (96).

B.2.3.2.7. Patient datasets

Analyses for both efficacy and safety endpoints were performed using the FAS, unless otherwise stated. The FAS was defined as all patients enrolled in the study who received pegzilarginase (96, 97).

B.2.3.2.8. Baseline characteristics

The baseline characteristics of patients in the Study 101A and LTE Study 102A, are shown below in Table 15.

Table 15: Patient demographics and baseline characteristics (Study 101A and Study 102A; FAS)

	Study 101A (n=16)	Study 102A (n=14)
Age (years)		
n	16	14
Mean (SD)	15.1 (8.47)	[redacted]
Median	15.0	14.0
Min, Max	5, 31	6, 32
Age categories (years), n (%)		
2-5 years	2 (12.5)	[redacted]
6-11 years	4 (25.0)	[redacted]
12-17 years	5 (31.3)	3 (21.4)

≥18 years	5 (31.3)	5 (35.7)
Height, cm		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Sex, n (%)		
Female	11 (68.8)	[redacted]
Male	5 (31.3)	[redacted]
Race, n (%)		
Asian	[redacted]	[redacted]
Black/African American	[redacted]	[redacted]
White	[redacted]	[redacted]
Other	[redacted]	[redacted]
Age at initial symptoms, years[a]		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
pArg level (µM)		
Mean (SD)	373.4 (91.31)	309.2 (97.60)
Median	389.3	[redacted]
Min, Max	237.8, 565.8	[redacted]
Level of spasticity, n (%)		
None	4 (25.0)	[redacted]
Mild	3 (18.8)	[redacted]
Moderate	5 (31.3)	[redacted]
Severe	4 (25.0)	[redacted]
History of hyperammonaemia, n (%)		
Yes	7 (43.8)	6 (42.9)
No	9 (56.2)	8 (57.1)
History of seizures, n (%)		
Yes	7 (43.8)	[redacted]
No	9 (56.2)	[redacted]
GMFCS Level, n (%)[b]		
I	9 (56.3)	7 (50.0)
II	4 (25.0)	4 (28.6)
III	2 (12.5)	2 (14.3)
IV	1 (6.3)	1 (7.1)
V	0	0
GMFM-E score, points		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
6MWT, metres		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
GMFM-D score, points		

n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Key: 6MWT: 6-Minute Walk Test; GMFCS: Gross Motor Function Classification System; GMFM-D; Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88; Part E; FAS: full analysis set; Min: minimum; Max: maximum; pArg: plasma arginine; SD: standard deviation.
Notes: Percentages are based on the total number of patients in the FAS.
[a]One patient was diagnosed via newborn screening and did not present with initial symptoms.
[b]The GMFCS is a 5-level scale that assesses current motor function and what mobility aids a subject may need in the future. Level I=walks without restrictions; Level II=walks without assistive devices; Level III=walks with handheld assistive mobility devices; Level IV=self-mobility with limitations, may use power mobility; Level V=self-mobility is severely limited even with the use of assistive technology. Two patients did not have a GMFCS assessment at the Study 101A Part 1 Baseline but were later assessed as Level III and Level I, respectively.
Sources: Table 10 & 11, Study 101A CSR (97); Table 12 & Table 13, Study 102A CSR (96).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. PEACE

B.2.4.1.1. Analysis population

In the PEACE study, all patients received at least one dose of blinded study treatment. Hence, the FAS was used for both efficacy and safety endpoints analysis (96).

B.2.4.1.2. Sample size

Based on the data from the Study 101A and Study 102A studies, arginine levels at 24 weeks post-baseline were reduced to -2.13 on the $\log_2$ scale, representing a 77% decrease from baseline. The $\log_2$ scale SD was estimated at 0.681. Given that it is unlikely that placebo would have any true treatment effect on arginine levels at 24 weeks, the reduction at 24 weeks for placebo was estimated to be zero (84).

Under these assumptions, a total sample size of 30 patients with 20 patients assigned to pegzilarginase and 10 patients assigned to placebo, provides over 95% power to detect a statistically significant difference in the reduction of arginine levels at the 2-sided α=0.05 level of significance (84).

Although an exact screen failure rate could not be accurately predicted based on data available, a sufficient number of patients were to be screened so at least 30 patients in the FAS would have at least one follow-up measurements on which clinical response could be assessed (i.e., 2MWT and GMFM-E) (84).

B.2.4.1.3. Statistical analysis

A summary of statistical analyses for PEACE is available below in Table 16.

Table 16: Summary of statistical analyses: PEACE

Trial number (acronym)	NCT03921541 (PEACE)
Hypothesis objective	The null hypothesis tested in this study was that there was no clinically significant difference in plasma arginine (pArg) concentrations between the pegzilarginase and placebo study groups
Statistical analyses	The primary analysis used a MMRM method. Results were presented as geometric mean values, ratios to baseline values, and changes with 95% CIs
Sample size, power calculations	A sample size of 30 patients was to provide >95% power to detect a statistically significant difference in the reduction of pArg levels between the pegzilarginase and placebo treatment arms at the 2-sided α=0.05 level of significance
Data management, patient withdrawals	For the primary efficacy endpoint (pArg) and one secondary endpoint (GCs and ornithine), when a final value was not available, change from baseline was imputed as zero. Missing data due to study withdrawal, death, COVID-19 were imputed as though the patient did not improve from baseline: a composite estimand strategy. Missing data for key secondary and secondary endpoints was not imputed.

Key: CI: confidence interval; GC: guanidino compound; MMRM: mixed effect model repeated measures.
Source: PEACE CSR (84).

a. Primary efficacy analysis

As described previously, the primary efficacy endpoint is the change from baseline in pArg after 24 weeks of study drug (84).

The primary analysis of the primary endpoint was change from baseline comparing the baseline logged arginine value to the endpoint logged arginine value (mean of the last four prior to dosing) using a mixed effect method repeated measures (MMRM) model. Results were presented as geometric mean values, ratios to baseline values, and changes with 95% confidence intervals [CIs]. The treatment effect was presented as a relative ratio to baseline and change with 95% CIs and a two-sided p-value. The baseline arginine value was included as a covariate in the MMRM model (84).

As sensitivity analysis to examine the robustness of the MMRM analysis when the primary data did not follow the normal distribution, change from baseline to final follow-up arginine level was compared between pegzilarginase and placebo using a Wilcoxon Rank Sum test (84).

b. Key secondary efficacy analysis

As described previously, the key secondary efficacy endpoints in PEACE were the mean changes from baseline at Week 24 in the 2MWT and GMFM-E (84).

Key secondary endpoints were analysed using an MMRM model with data from Week 12 and Week 24, least squares (LS) mean estimates, and differences between treatments from both timepoints were presented, but the test of difference from 24 weeks was the key secondary endpoint analysis (84).

The MMRM produced estimates, which were consistent with a missing-at-random assumption for missing data. The tipping point analysis was designed to assess the potential impact of informative missingness by progressively penalizing subjects with missing data in the selected treatment group. To assess the reliability of results arising with the MMRM, an additional tipping point sensitivity analysis using multiple imputation methods was planned but not conducted due to lack of substantial missing data (84).

In order to examine the robustness of the normal distribution assumption in the MMRM analysis, Wilcoxon Rank Sum tests were performed as sensitivity analyses for the key secondary endpoints did not achieve statistical significance (84).

c. Secondary efficacy endpoints

For all responder analyses, a two-sided Fisher's exact test was used. The proportion of patients with an endpoint arginine value <200 μM were compared with those with an endpoint arginine value ≥200 μM for each of the treatment groups. This was also the case when analysing the proportion of patients with a normal endpoint arginine value (≥40 - ≤115 μM) versus those with an endpoint arginine value outside of the normal range (84).

Changes from baseline in GCs and ornithine after 24 weeks of study treatment were analysed and summarised using the same methods as for the primary endpoint described in Section B.2.4.1.3.a.

Changes from baseline at Week 24 with respect to neuromotor and adaptive behaviour assessments were analysed and summarised using the same methods as the key secondary endpoints described above in Section B.2.4.1.3.b.

d. Tertiary efficacy endpoints

All neurocognitive and HRQoL assessments were summarised using descriptive statistics by treatment group (84).

e. Subgroup analyses

Subgroup analyses were performed on the primary analysis of change from baseline in pArg, and the key secondary analyses of change from baseline in 2MWT and change from baseline in GMFM-E (if numbers within subgroups were sufficient) (84).

f. Safety analyses

All evaluations of safety data were performed on the FAS (84).

B.2.4.1.4. Participant flow

Details of participant flow in PEACE are provided in Appendix D1.2.

B.2.4.2. Study 101A/102A

B.2.4.2.1. Analysis population

The FAS included all patients who received any study medication. The FAS was used for evaluating patient characteristics, treatment administration, and safety endpoints (96, 97).

B.2.4.2.2. Sample size

A sample size of at least 10 paediatric and adult patients was determined using clinical, rather than statistical considerations and was deemed appropriate for the patient population under study and the risk/benefit of the proposed protocol therapy. The

study was exploratory and did not employ hypothesis testing; thus, no power or sample size calculation was performed (96).

B.2.4.2.3. Statistical analysis

A summary of statistical analyses for Study 101A/102A is available below in Table 17.

Table 17: Summary of statistical analyses: Study 101A/102A

Trial number (acronym)	NCT02488044 (CAEB1102-101A)	NCT03378531 (CAEB1102-102A)
Hypothesis objective	Study 101A is an exploratory study and did not employ hypothesis testing.	As per Study 101A
Statistical analyses	Efficacy endpoints were summarised using descriptive statistics. Statistical tests could be performed as part of the descriptive analyses, as a within-patient measure of observed effects of pegzilarginase relative to observed variability.	As per Study 101A
Sample size, power calculations	A sample size of 10 paediatric and adult patients was determined using clinical, rather than statistical, considerations. No power or sample size calculation was performed for this study.	As per Study 101A
Data management, patient withdrawals	No imputations of missing data were performed, and the analyses were performed on the observed cases, unless otherwise stated.	As per Study 101A.

Key: CAEB1102-101A: Study 101A; CAEB1102-102A: Study 102A.
Source: Study 101A CSR (97); Study 102A CSR (96).

B.2.4.2.4. Primary efficacy analysis

The frequency of patients with adverse events (AEs) was the primary endpoint for Study Study 101A and 102A (96, 97).

B.2.4.2.5. Secondary efficacy analysis

PArg concentration was summarised with descriptive statistics (n, mean, SD, median, minimum, maximum). Descriptive statistics were used to summarise these data based on the actual value and change (Study 101A and Study 102A) baseline value at each timepoint of assessment by dose, day, and nominal timepoints (96).

The efficacy of pegzilarginase on neuromotor outcome assessments outlined in Table 14, Section B.2.3.2.6, was summarised with descriptive statistics for the measures outlined in Table 14, Section B.2.3.2.6 (96).

B.2.4.2.6. Exploratory analysis

The efficacy of pegzilarginase on neurocognitive, developmental and HRQoL outcome assessments outlined in Table 14, Section B.2.3.2.6 was summarised with descriptive statistics (96).

B.2.4.2.7. Safety analyses

All evaluations of safety data were performed on the FAS (96).

B.2.4.2.8. Participant flow

Details of participant flow in Study 101A and Study 102A are provided in Appendix D1.2.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from PEACE, a Phase 3, randomised study consisting of a 24-week double-blind, placebo-controlled period followed by an open-label LTE, Study 102A, an open-label LTE study. Clinical effectiveness evidence from Study 101A, a two-part (Part 1 [single ascending dose escalation] and Part 2 [repeated dosing] open-label study is presented in Appendix P.

The critical appraisal of PEACE was conducted using the quality assessment tool developed by the University of York's Centre for Reviews and Dissemination (CRD), as recommended by NICE. The quality assessments of Study 101A and Study 102A

was conducted using the Downs & Black checklist. Full results are presented in Appendix D1.

B.2.6 Clinical effectiveness results of the relevant studies

Summary of clinical effectiveness results

- *The efficacy and safety of pegzilarginase in the treatment of ARG1-D patients aged 2 years and older has been demonstrated in the pivotal Phase 3, randomized, double-blind, placebo-controlled PEACE study and a supporting Phase 2 open-label study (Study 102A).*
- *After 24 weeks of treatment in PEACE, pegzilarginase demonstrated a consistent, clinically meaningful, and sustained reduction in pArg versus placebo ($p<0.0001$), with almost all patients (90.5%) treated with pegzilarginase achieving pArg levels that met guideline recommendations (<200 μM) and were within the normal range (≥40 - ≤115 μM).*
- *The reductions in pArg levels were associated with clinically relevant improvements in mobility. Pegzilarginase demonstrated a clinically meaningful and statistically significant improvement in GMFM-D versus placebo at Week 24 of the double-blind period ($p=0.0208$). Positive trends in GMFM-E versus placebo, while numerical improvements were observed in the 2MWT.*
- *More patients treated with pegzilarginase met response criteria across multiple domains, with generally greater magnitude of response compared to placebo-treated patients.*
- *During the LTE period of PEACE, patients continued to maintain normal arginine levels after receiving SC dosing and either maintained or demonstrated further improvement in mobility through up to 150 weeks of follow-up.*
- *Over the course of Study 102A, patients administered with IV or SC dosing demonstrated a consistent and sustained reduction in pArg level to therapeutic levels, associated decreased in plasma GC levels, increases in ornithine levels, and clinically relevant improvements in mobility as assessed by neuromotor function through up to 262 weeks of follow-up.*
- *Overall, the results support pegzilarginase as a potentially transformative therapy to normalize arginine, and to improve functional mobility outcomes compared with existing IDM approaches alone.*

B.2.6.1. PEACE

As depicted in Figure 12, PEACE is comprised of two study periods: a 24-week-randomised, placebo-controlled, double-blind period, and a subsequent open-label LTE period for up to 150 weeks. The double-blind period provides outcomes data for pegzilarginase plus IDM versus placebo plus IDM (current standard of care). The primary analysis of study endpoints occurred upon completion of the double-blind period (Week 24), and are described in detail below in Section B.2.6.1.1. Meanwhile,

the LTE provides long-term data on study endpoints for pegzilarginase plus IDM.. Clinical effectiveness results from the LTE are presented in Section B.2.6.1.2.

PEACE began in May 2019, and included the period in which the COVID-19 pandemic was occurring globally. When the pandemic occurred, the study was partially enrolled, and impact was generally limited to screening pauses, study suspension, and visit attendance on schedule. No formal adjustments or mitigations to study visits or study procedures were required despite the ultra-rare population, frailty of patients, as weekly study drug administration and evaluation at home after sufficient safety, were already part of the study. Second, after careful evaluation, additional potential adjustments or mitigations to visits or procedures were not considered feasible for this study.

In the double-blind period, 9.5% of patients (2 of 21 patients) in the pegzilarginase arm, and 27.3% of patients (3 of 11 patients) in the placebo group had pauses in the study due to COVID-19 that ranged from [redacted] days to [redacted] days. In the double-blind period, [redacted] ([redacted] patients) in the pegzilarginase group and [redacted] ([redacted]) in the placebo group had pauses in the study that ranged from [redacted] to [redacted] days. In the LTE period, [redacted] had a pause in the study that was [redacted] days. For patients with COVID-19 pause (n=), the mean (SD) duration was similar in both treatment groups with [redacted] ([redacted]) weeks in the pegzilarginase group and [redacted] ([redacted]) weeks in the placebo group (84).

Any variances from the study's assessments and procedures were clearly documented and captures as protocol deviations and annotated as a result of the COVID-19 pandemic. As of the study completion, a total of [redacted] patients ([redacted]) experienced important protocol deviations that were COVID-19 related. Most of these deviations involved 'screening pause' ([redacted] of 32 patients, [redacted]), 'study suspension' ([redacted] of 32 patients, 9.4%), and 'visit schedule criteria' ([redacted] of 32 patients, [redacted]) (84).

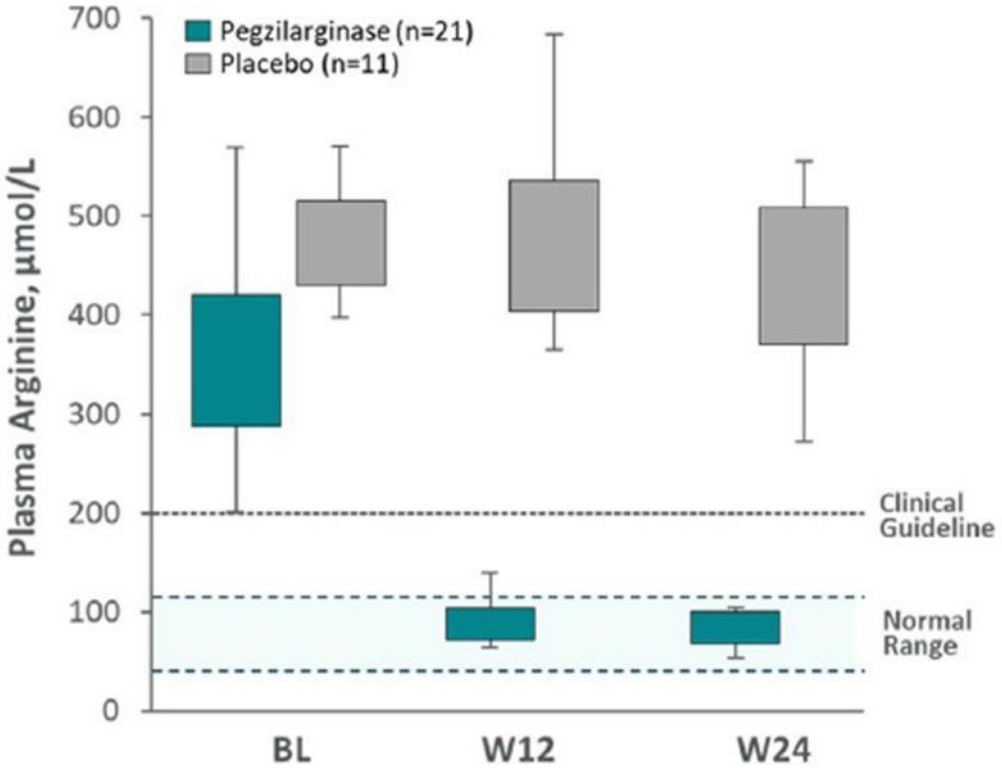
B.2.6.1.1. Double-blind period

a. Primary efficacy endpoint

Treatment with pegzilarginase resulted in significant reductions in pArg starting at Week 6 which were maintained through Week 24 of treatment. At Week 24,

pegzilarginase demonstrated a 76.7% reduction in mean pArg compared to placebo (95% CI: -67.1%, -83.5%; p<0.0001). Mean (SD) pArg levels at Week 24 were 86.4 (0.50) µM and 426.5 (1.31) µM in the pegzilarginase and placebo groups, respectively (Figure 14) (59, 84). A summary of the change from baseline in pArg levels are presented in Table 92, Appendix M.

Figure 14: Effect of pegzilarginase on pArg levels during the double-blind period (PEACE; FAS)



Key: BL: baseline, FAS: Full Analysis Set; LTE: long-term extension; pArg: plasma arginine; SD: standard deviation; W: week.
Notes: Boxes represent middle 50%; error bars represent 95% CIs. Statistical significance was based on geometric means with any missing post-baseline values imputed as change from baseline = 0. Normal range for pArg is ≥40 - ≤115 µM (80).
Source: Figure 2, Sanchez Russo *et al.* (2024) (59).

When assessing the reduction in pArg by individual patient, 19 of 21 patients in the pegzilarginase treatment group (90.5%) had a clinically meaningful change and normalised pArg at Week 24 compared to the placebo group (normal pArg level: ≥40 - ≤115 µM) (59, 80, 84). As noted in Section B.1.3.2.3, the currently recommended treatment goal of reducing pArg to <200 µM is difficult to achieve with current IDM, while reducing pArg levels to within or close to the normal range is considered even more challenging. By achieving normal pArg levels in 90.5% of patients,

pegzilarginase has the potential to slow or halt the progression of neuromotor, neurocognitive, and/or adaptive behavioral deterioration in patients with ARG1-D.

Details on the two patients who did not achieve clinically meaningful changes in pArg are described below (84).

- One patient withdrew consent from the study at Week 6.
- One patient had an uncharacteristic change from baseline at Week 24. In this patient, pArg was well-controlled for most of the double-blind period, with values close or within the normal range. At Week 23 of the double-blind period, the pArg level value was markedly elevated at [redacted] µM, which was substantially higher than the weeks preceding. At this site, another patient who was related and receiving placebo demonstrated an anomalous marked reduction in pArg down to [redacted] µM also at Week 23 of the double-blind period, which was substantially lower than weeks preceding. Based on the comparison of the overall arginine data by timepoint, the discrepant findings most likely reflect a dosing error at Week 23, although the possibility of a sample mix as an alternative explanation cannot be excluded.

Details on the long-term effects of pegzilarginase on pArg are described in Section B.2.6.1.2.a.

b. Key secondary efficacy endpoints

i. 2-Minute Walk Test (2MWT)

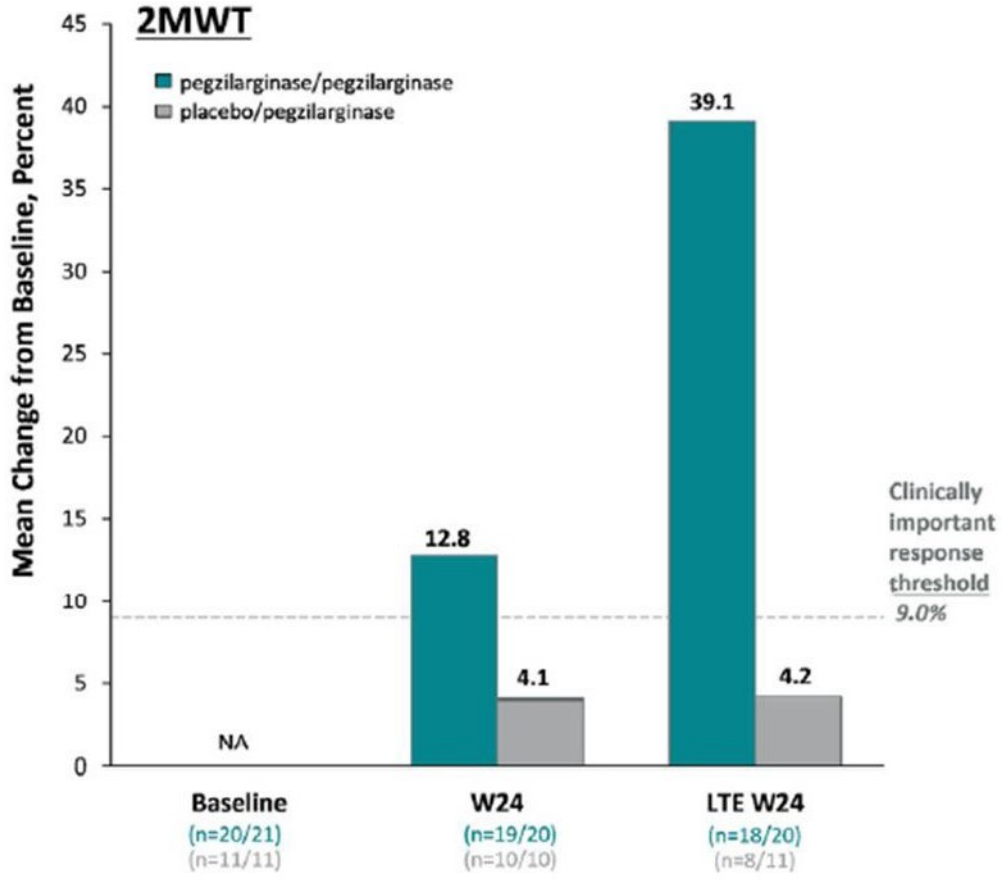
The 2MWT evaluates distance travelled on a flat surface after two minutes (with bracing or assistive devices). The 2MWT has been validated over a large spectrum of age groups (98, 99), and has been applied successfully in children and adults with CP, which is also characterised by spasticity (100, 101). Applied thresholds for clinically important response were based on a 9% change from baseline in distance travelled for all patients for the 2MWT, defined using criteria established from CP (95).

At Week 24, patients treated with pegzilarginase demonstrated an improvement in the 2MWT compared to the placebo group. The mean (SD) distance walked over two minutes in the pegzilarginase group was 115.9 (51.8) metres, representing a 7.3-metre

increase (+12.8%) from baseline, compared to the mean (SD) distance walked in the placebo group of 102.3 (51.1) metres, representing a 2.7-metre difference (+4.1%) from baseline (LS mean difference: 5.5 metres; 95% CI: -15.6%, 26.7%; p=[redacted]). Although the change from baseline to Week 24 for the LS mean difference in 2MWT between the pegzilarginase and placebo groups did not meet statistical significance, changes from baseline exceeded the minimal clinically important difference (MCID) threshold and demonstrated clinically meaningful improvement (Figure 15) (59, 84). A summary of the change from baseline in 2MWT scores are presented in Table 93, Appendix M.

Details on the long-term effects of pegzilarginase on 2MWT are described in Section B.2.6.1.2.b.

Figure 15: Effect of pegzilarginase on 2MWT at Week 24 and LTE Week 24 (PEACE; FAS)



Key: 2MWT: 2-Minute Walk Test; FAS: Full Analysis Set; LTE: long-term extension; W: week.
Notes: Group sizes reflect all patients with data at each time point; there was no imputation for missing values. LTE data cut-off date: March 24th 2022.
Source: Figure 4, Sanchez Russo *et al.* (2024) (59).

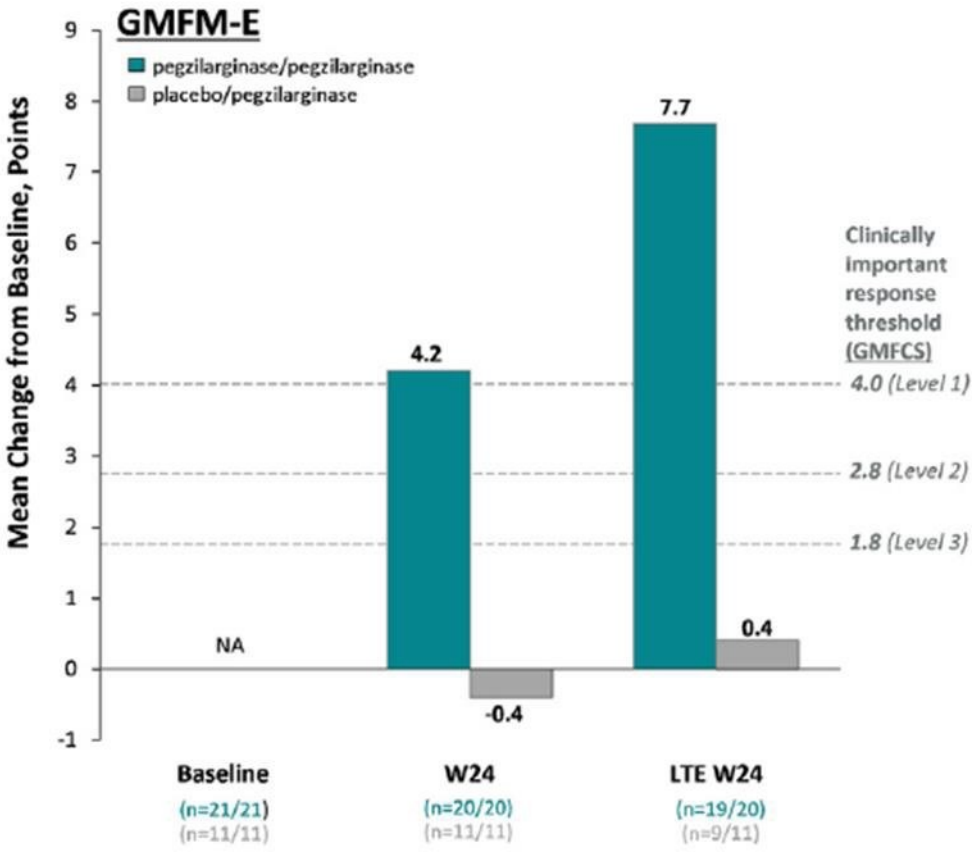
ii. Gross Motor Function Measure, Part E (GMFM-E)

The Gross Motor Function Measure (GMFM) evaluates unaided mobility (performed without bracing or assistive devices) over time using a range of activities. The GMFM-E evaluates a subject's ability to walk, run, and jump via assessment of 24 activities, each of which is scored on a scale of 0 to 3, for a maximum total score of 72. A higher GMFM-E score indicates greater ability, with increasing scores indicating improvement in walking, running, and jumping (59).Clinically important response thresholds were defined using criteria established for CP, ranging from ≥1.8 to ≥4.0 points based on baseline GMFCS classification (95).

After 24 weeks, patients treated with pegzilarginase demonstrated an improvement in GMFM-E compared to the placebo group. The mean (SD) GMFM-E score in the pegzilarginase group was 52.0 (21.3), representing a 4.2-point increase from baseline, compared to the mean (SD) score of 46.1 (25.7) in the placebo group, representing a 0.4-point decrease from baseline (LS mean difference: 4.6 points; 95% CI: -1.1, 10.2; p=[redacted]). Although the improvement demonstrated was not statistically significant, the mean change from baseline GMFM-E score in the pegzilarginase group was above MCID thresholds (Figure 16) (59, 84). A summary of the change from baseline in GMFM-E scores during the double-blind period are presented in Table 94, Appendix M.

Details on the long-term effects of pegzilarginase on GMFM-E are described in Section B.2.6.1.2.c.

Figure 16: Effect of pegzilarginase on GMFM-E at Week 24 and LTE Week 24 (PEACE; FAS)



Key: FAS: Full Analysis Set; GMFCS: Gross Motor Function System Classification; GMFM-E: Gross Motor Function Measure-88, Part E; LTE: long-term extension; W: week.
Notes: Group sizes reflect all patients with data at each time point; there was no imputation for missing values. LTE data cut-off date: March 24th 2022.
Source: Figure 4, Sanchez Russo *et al*. (2024) (59).

c. Secondary endpoints

i. Changes in ornithine and guanidino compounds at Week 24

Ornithine and urea are products of the hydrolysis of arginine by ARG1 in the final step of the urea cycle. Ornithine levels are generally low in patients with ARG1-D due to the lack of the enzyme ARG1 activity required to convert arginine to ornithine (84). Ornithine is a key intermediate in the urea cycle, hence restoring ornithine to near normal levels could aid in the prevention hyperammonaemia in ARG1-D (49).

At baseline, median ornithine levels were outside of the normal range of ornithine (2 to 17 years: 22 - 97 μM; ≥18 years: 38 - 130 μM) in both the pegzilarginase group

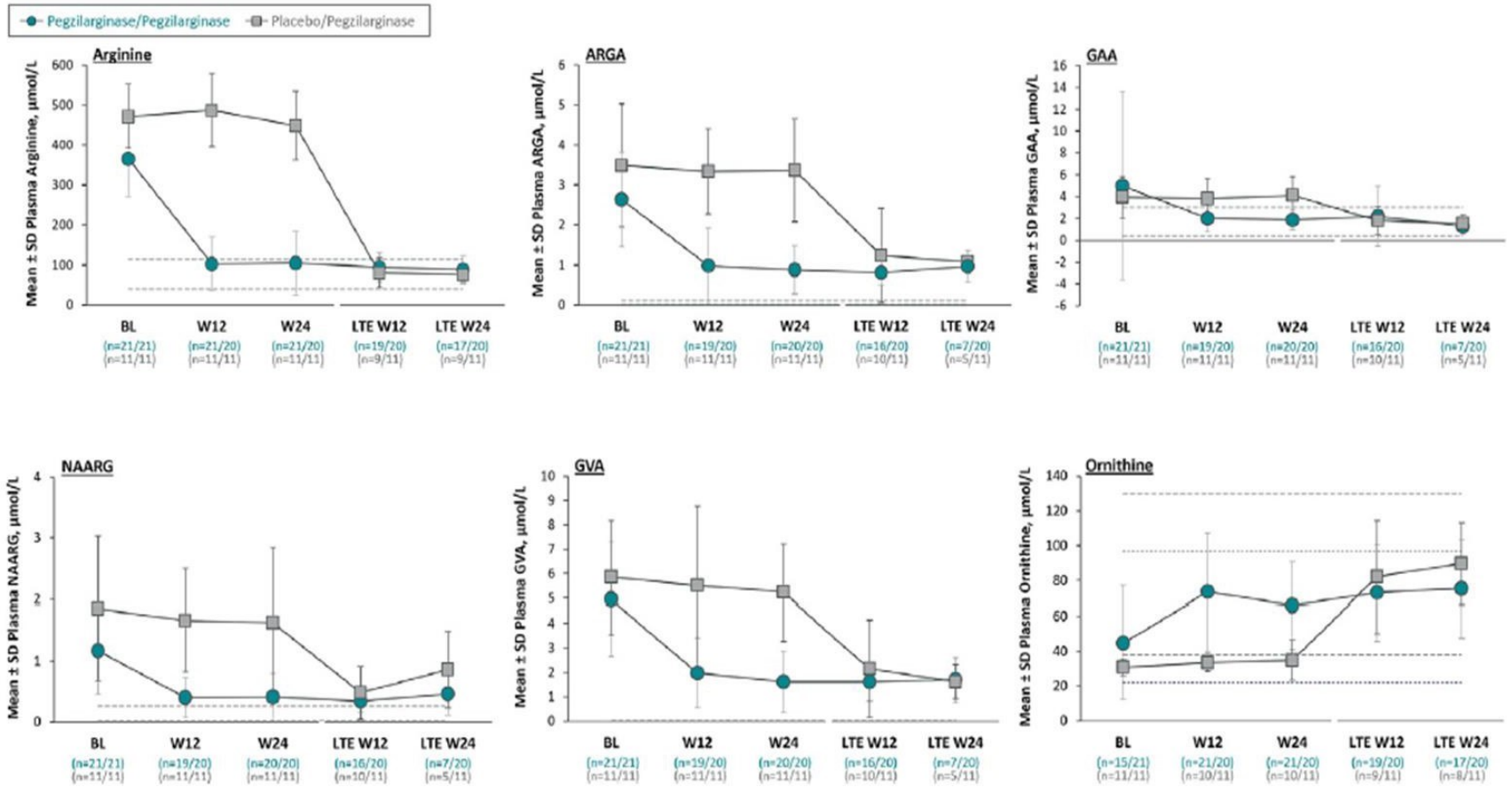
(32.1 µM) and the placebo group (29.2 µM) (102). At Week 24, patients treated with pegzilarginase had a clinically relevant and statistically significant 106.9% increase in mean ornithine (70.2 µM, 15 of 21 patients) compared to the placebo group (31.9 µM, 10 of 11 patients) (95% CI: 1.567, 2.731; p<0.0001) (59, 84).

In addition, GCs are direct and indirect products of arginine metabolism and are generally elevated in ARG1-D. Elevated levels of these compounds are thought to be a contributory factor causing seizures in patients with ARG1-D (see Section B.1.3.1.2.a.iii) (16, 21, 31, 55).

At baseline, plasma levels of GC were similarly elevated between the treatment groups, although the values of alpha-keto-δ-guanidinovaleric acid (GVA) and alpha-N-acetylarginine (NAArg) were incrementally higher in the placebo arm. During the double-blind portion of the study, plasma levels of GCs statistically significantly decreased from baseline with pegzilarginase, which started at Week 1 and was maintained over time through Week 24 at the end of the double-blind period. Relative reductions in GCs ranged from 53.3% (95% CI: -32.2%, -67.8%; p=0.00003) to 69.8% (95% CI: -51.8%, -81.8%) with demonstrated strong correlations with pArg. By contrast, for the placebo group, levels of all four GCs fluctuated over time but remained similar to baseline levels through Week 24 (Figure 17). (59, 84).

Details on the long-term effects of pegzilarginase on ornithine and GCs are described in Section B.2.6.1.2.d.

Figure 17: Effect of pegzilarginase on ornithine and GC levels (µM) over time during the double-blind period and LTE through Week 24 (PEACE; FAS)



Key: ARGA: argininic acid; BL: baseline; FAS: Full Analysis Set; GAA: guanidinoacetic acid; GVA: α-keto-δ-guanidinovaleric acid; LTE: long-term extension; NAARG: α-N-acetylarginine; W: week.
Notes: Group sizes reflect all patients with data at each time point; there was no imputation for missing values. Normal range for plasma arginine is ≥40 - ≤115 µM (80). Normal ranges for GCs are: ARGA, 0.025–0.1 µM (dashed lines); GAA, 0.4–3.0 µM (dashed lines); GVA, <0.05 µM (dashed lines); NAARG, 0.025–0.255 µML (dashed lines) (53). Normal range for ornithine is age-dependent: ages 2–17 years, 22–97 µM (dotted lines); ages ≥18 years, 38–130 µM (dashed lines) (102). LTE data cut-off date: March 24th 2022.
Source: Figure 3, Sanchez Russo *et al*. (2024) (59).

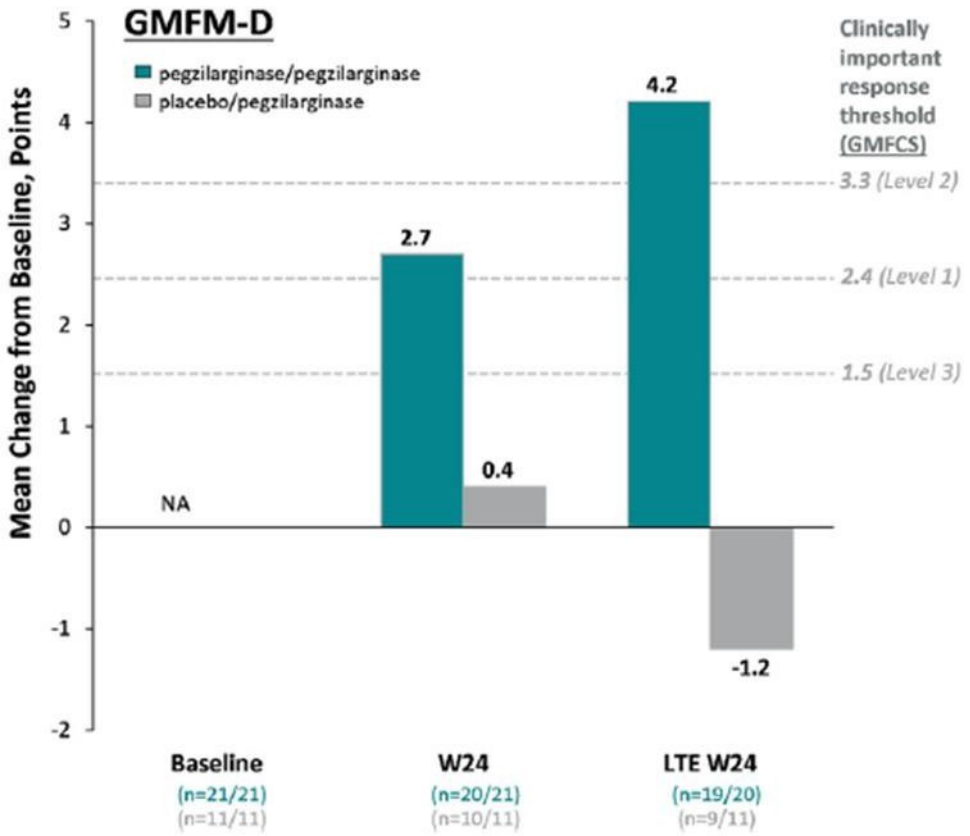
ii. Gross Motor Function Measure, Part D (GMFM-D)

The GMFM-D evaluates the subject's ability to stand via assessment of 13 activities, each of which is scored on a scale of 0 to 3, for a maximum total score of 39. An increase in GMFM-D score indicates improvement in standing.(59). Clinically important response thresholds were defined using criteria established for CP, ranging from ≥1.5 to ≥3.3 points based on baseline GMFCS classification) (95).

After 24 weeks, patients treated with pegzilarginase demonstrated a statistically significant improvement in GMFM-D compared to the placebo group, and observed a change from baseline in GMFM-D score above the MCID threshold (95).The mean (SD) GMFM-D score in the pegzilarginase group was 30.5 (10.1), representing a mean 2.7-point increase from baseline, compared to the mean (SD) score of 28.2 (13.33) in the placebo group, representing a mean 0.4-point increase from baseline (LS mean difference: 2.3 points, 95% CI: 0.4, 4.2, p=0.0208) (Figure 18) (59, 84). A summary of the change from baseline in GMFM-D scores during the double-blind period are presented in Table 95, Appendix M.

Details on the long-term effects of pegzilarginase on GMFM-D are described in Section B.2.6.1.2.e.

Figure 18: Effect of pegzilarginase on GMFM-D at Week 24 and LTE Week 24 (PEACE; FAS)



Key: FAS: Full Analysis Set; GMFCS: Gross Motor Function System Classification; GMFM-D: Gross Motor Function Measure-88, Part D; LTE: long-term extension; W: week.
Notes: Group sizes reflect all patients with data at each time point; there was no imputation for missing values. LTE data cut-off date: March 24th 2022.
Source: Figure 4, Sanchez Russo *et al*. (2024) (59).

iii. Vineland Adaptive Behaviour Scale, Second Edition (VABS-II)

The VABS-II is a scale designed to measure the adaptive behaviour of individuals from birth to age 90 years (103). The VABS-II scoring system describes adequate adaptive behavior by subdomain as 13-17 and 86-114 for the composite score, with higher scores indicating better adaptive behaviour (104).

At baseline, the mean (SD) VABS-II adaptive behaviour composite score for patients in the pegzilarginase group was [redacted] and [redacted] in the placebo group, reflecting moderately low (71 to 85) to low range (20 to 70), respectively (104). At Week 24 of the double-blind period, the mean (SD) change from baseline was an increase of [redacted] points in the pegzilarginase group, compared to a decrease of

[redacted] points in the placebo group (LS mean difference: [redacted], 95% CI: [redacted]). The change from baseline to Week 24 indicates numerical improvement in VABS-II score in the pegzilarginase group (97).

d. Tertiary endpoints

i. Responder analysis and composite clinical outcomes

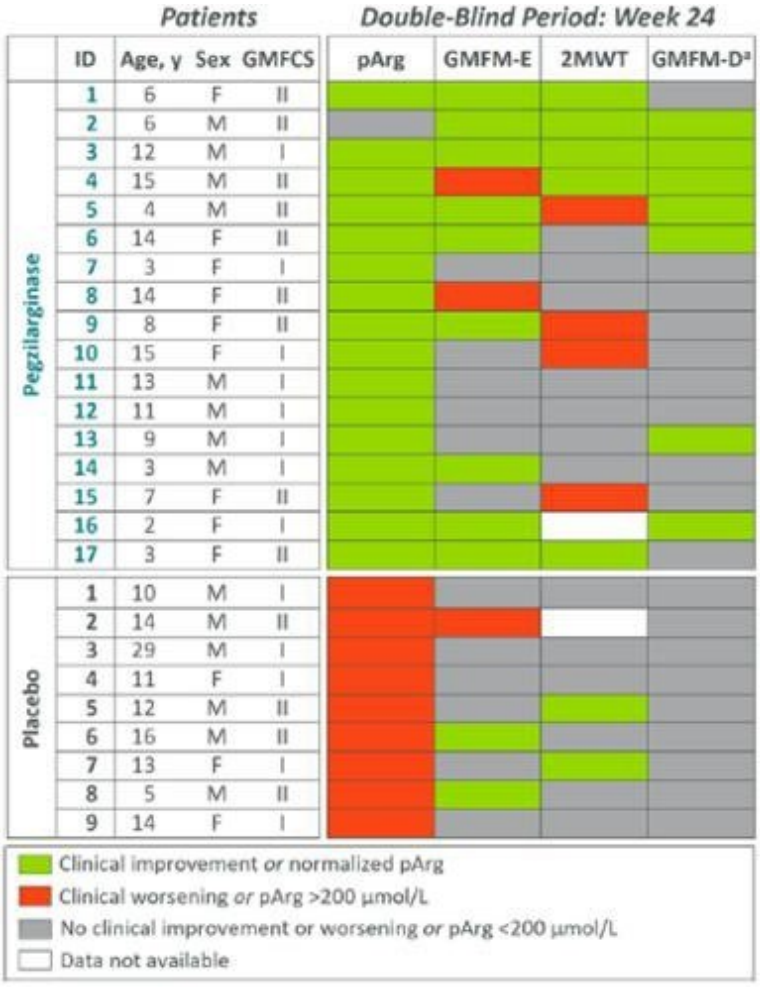
Mobility assessments (2MWT, GMFM-D, and GMFM-E) were evaluated further to determine clinical responders based on MCIDs both individually and in a composite fashion. Responder definitions using published change thresholds in CP were applied to the ARG1-D patient data to assess improvement in mobility in the absence of ARG1-D specific thresholds (95, 98). Of note, there is no published MCID for response in the described mobility assessments, so enrolled patients classified as GMFCS-IV were excluded from this analysis.

As previously described in Section B.2.6.1.1.a, pegzilarginase demonstrated a consistent reduction in pArg levels to or below treatment guidelines (<200 μM). Figure 24 provides evidence that a reduction in arginine is associated with clinical improvements in functional mobility across multiple domains. For patient level analysis, 26 patients were eligible; five patients were excluded because of baseline GMFCS Level VI and one patient withdrew before Week 24.

At Week 24, predefined clinical response criteria for ≥2 functional mobility assessments were met by 47.1% of patients treated with pegzilarginase (8 of 17 patients) versus non receiving placebo. Of those eight patients achieving ≥2 response thresholds, 75.0% of patients (6 of 8 patients) had no worsening or missing data on any individual component in the pegzilarginase group compared to none (0%) in the placebo group. The magnitude of change was greater in the pegzilarginase arm versus placebo. Clinical improvement in 2MWT exceeded the MCID (improvement from baseline ≥9%) for 29.4% of patients treated with pegzilarginase (5 of 17 patients) at Week 24. Furthermore, clinical improvement in GMFM-D and GMFM-E exceeded the MCIDs (GMFM-D: ≥1.5 to ≥3.3 points based on baseline GMFCS classification; GMFM-E: ≥1.8 to ≥4.0 points based on baseline GMFCS classification) for 41.2% (7 of 17 patients) and 52.9% (9 of 17 patients), respectively, at Week 24. No patient in

the placebo group normalised their arginine levels, albeit 44.4% of evaluable patients (4 of 9 patients) did have clinically meaningful improvements in a single assessment domain (Figure 19) (59, 84).

Figure 19: Patient-level analysis of pegzilarginase effect on plasma arginine and clinical responses in the double-blind period (PEACE; FAS)



Key: 2MWT: 2-Minute Walk Test; GMFCS: Gross Motor Function Classification System; GMFM-D: Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88, Part D; pArg: plasma arginine.
Source: Figure 5, Sanchez Russo *et al.* (2024) (59).

ii. Neurocognition and memory (BSID-III and Wechsler intelligence batteries)

PEACE utilised four separate assessments to assess neurocognitive functioning, each dependent on age: WAIS-IV (16 years and older), WISC-V (6 to 16 years 11 months), WPPSI-IV (2.5 to 7.6 years), and BSID-III (2 to 3.5 years). The three Wechsler tests all report a FSIQ score. FSIQ scores can range from 40-160, with a score of 90-109 considered 'average' in the general population.

In PEACE, no meaningful change in neurocognition and memory assessments between treatment groups were observed during the double-blind portion of the study. At baseline, patients across both treatment groups had extremely low FSIQ scores (FSIQ <70), suggesting significantly below average intellectual functioning. By Week 24 of the double-blind period, the mean (SD) FSIQ in both treatment groups had similar numeric improvements, with the pegzilarginase group observing a mean (SD) change from baseline of [redacted] compared to a [redacted] increase in the placebo group (Table 18). The sample size of the placebo group at Week 24 is considered insufficient for robust analysis, so results should be interpreted with caution (84).

Of note, only one patient completed the BSID-III, hence results from this questionnaire are not presented in the submission.

Table 18: Summary of combined FSIQ score for patients who received either WAIS-IV, WISC-V, WPPSI-IV in the double-blind period (PEACE; FAS)

Visit	Pegzilarginase (n=21)	Placebo (n=11)
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Week 24		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change from baseline at Week 24		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Key: FAS: Full Analysis Set; FSIQ: full-scale IQ; Max: maximum; Min: minimum: SD: standard deviation; WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition; WISC-V: Wechsler Intelligence Scale for Children, Fifth Edition; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.
Source: Table 14.2.13.5, PEACE CSR (84).

iii. Modified Ashworth Scale (MAS)

The MAS was developed to assess the spasticity of patients with central nervous system lesions and is used to measure the resistance to passive movement about a joint due to spasticity. As a hallmark of ARG1-D is spastic diplegia (see Section B.1.3.1.2.a.iv), this assessment is particularly relevant for this patient population. The

scale utilizes a scoring scale of 0 (no spasticity) to 4 (total rigidity). The MAS was introduced during the study with a protocol amendment, and the number of patients assessed was more limited ([redacted] of 32 patients, [redacted]) (84).

At baseline, the mean (SD) MAS lower body score was [redacted] in the pegzilarginase group and [redacted] in the placebo group. By the end of the double-blind period at Week 24, there was a numeric improvement in the pegzilarginase group (n=[redacted]) versus the placebo group (n=[redacted]). The mean (SD) change from baseline in the MAS lower body scores for patients in the pegzilarginase and placebo groups was [redacted] and [redacted], respectively. Thes improved scores indicate that [redacted] of patients ([redacted] of [redacted]patients) with baseline spasticity in the pegzilargnase group demonstrated improvements, compared to [redacted] ([redacted] of [redacted] patients) in the placebo group (84).

iv. Paediatric Quality of Life Inventory (PedsQL)

The 23-item PedsQL Generic Core Scales, which measures the core dimensions of health (includes multidimensional scales for physical functioning, emotional functioning, social functioning, and school functioning) to generate three summary scores (total health, physical health, and physiological health). For each summary and dimension score, higher values indicate a better quality of life (scale: 0-100).

Mean total scale scores improved from baseline to Week 24 for patients treated with pegzilarginase, with a mean change from baseline at Week 24 of [redacted] points in parent reported PedsQL (84).

With regards to the individual domains of PedsQL, at Week 24, the mean (SD) change from baseline emotional functioning score increased by [redacted] from baseline in the pegzilarginase group (n=[redacted]), exceeding the MCID threshold of 6.5 (irrespective of GMFCS level) outlined by Oeffinger *et al*. (2008) (95), while patients treated with placebo observed a decline of [redacted] from baseline (n=[redacted]). A numerical improvement in social functioning score from baseline was also observed in the pegzilarginase group ([redacted]) compared to the placebo group [redacted]). Patients in both treatment groups experienced a decline from baseline in physical functioning (pegzilarginase: n=[redacted]; placebo: n=[redacted]) and school functioning

(pegzilarginase: n=[redacted] ; placebo: n=[redacted]) scores at Week 24, albeit the decline across both domains was more pronounced in those patients treated with placebo compared to those treated with pegzilarginase (physical functioning: [redacted] vs [redacted] ; school functioning: [redacted]) (84).

v. 36-Item Short Form Health Survey (SF-36)

The SF-36 questionnaire was intended for completion by patients ≥19 years (Table 9). Overall, [redacted] patients completed the SF-36 questionnaire ([redacted] from the pegzilarginase group and [redacted] patients from the placebo group). Given the low sample sizes across treatment groups, results are not reported in the submission, with results instead provided as data on file (105).

vi. Short-Form Zarit Burden Interview (ZBI-12)

The ZBI-12 is a 12-item, short version of the ZBI used to describe caregiver burden. It consists of 12 items in two domains: personal strain and role strain. Each question is scored on a 5-point Likert scale, with the sum of scores ranging from 0-48. A higher score represents a greater caregiver burden (72).

At baseline, the mean (SD) ZBI-12 score was [redacted] in the pegzilarginase group and [redacted] was recorded for the placebo group out of a potential range of 0-48, indicating the burden to caregivers was not significant or low. By Week 24, the mean (SD) total ZBI-12 score decreased by [redacted] in the pegzilarginase group compared to a [redacted] increase in the placebo group, demonstrating a small numerical reduction in caregiver burden in the pegzilarginase group (84) (Table 19).

Table 19: Summary of ZBI-12 scores during the double-blind period (PEACE; FAS)

Visit	Pegzilarginase (n=21)	Placebo (n=11)
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Week 24		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Change from baseline at Week 24		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Key: FAS: Full Analysis Set: Max: maximum; Min: minimum: SD: standard deviation; ZBI-12: Zarit Burden Interview Short: 12 items.
Source: Table 14.2.12, PEACE CSR (84).

B.2.6.1.2. Long-term extension

The LTE portion of the PEACE study was planned to be performed for up to 150 weeks and was completed on February 1st 2023. At this timepoint, patients who entered the LTE had variable durations of study participation (range: 86-176 weeks).

Clinical effectiveness results for the LTE are sourced from the PEACE CSR, unless otherwise stated. The data are summarised herein for patients continuing treatment with pegzilarginase (pegzilarginase/pegzilarginase). Clinical effectiveness results for patients initially randomised to placebo in the double-blind period who subsequently received treatment with pegzilarginase in the LTE (placebo/pegzilarginase) are summarised in Appendix N.

a. Change in plasma arginine (pArg)

The reduction in pArg from baseline observed in the pegzilarginase group upon completion of the 24-week double-blind period was sustained in the pegzilarginase/pegzilarginase group over the LTE period. At LTE Week 24, the mean (SD) change from baseline was [redacted] µM, demonstrating sustained improvement with longer duration of therapy (n=[redacted]). This improvement continued through LTE Week 48 [redacted] µM; n=[redacted]), LTE Week 96 [redacted] µM, n=[redacted]), and end of study, although the number of patients in the pegzilarginase/pegzilarginase group receiving treatment beyond LTE Week 96 were low ([redacted] patients at each assessment timepoint, up to LTE Week 138) (84). Summary data for the change in pArg over time during the LTE period is presented in Table 96, Appendix M.

b. 2-Minute Walk Test (2MWT)

The increase from baseline in the 2MWT in the pegzilarginase group at Week 24 of the double-blind period was sustained with further improvements in the

pegzilarginase/pegzilarginase group at LTE Week 24, and this improvement was maintained throughout the study, demonstrating sustained improvement with longer duration of treatment. Across each LTE timepoint, the mean improvement from baseline in the pegzilarginase/pegzilarginase group exceeded the MCID threshold for the 2MWT (>9% increase from baseline) (84). Summary data for the change in 2MWT distance covered over time during the LTE period is presented in Table 97, Appendix M.

c. Gross Motor Function Measure, Part E (GMFM-E)

The increase from baseline in GMFM-E observed in the pegzilarginase group at Week 24 of the double-blind period was sustained with further improvement in the pegzilarginase/pegzilarginase group during the LTE period. The mean (SD) change from baseline at the end of the double-blind period was 4.2 (7.7) points, increasing to [redacted] points at LTE Week 24 (n=[redacted]). The mean change from baseline in GMFM-E remained stable throughout the remainder of the LTE period to end of study, demonstrating sustained improvement with longer duration of therapy (84). Summary data for the change in GMFM-E score over time during the LTE period is presented in Table 98, Appendix M.

d. Changes in ornithine and guanidino compounds

As highlighted in Section B.2.6.1.1.c.i, median ornithine levels in the pegzilarginase group increased from 32.1 µM at baseline to 70.2 µM at the end of the double-blind period. Increased ornithine levels were maintained during the LTE period (84).

Decreased levels of GCs were also observed during LTE follow-up in all patients. During the double-blind period, decreases in all four GCs were observed at Week 1 and maintained through Week 24 (see Section B.2.6.1.1.c.i). These reductions were sustained in all four GCs compounds across the entire LTE period, and further decreases over time were noticed in several of the analytes (84).

e. Gross Motor Function Measure, Part D (GMFM-D)

The increase from baseline for GMFM-D observed in the pegzilarginase/pegzilarginase group at Week 24 of the double-blind period was sustained with further improvement during the LTE period. The mean (SD) change

from baseline at the end of the double-blind period was 2.7 (3.9) points, compared to a mean (SD) change of [redacted] points (n=[redacted]), [redacted] points (n=[redacted]), and [redacted] points (n=[redacted]), at LTE Weeks 24, 48, and 96, respectively, demonstrating sustained improvement with longer duration of treatment (84). Summary data for the change in GMFM-D score over time during the LTE period is presented in Table 99, Appendix M.

f. Vineland Adaptive Behaviour Scale, Second Edition (VABS-II)

At LTE baseline, the mean (SD) VABS-II adaptive behaviour composite score for patients in the pegzilarginase/pegzilarginase group (n=20) was 71.6 (24.3), reflecting a moderately low score (71 to 85). Throughout the LTE, the mean VABS-II adaptive behaviour composite score remained stable, with the mean (SD) score ranging from [redacted] points at LTE Week 24 (n=[redacted]) to [redacted] points at LTE Week 150 (end of study) (n=[redacted]) (84). Due to the detrimental manifestation of ARG1-D, a demonstration of stabilisation in VABS-II is clinically relevant.

g. Responder analysis and composite clinical outcomes

The heatmap developed for the double-blind period (see Section B.2.6.1.1.d.i, Figure 19) was updated for the LTE period to represent patients who met the criteria for response in the 2MWT, GMFM-D, and GMFM-E to further visualise the treatment effect of pegzilarginase over time (see Section B.2.6.3, Figure 24). Overall, the benefits observed in the mobility assessments, 2MWT, GMFM-D and GMFM-E during the double-blind period continued to improve through the LTE treatment with longer-term treatment, increasing 2MWT distance, GMFM-D and GMFM-E scores (84, 89). Summary data for the composite clinical responder outcome during the LTE period is presented in Table 100, Appendix M.

As highlighted in Section B.2.2, the most-recent patient-level analyses of pegzilarginase effect on plasma arginine and clinical response in the LTE up to LTE Week 120 was recently shared with the EMA as part of mandatory post-authorisation measures for the marketing authorisation under exceptional circumstances (23). To account for missing visits in the visualisation in the PEACE CSR, wider protocol visits were applied to the heat map, where the most recent assessments were included for LTE Week 24, LTE Week 48, LTE Week 120. LTE Week 48 included a window of most

recent assessment between LTE Week 41 to LTE Week 48, LTE Week 72 included a most recent assessment visit of LTE Week 60 to LTE Week 84, and LTE 120 included a window of most recent assessment between LTE Week 84 and LTE Week 124. If the timepoint included in the heatmap differed from the assigned heatmap timepoint, the data was marked in the heatmap (84, 89).

h. Neurocognition and memory (BSID-III and Wechsler intelligence batteries)

LTE baseline FSIQ data was available for 15 patients in the pegzilarginase/pegzilarginase arm. At LTE Week 24, the mean (SD) change from baseline in FSIQ in the pegzilarginase/pegzilarginase group improved by [redacted] (n=[redacted]), with a similar improvement recorded at LTE Week 48 ([redacted]) (n=[redacted]). At LTE Week 96, mean (SD) FSIQ score increased by [redacted] from baseline (n=[redacted]). [redacted] patients with data at LTE Week 150 (end of study) had a mean (SD) change from baseline of [redacted] (84).

i. Modified Ashworth Scale (MAS)

The frequency of patients with results beyond LTE Week 96 were low (≤2 patients at each assessment timepoint, up to LTE Week 150). At LTE Week 48, there was a numeric improvement in MAS lower body score, with a mean (SD) change from baseline of [redacted] (n=[redacted]) (84).

From a review of patient listings, [redacted] pegzilarginase/pegzilarginase patients had spasticity in the lower limbs at baseline or at their first assessment of MAS. Of these, [redacted] of patients ([redacted] of [redacted] patients) in the pegzilarginase/pegzilarginase group improved in lower limb spasticity. For [redacted] of patients ([redacted] of [redacted] patients) with lower-limb spasticity, their lower-limb spasticity improved to zero (i.e., no spasticity) at the last assessment. [redacted] of the remaining patients ([redacted]) improved with some remaining lower-limb spasticity in the last assessment, while the lower-limb spasticity of [redacted] remained unchanged (84).

j. Paediatric Quality of Life Inventory (PedsQL)

The frequency of patients with results for each individual dimension beyond LTE Week 96 were low (≤4 patients at each assessment timepoint, up to LTE Week 150). At LTE

Week 48, a mean (SD) decrease from baseline was recorded across each individual dimension,with the magnitude of decline ranging from [redacted] (n=[redacted]) in physical functioning score to [redacted] (n=[redacted]) in emotional functioning score (84).

k. 36-Item Short Form Health Survey (SF-36)

No patients in the pegzilarginase/pegzilarginase arm had data reported in the LTE (84).

l. Short-Form Zarit Burden Interview (ZBI-12)

At LTE Week 24, the mean (SD) ZBI-12 score decreased by [redacted] from baseline in the pegzilarginase/pegzilarginase group (n=[redacted]). At LTE Week 48, the mean ZBI-12 score remained below baseline, with mean changes (SD) from baseline of [redacted] (n=[redacted]), but demonstrated an mean (SD) increase of [redacted] (n=[redacted]) at LTE Week 96. At LTE Week 150, a small numerical improvement in ZBI-12 score was observed, with a mean (SD) change from baseline of [redacted] (n=[redacted]) recorded (84).

B.2.6.2. Study 102A

The Study 102A CSR reports results from data analysis that was completed when all patients completed the study (December 15th 2022). At this timepoint, one patient had withdrawn from the study at Week 26, the first two patients recruited into the study had completed Week 260 and the remaining 11 patients had completed between 191 and 224 weeks of treatment. The final analysis includes descriptive summaries of all neuromotor efficacy data up to and including Week 144 and follow-up pArg data to Week 192. Follow-up assessments were conducted at the end of the study, and this occurred between Week 189 and Week 215 for 10 patients, and for two patients the follow-up occurred at Week 262 (96).

The study began in December 2017 and concluded on December 15th 2022, which included the period during which the COVID-19 pandemic was occurring globally. When the pandemic occurred, the study was fully enrolled, and impact was generally limited to visit attendance and assessment performance. No formal adjustments or mitigations to study visits or study procedures were made as a result of the COVID-19 pandemic, as the option for treatment administration and evaluation at home, after demonstration of sufficient safety, were already part of the study (96).

Of note, [redacted] patients missed at least one dose of pegzilarginase due to the COVID-19 pandemic ([redacted]); these were captured as important protocol deviations related to 'investigational product compliance' (96).

B.2.6.2.1. Changes in plasma arginine (pArg)

The rapid onset and prolonged half-life of pegzilarginase resulted in early, consistent, and sustained reductions in pArg levels through Week 192. At Study 102A baseline, median pArg levels were approximately >2.5-fold above the normal range (≤40 - ≤115 µM) and >1.5-fold above the treatment guidelines (<200 µM) (see Table 15, Section B.2.3.2.8). At Week 96, all patients (100.0%) had achieved pArg levels at the guideline-recommended level, while 76.9% (10 of 13 patients) achieved pArg levels within normal limits (93, 96). This reduction was sustained through Week 192, irrespective of the method of administration for pegzilarginase (Table 20) (96).

Table 20: Summary of pArg reduction at 168 hours post-dose (Study 102A; FAS)

	BL	Wk 12	Wk 24	Wk 48	Wk 72	Wk 96	Wk 120	Wk 144	Wk 168	Wk 192	Wk 240
n	14	14	[redacted]	[redacted]	[redacted]	13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	118.9 (43.79)	[redacted]	[redacted]	[redacted]	100.6 (33.63)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51.65, 189.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Below the guideline-recommended level, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13 (100)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within the normal range, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (76.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Study 102A baseline											
n	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BL: baseline; FAS: Full Analysis Set; Max: maximum, Min: minimum; pArg: plasma arginine; SD: standard deviation; Wk: week.
Notes: Every week represents the average of the last four non-missing doses up to and including the week number. Concentrations below the level of quantitation were inputted as half the quantitation limit. Twelve of the 14 patients commenced subcutaneous injections at Week 25; the remaining two patients switched to subcutaneous injections at Week 38.
[a]Guideline-recommend level: <200 µM
[b]Normal range: ≥40 - ≤115 µM
Source: Table 18, Study 102A CSR (96); McNutt *et al*. (2023) (93).

B.2.6.2.2. Changes in ornithine and guanidino compounds

Pegzilarginase administration resulted in increases in ornithine levels that were maintained through Week 140. At Study 102A baseline, the median ornithine level was outside of the normal range ([redacted] mg/dL, normal: 22 – 130 mg/dL). At 168 hours after the first administration of IV pegzilarginase, the median ornithine level had risen to [redacted] mg/dL (range: [redacted] - [redacted]). Median ornithine levels increased further to [redacted] mg/dL (range: [redacted] – [redacted]) at Week 24, and to [redacted] mg/dL (range: [redacted]) at Week 48. This increase was sustained through Week 192, with a median level of [redacted] mg/dL (range: [redacted]). Up to Week 240, although only [redacted] patients reported data, the sustained effect was demonstrated (96).

Furthermore, the rapid onset and prolonged half-life of pegzilarginase resulted in early, consistent, and sustained reductions in plasma GCs levels through Week 240, except for the Week 240 timepoint for guanidinoacetic acid (GAA). Relative reductions in median GC concentrations ranged from [redacted] at Week 24 and from [redacted] at Week 48. The timing and pattern of reduction in plasma GCs corresponded with decreases in pArg (Figure 20) (96).

Figure 20: Mean plasma guanidino compounds and arginine reduction (Study 102A; FAS)

Key: ARG: arginine; ARGA: argininic acid; BL: baseline; FAS: Full Analysis Set; GAA: guanidinoacetic acid; GVA: α-keto-δ-guanidinovaleric acid; NAARG: α-N-acetylarginine.

Source: Figure 3; Study 102A CSR (96).

B.2.6.2.3. 6-Minute Walk Test (6MWT)

The 6-Minute Walk Test (6MWT) measures the distance a patient can walk on a flat surface in six minutes; with an MCID of ≥9% change from baseline considered to be a conservative benchmark for improvement in the absence of an established MCID for 6MWT in ARG1-D patients (106).

Pegzilarginase administration resulted in an increase from baseline in the mean distance walked over 6 minutes as measured by the 6MWT that was sustained up to 262 weeks. The mean (SD) 6MWT distance at Week 24 was 322.6 (161.4) metres, representing a mean increase of [redacted] metres from baseline. At Week 48, the mean 6MWT distance increased by [redacted] metres from baseline to 346.2 (177.3) metres. Beyond Week 48, changes from baseline in the 6MWT exceeded the MCID. Clinically meaningful improvement was demonstrated from Week 48 (mean percentage change: [redacted]) which was sustained throughout the remainder of the study to Week 144, ranging from [redacted] (Figure 21) (96).

Of note, two patients were administered botulinum toxin during the study, with last dose in the latter part of the study, potentially confounding results. The last dose of botulinum toxin administered for one patient was on Week 95, and the improvement observed with pegzilarginase treatment can be seen to be reduced after this timepoint. The other patient had their last dose of botulinum toxin at Week 131, and at the end of the study improvements in pegzilarginase were reduced slightly (96).

Figure 21: Sustained effect of pegzilarginase on 6MWT to Week 144 (Study 102A; FAS)

Key: 6MWT: 6-Minute Walk Test; FAS: Full Analysis Set; W: week.
Notes: Group sizes reflect all patients with data at each time point; there was no imputation for missing values. The 6MWT was not evaluated in one patient, who was non-ambulatory (i.e., unable to walk). A higher 6MWT score indicates a longer walking distance and, therefore, improvement. The minimal clinically important difference for the 6MWT is 9%. Twelve of the 14 patients commenced subcutaneous injections at Week 25; the remaining two patients switched to subcutaneous injections at Week 38.
Source: Table 24 and Table 14.2.2.1.1, Study 102A CSR (96).

B.2.6.2.4. Gross Motor Function Measure (GMFM)

a. Gross Motor Function Measure, Part D (GMFM-D)

Details of the GMFM-D assessment tool are briefly described in Section B.2.6.1.1.c.ii.

Pegzilarginase administration resulted in improvements from baseline in ability to stand as measured by GMFM-D. The mean (SD) GMFM-D score at Week 24 was 29.1 (11.0) points, representing a mean increase of [redacted] points from baseline. At Week 48, the mean GMFM-D score increased by [redacted] from baseline to 31.8 (8.4) points (Figure 22). The improvement in the mean (SD) GMFM-D score was sustained through Week 144 ([redacted] points) (96).

As highlighted in Section B.2.6.2.3, two patients were administered botulinum toxin during the study, with the last dose in the latter part of the study, potentially confounding results (96).

Figure 22: Sustained effect of pegzilarginase on GMFM-D to Week 144 (Study 102A; FAS)

Key: FAS: Full Analysis Set; GMFM-D: Gross Motor Function Measure-66, Part D; MCID: minimally important clinical difference; W: week.
Notes: One patient, who was GMFCS Level IV and non-ambulatory (ie, unable to walk), discontinued the study at Week 26. A higher GMFM-D score indicates improvement in standing abilities. The MCID for the GMFM-D is 2.4, 3.3, and 1.5 for GMFCS Levels I, II, and III, respectively.
Source: Table 26, Study 102A CSR (96).

b. Gross Motor Function Measure, Part E (GMFM-E)

Details of the GMFM-E assessment tool are briefly described in Section B.2.6.1.1.b.ii.

Pegzilarginase administration resulted in improvements from baseline in ability to walk, run and jump as measured by GMFM-E. The mean (SD) GMFM-E score at Week 24 was 48.9 (24.6) points, representing a mean increase of [redacted] points from Study 102A baseline. At Week 48, the mean GMFM-E score increased by [redacted] from baseline to 53.6 (20.7) points (Figure 23). The improvement in the mean (SD) GMFM-E score was sustained through Week 144 ([redacted] points) (96).

As highlighted in Section B.2.6.2.3, two patients were administered botulinum toxin during the study, with the last dose in the latter part of the study, potentially confounding results (96).

Figure 23: Sustained effect of pegzilarginase on GMFM-E to Week 144 (Study 102A; FAS)

Key: FAS: Full Analysis Set; GMFM-D: Gross Motor Function Measure-66, Part D; MCID: minimally important clinical difference; W: week.
Notes: One patient, who was GMFCS Level IV and non-ambulatory (ie, unable to walk), discontinued the study at Week 26 A higher GMFM-D score indicates improvement in standing abilities. The MCID for the GMFM-D is 3,3, 2.4, and 1.5 for GMFCS Levels I, II, and III, respectively.
Source: Table 26, Study 102A CSR (96).

B.2.6.2.5. Modified Ashworth Scale (MAS)

A brief description of the MAS is provided in Section B.2.6.1.1.d.iii. In Study 102A, the MAS score was provided for all 14 patients.

At Study 102A baseline, 10 patients (71.4%) had spasticity, all of whom reported spasticity in both lower limbs. It should be noted two patients were administered botulinum toxin prior to and during Study 102A, up to Week 95 and Week 131, respectively. This had the potential to confound the assessment of reduction in spasticity due to pegzilarginase treatment in these two patients upon withdrawal of spasticity medication (96).

At Week 24, the mean (SD) MAS score per impacted muscle group was [redacted] (n=[redacted]), representing a mean (SD) decrease of [redacted]. At Week 48, the mean (SD) MAS score impacted per muscle group was [redacted] (n=[redacted]), representing a mean (SD) decrease of [redacted]. Improvements in spasticity continued through up to Week

262, with mean (SD) MAS scores per muscle group of [redacted] and [redacted] at Week 96, Week 144 and follow-up, respectively (96).

All patients assessed at Week 48 ([redacted] of [redacted] patients), Week 96 ([redacted] of [redacted] patients), Week 144 ([redacted] of [redacted] patients) and at follow-up ([redacted] of [redacted] patients) demonstrated improvements in spasticity. At Study 102A baseline, the mean number of muscle groups with MAS scores of zero (no spasticity) was [redacted] , which improved to [redacted] muscle groups at Week 144 and [redacted] muscle groups at follow-up. At Week 96, [redacted] patients were reported to have no spasticity in two out of the four muscle groups impacted at baseline; at Week 144, [redacted] patients achieved a score of zero (no spasticity) in one or two of the four muscle groups impacted at baseline, while [redacted] had a score of zero for all four muscle groups, indicating that they no longer had any spasticity in their lower limbs.(96)

B.2.6.2.6. Composite responder analysis

In Study 102A, the percentage of patients considered to be 'clinical responders' was defined in two ways: a patient who improved by at least on MCID on either the 6MWT, GMFM-D, or GMFM-E; and a patient who improved by at least one MCID on either the 6MWT, GMFM-D, or GMFM-E, but did not have clinically meaningful worsening on either of the other two assessments. Of note, MCIDs using published change thresholds in Morquio syndrome (6MWT) and CP (GMFM-D and GMFM-E) were applied to the ARG1-D patient data to assess improvement in mobility in the absence of ARG1-D specific thresholds.

Overall, the majority (range: [redacted]) of evaluable patients at each timepoint exceeded the MCID on at least one mobility assessment. Similar proportions were also observed (range: [redacted]) amongst patients who exceeded the MCID on at least one mobility assessment, irrespective of worsening for the other two mobility assessments (96).

To further characterise the treatment effect of pegzilarginase over time, a heatmap was developed to represent patients who met the criteria for response in the 6MWT, GMFM-D, and GMFM-E. Overall, the majority of patients treated with pegzilarginase in Study 102A demonstrated clinically meaningful improvements in mobility

assessments based on MCIDs from Week 12 through up to 262 weeks (see Section B.2.6.3, Figure 24) (89, 96).

As highlighted in Section B.2.2, the most-recent patient-level analyses of pegzilarginase effect on plasma arginine and clinical response to Week 190 was recently shared with the EMA as part of mandatory post-authorisation measures for the marketing authorisation under exceptional circumstances (23). To account for missing visits in the visualisation, wider protocol visits were applied to the heat map, where the most recent assessments were included for Week 190 (range: Week 188 to Week 258).

B.2.6.2.7. Neurocognition and memory (Wechsler intelligence batteries)

In Study 102A, neurocognitive functioning was assessed via the WAIS-IV, WISC-V, and WPPSI-IV tests. These tests are described briefly in Section B.2.6.1.1.d.ii.

Of note, there was a discrepancy between the performance of adult patients and paediatric patients, with adult patients performing at a lower level (moderately to mild impaired range) than for paediatric patients (average to borderline range), which is expected in a progressive disease but has not been well documented for ARG1-D. Two patients in Portugal were not assessed due to lack of translations.

FSIQ scores were assessed for [redacted] patients. [redacted] patients ([redacted]) had stable scores, [redacted] patients ([redacted]) had improved FSIQ scores, and [redacted] had scores fluctuating between stable to worsening over the study (96).

B.2.6.2.8. Vineland Adaptive Behaviour Scale, Second Edition (VABS-II)

Data are available for the VABS-II for [redacted] of 14 patients. At Study 102A baseline, median domain standard scores and adaptive behaviour composite score were all below average, with adult scores worse than those of paediatric patients. A numerical decrease that was not clinically significant was observed in the mean (SD) group adaptive composite behaviour scores over time [redacted] at Week 144 (96).

Based on the adaptive behaviour composite scores for individual patients, at the last on-treatment visit (144 weeks of treatment) [redacted] patients were assessed to be stable, [redacted] patients had declined, and [redacted] had improved on study (96).

B.2.6.2.9. Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS Paediatric Profile-25, Paediatric/Parent Proxy Profile 25, and PROMIS-29 are disease non-specific measures of health-related domains. The Pediatric/Parent Proxy Profile, for use in patients 2 - 18 years of age, is a collection of 4-item short forms assessing anxiety, depressive symptoms, fatigue, pain interference, physical function-mobility, and peer relationships, as well as a single pain-intensity item. PROMIS-29, for use in patients ≥18 years of age, is a collection of 4-item short forms assessing anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, and ability to participate in social roles and activities, as well as a single pain-intensity item.

When data from all PROMIS tools is combined (n=[redacted]), a decrease in pain was reported in [redacted] of [redacted] patients ([redacted]) and a decrease in fatigue in [redacted] of [redacted] patients ([redacted]), with [redacted] patients having a reduction in both. Anxiety was reported as increased in [redacted] of [redacted] patients ([redacted]) and improved in [redacted] of [redacted] patients ([redacted]). No other obvious trends were observed over time (96).

Results for the PROMIS-29 (through Week 144), PROMIS Paediatric/Proxy Profile-25 (through Week 48), and PROMIS Paediatric Profile-25 (through Week 24) are presented in Table 101 – Table 103, Appendix O.

B.2.6.2.10. Paediatric Quality of Life Inventory (PedsQL)

PedsQL was only completed for two patients who did not complete PROMIS in the parent study Study 101A. For the parent proxy PedsQL, both patients showed stability on the Physical health summary score and one patient showed an improvement in the Psychosocial health summary score over time ([redacted] at baseline versus [redacted] at follow-up). For the Child reported PedsQL, one patient showed improvement in Psychosocial health summary score ([redacted] at baseline versus [redacted] at follow-up) and Physical health

summary score ([redacted] at baseline versus [redacted] at follow-up), while the other showed stability on both (96).

B.2.6.2.11. Short-Form Zarit Burden Interview (ZBI-12)

At baseline, the median total ZBI-12 score was [redacted] (range: [redacted]). At Week 24 and Week 48, the median total ZBI-12 score was [redacted] (range: [redacted]) and [redacted] (range: [redacted]), respectively. In the majority of patients, ZBI-12 score remained similar over time; one patient had a decrease in ZBI-12 score from [redacted] at baseline to [redacted] at Week 48. Results were consistent through Week 144 (median: [redacted] [range: [redacted]) (96).

B.2.6.3. Summary of responder analyses – PEACE and Study 102A

As described in Section B.2.6.1.1.d.i, Section B.2.6.1.2.g (PEACE) and Section B.2.6.2.6 (Study 102A), the mobility function assessments (2MWT/6MWT, GMFM-D and GMFM-E) were further evaluated to determine clinical responders based on MCIDs both individually and in a composite fashion for PEACE and Study 102A. Overall, a majority of patients treated with pegzilarginase met criteria for response, often across multiple domains. The degree of response across studies was generally similar, taking into account the baseline GMFCS status, demonstrating the treatment effect of pegzilarginase with further improvement over long-term treatment (Figure 24).

Figure 24: Heatmap of responders in PEACE and Study 102A (evaluable patients)

Key: 2MWT: 2-Minute Walk Test; GMFCS: Gross Motor Function Classification System; GMFM-D: Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88, Part E; LTE: long-term extension; MCID: minimally clinical important difference; pArg: plasma arginine.
Notes: There are no response thresholds available for GMFCS Level IV, therefore patients with GMFCS Level IV at baseline were excluded from these analyses, as were those without a post-baseline assessment at the relevant timepoint. Placebo/pegzilarginase group at Week 24 is not on active treatment.
* Actual timepoint not at defined timepoint but within specified range.
# Met MCID criteria and also reached normal range for age-/sex-matched 2WT distance or maximum score on GMFM-E or GMFM-D.
Source: PEACE CSR (84); Study 102A CSR (96); Data on File – EMA Responder Analysis Heatmap (89).

B.2.6.4. Study 101A

The clinical effectiveness results for pegzilarginase from Study 101A are described in Appendix P.

B.2.7 Subgroup analysis

Pre-planned subgroup analyses based on baseline disease covariates were prespecified and conducted for the primary and key secondary endpoints in the pivotal PEACE study for the placebo-controlled double-blind period. The FAS was stratified by age (<18 years of age and ≥18 years of age) sex (male and female), region (US and ex-US), and GMFCS classification (Level I and Level >I).

The patient numbers within the age subgroup were insufficient for any robust analysis, as almost all patients in the study cohort were <18 years of age; there were only three patients enrolled ≥18 years of age (one patient in the pegzilarginase group and two patients in the placebo group). Across the remaining subgroups, results were consistent with findings in the primary analysis presented in Section B.2.6.1, and demonstrate the clinical benefit of pegzilarginase in all patients, regardless of sex, region, and GMFCS classification. It must be noted that subgroup analyses should be interpreted with caution given the small sample sizes and overlapping 95% CIs (84). Full results of the subgroup analysis of the primary endpoint are presented in Appendix E.

Of note, while improvements were observed in both subgroups, patients treated with pegzilarginase with more severely restricted mobility (GMFCS Level ≥II) had greater gains in both the 2MWT and GMFM-E compared to patients classified as GMFCS Level I (See Figure 39 and Figure 40, Appendix E) (84). These differences may reflect a lesser capacity to capture improvements in clinical benefit with these assessment tools in patients with near-normal baseline scores. Despite this, patients in GMFCS Level I continued to demonstrate improvement in mobility outcomes assessments with pegzilarginase treatment.

B.2.8 Meta-analysis

PEACE is the only randomised clinical study of pegzilarginase in ARG1-D. Hence, a meta-analysis was not deemed feasible and was not conducted for the submission.

B.2.9 Indirect and mixed treatment comparisons

An SLR was conducted to identify studies reporting on the efficacy and safety of interventions for ARG1-D. No relevant published randomised controlled trials on the comparator specified in the decision problem were identified, and the publications that where identified consisted of case reports or cohort studies involving few patients. Furthermore, given that lack of standardisation of comparator, defined as IDM in the decision problem, an indirect or mixed treatment comparison was not deemed feasible. As a result, no indirect or mixed treatment comparisons could be conducted.

B.2.10 Adverse reactions

B.2.10.1. PEACE

The safety and tolerability of pegzilarginase for the treatment of ARG1-D patients aged 2 years and older was evaluated for the FAS. As highlighted previously in Section B.2.3.1.7, the FAS included all patients who were randomised and received at least one dose of blinded study treatment (59, 84). AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0

B.2.10.1.1. Exposure to pegzilarginase

The median treatment exposure throughout the study was similar across the pegzilarginase and placebo groups during the double-blind period (24 weeks [range: 6-25 weeks] and 24 weeks [range: 22-25 weeks], respectively) and the pegzilarginase/pegzilarginase and placebo/pegzilarginase groups during the LTE ([redacted] weeks [range: [redacted] weeks] and [redacted] weeks [range: [redacted] weeks], respectively). Dosing compliance was high throughout the duration of the study (mean overall compliance rate [redacted]) (Table 21) (59, 84).

Table 21: Summary of dosing exposure and compliance during the double-blind period and the LTE (PEACE; FAS)

	Double-Blind Period		Long-Term Extension	
	Pegzilarginase (n=20)	Placebo (n=11)	Pegzilarginase /Pegzilarginase (n=20)	Placebo/ Pegzilarginase (n=11)
Treatment exposure, weeks[a]				
n	21	11	20	11
Mean (SD)	23.1 (3.9)	23.8 (0.75)	[redacted]	[redacted]
Median	24.0	24.0	[redacted]	[redacted]
Min, Max	6, 25[b]	22, 25	[redacted]	[redacted]
Dosing compliance, %[c]				
n	21	11	20	11
Mean (SD)	94.1 (7.1)	97.7 (2.9)	[redacted]	[redacted]
Median	95.8	100.0	[redacted]	[redacted]
Min, Max	71, 100	92, 100	[redacted]	[redacted]

Key: FAS: Full Analysis Set; Max: maximum; Min: minimum; SD: standard deviation.
Notes: Patients received pegzilarginase for ≥24 weeks in the LTE, in addition to the 24-week double-blind period.
[a]Treatment exposure was calculated using the dates of absolute first and absolute last drug administrations per patient. If the drug was paused, then the time that the drug was paused was subtracted from total exposure. Treatment exposure was calculated as: (Date of Last Drug Administration – Date of First Drug Administration +1) +7. Patients were allowed to restart the study if they had a temporary pause due to the COVID-19 pandemic. The number of expected doses includes COVID-19 pauses.
[b]One patient randomised to pegzilarginase withdrew from the study at Week 6 due to personal reasons.
[c]Dosing compliance was defined as the number of doses taken/number of expected doses.
Source: Table 3 and Table 4, Sanchez Russo *et al*. (2024) (59); Table 54 and Table 61, PEACE CSR (84).

B.2.10.1.2. Summary of adverse events

In total, 187 treatment emergent adverse events (TEAEs) were reported in 90.6% of participating patients (18 of 32 patients) during the double-blind portion of the study, with 139 TEAEs reported in 85.7% of patients in the pegzilarginase group (18 of 21 patients). By contrast, all patients (11 of 11 patients, 100.0%) in the placebo group reported a TEAE, albeit the frequency of TEAEs observed were lower than that of the pegzilarginase group (48 vs 139). TEAEs related to pegzilarginase were recorded in 23.8% of patients with any TEAE (5 of 18 patients). Overall, the majority of TEAEs recorded were mild in severity, with a similar incidence of mild TEAEs observed across both treatment groups, (47.6% of patients [10 of 21 patients] in the pegzilarginase group versus 45.5% of patients [5 of 11 patients] in the placebo group). No patient in either treatment group experienced TEAEs requiring dose reduction or TEAEs leading to the discontinuation of study treatment (59, 84).

More AEs were reported during the LTE period compared with the double-blind portion of the study, as expected with longer observation. During the LTE, all patients had at least one TEAE. As in the double-blind period, most of the TEAEs were mild or

moderate in severity in the pegzilarginase/pegzilarginase group ([redacted] of 20 patients, [redacted]) compared to the placebo/pegzilarginase group ([redacted] of 11 patients, [redacted]). Treatment-related TEAEs were reported in similar proportions of patients across the pegzilarginase/pegzilarginase (8 of 20 patients, 40.0%) and placebo/pegzilarginase arms (4 of 11 patients, 36.4%). No patients experienced TEAEs leading to the discontinuation of study treatment. [redacted] patients, [redacted] in the pegzilarginase/pegzilarginase group ([redacted]) and [redacted] in the placebo/pegzilargonase group ([redacted]) had a TEAE requiring a dose reduction (Table 22) (59).

Table 22: Summary of AEs observed in the double-blind period and the LTE (PEACE; FAS)

	Double-Blind Period				Long-Term Extension			
	Pegzilarginase (n=21)		Placebo (n=11)		Pegzilarginase/ Pegzilarginase (n=20)		Placebo/ Pegzilarginase (n=11)	
	Patients[a], n (%)	Events[b], n	Patients[a], n (%)	Events[b], n	Patients[a], n (%)	Events[b], n	Patients[a], n (%)	Events[b], n
Patients with any TEAE	18 (85.7)	139	11 (100.0)	48	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs by maximum severity								
Mild	10 (47.6)	104	5 (45.5)	36[c]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	7 (33.3)	31	6 (54.5)	12[c]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	1 (4.8)	4	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs	5 (23.8)	27	1 (9.1)	2	[redacted]	[redacted]	[redacted]	[redacted]
TEAE requiring dose reduction	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
TEAE requiring dose interruption	8 (38.1)	20	1 (9.1)	2	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to discontinuation of study drug	0	0	0	0	0	0	0	0
Patients with serious TEAE (SAE)	4 (19.0)	5	4 (36.4)	5	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related SAE	1 (4.8)	1	0	0	[redacted]	[redacted]	[redacted]	[redacted]
SAE leading to a fatal outcome	0	0	0	0	0	0	0	0

Key: AE: adverse event; FAS: Full Analysis Set; LTE: long-term extension; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Notes: Percentages were based on the total number of subjects for the FAS. Any AE that began or worsened during the study was recorded as a new AE. TEAEs were AEs that started or worsened after the first dose of study drug was initiated. If a patient experienced more than one AE, the patient was counted only once for the maximum severity. AEs with missing severities were counted as unknown. If a subject experienced more than one AE, the patient was counted only once for the closest relationship to study treatment. Related AEs consist of possibly related, probably related, and definitely related AEs. AEs with missing relationships were counted as related. AEs were coded using MedDRA Version 24.0. Events' columns summarise the number of individual occurrences of the TEAE.

[a]Patients were only included in the category denoting the highest severity reported for all AEs in the study.

[b]Total study AEs for all subjects were included in the category for their corresponding severity.

[c]For mild and moderate event counts, there should be one additional event in the placebo group for each severity, as one event that started on the first day of the LTE dosing but prior to the administration of the LTE dose while one dose was programmatically assigned in error without consideration of timing of treatment administration to the placebo-pegzilarginase group of the LTE period instead of the placebo-controlled double-blind period.

Source: Table 3, Sanchez Russo *et* al. (2024) (59); Table 55 and Table 62, PEACE CSR (84).

B.2.10.1.3. Common adverse events

TEAEs that occurred in ≥15% of patients in either treatment arm in the double-blind period and/or LTE are summarised in Table 23 below.

Table 23: TEAEs by MedDRA preferred term occurring in ≥15% of patients in the double-blind period and LTE (PEACE; FAS)

	Double-Blind Period		Long-Term Extension	
Preferred Term	**Pegzilarginase (n=21)**	**Placebo (n=11)**	**Pegzilarginase /Pegzilarginase (n=20)**	**Placebo /Pegzilarginase (n=11)**
Any TEAE, n (%)	**18 (85.7)**	**11 (100.0)**	[redacted]	[redacted]
Vomiting	6 (28.6)	3 (27.3)	[redacted]	[redacted]
Nausea	1 (4.8)	3 (27.3)	[redacted]	[redacted]
Abdominal pain[a]	1 (4.8)	3 (27.3)	[redacted]	[redacted]
Pyrexia	4 (19.0)	0	[redacted]	[redacted]
Ammonia increased[a]	3 (14.3)	2 (18.2)	[redacted]	[redacted]
Hyperammonaemia	2 (9.5)	3 (27.3)	[redacted]	[redacted]
Decreased appetite	0	2 (18.2)	[redacted]	[redacted]
Cough	4 (19.0)	1 (9.1)	[redacted]	[redacted]
Fatigue	0	0	[redacted]	[redacted]
Alanine aminotransferase increased	2 (9.5)	0	[redacted]	[redacted]
Aspartate aminotransferase increased	2 (9.5)	0	[redacted]	[redacted]
SARS-CoV-2 test positive[b]	0	0	[redacted]	[redacted]
COVID-19	0	0	[redacted]	[redacted]
Amino acid level increased	1 (4.8)	0	[redacted]	[redacted]
Rhinorrhoea	1 (4.8)	0	[redacted]	[redacted]
Headache	2 (9.5)	1 (9.1)	[redacted]	[redacted]
Oropharyngeal pain	0	0	[redacted]	[redacted]
Upper respiratory tract infection	0	0	[redacted]	[redacted]
Constipation	0	0	[redacted]	[redacted]
Diarrhoea	0	0	[redacted]	[redacted]
Rhinitis	0	0	[redacted]	[redacted]
Blood potassium decreased	0	0	[redacted]	[redacted]
Hypoacusis	0	0	[redacted]	[redacted]
Insulin-like growth factor decreased	0	0	[redacted]	[redacted]

Key: AE: adverse event; FAS: Full Analysis Set; LTE: long-term extension; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment-emergent adverse event.
Notes: Percentages were based on the total number of subjects in each treatment group. The patients column shows the total number of patients with at least one event. AEs were coded using MedDRA Version 24.0. Patients experiencing more than one TEAE within

a given preferred term were counted once within that PT. TEAEs are AEs that started or worsened on or after the date of the first dose. SOCs that met the criteria of ≥15% were included in the table.
[a]For the preferred term of ammonia increased and the SOC of investigations, there should be one additional patient in the placebo group, as one event that started on the first day of LTE dosing but prior to the administration of the LTE dose was assigned to the placebo-pegzilarginase group in the LTE period in error instead of the placebo group in the double-blind period.
[b]Patients with a positive SARS-CoV-2 test are distinct from those with COVID-19 illness.
Source: Table 3, Sanchez Russo *et al.* (2024) (59); Table 14.3.2.1, Table 63 & Table 14.3.3.1.1, PEACE CSR (84).

The majority of TEAEs were of mild or moderate severity. Only one patient (4.8%) in the pegzilarginase group experienced a TEAE of aspartate aminotransferase increase that was considered to be severe during the double-blind period of the study. This event was considered possibly related to pegzilarginase by the investigator. During the LTE, [redacted] in the pegzilarginase/pegzilarginase group experienced a severe TEAE. In the placebo/pegzilarginase group, [redacted] of patients ([redacted] of 11 patients) reported severe TEAEs during the LTE versus none in the placebo-group during the placebo-controlled double-blind period (84).

B.2.10.1.4. Summary of serious adverse events

A similar frequency of patients experienced a serious adverse event (SAE) across each treatment group. Across the double-blind and LTE portions of the study, the most frequently reported SAE was hyperammonaemia, which was recorded in a higher proportion of patients in the placebo group (3 of 11 patients, 27.3%) compared to the pegzilarginase group (2 of 21 patients, 9.5%) during the double-blind period. In the LTE, events of hyperammonaemia were more frequent in patients who transitioned from placebo to pegzilarginase ([redacted] of 11 patients, [redacted]) compared to patients who continued pegzilarginase treatment ([redacted] of 20 patients, [redacted]) (Table 24). During the double-blind period, one patient in the pegzilarginase group experienced an SAE of moderate hyperammonaemic encephalopathy that was considered probably related to study treatment and led to treatment interruption. This event occurred during concurrent urinary tract infection and constipation, was not life threatening, and was resolved in one week. Long-term exposure did not lead to a meaningful increase in the proportion of SAEs (59, 84).

Table 24: SAEs by MedDRA preferred term in the double-blind period and LTE (PEACE; FAS)

	Double-Blind Period		Long-Term Extension	
Preferred Term	**Pegzilarginase (n=21)**	**Placebo (n=11)**	**Pegzilarginase /Pegzilarginase (n=20)**	**Placebo /Pegzilarginase (n=11)**
Any SAE, n (%)	**4 (19.0)**	**4 (36.4)**	[redacted]	[redacted]
Hyperammonaemia	2 (9.5)	3 (27.3)	[redacted]	[redacted]
Hyperammonaemic encephalopathy	1 (4.8)	1 (9.1)	[redacted]	[redacted]
Vomiting	1 (4.8)	0	[redacted]	[redacted]
Gastroenteritis	0	0	[redacted]	[redacted]
Abdominal pain	0	0	[redacted]	[redacted]
Constipation	0	0	[redacted]	[redacted]
Hand-foot-and-mouth disease	0	0	[redacted]	[redacted]
Alanine aminotransferase increased	0	0	[redacted]	[redacted]
Ammonia increased	0	0	[redacted]	[redacted]
Aspartate aminotransferase increased	0	0	[redacted]	[redacted]
Haematuria	0	0	[redacted]	[redacted]

Key: AE: adverse event; FAS: Full Analysis Set; MedDRA: Medical Dictionary for Medical Activities; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Notes: Percentages were based on the total number of patients in each treatment group. The patient's column shows the total number of subjects with at least one event. AEs were coded using MedDRA Version 24.0. Subjects who experienced more than one TEAE within a given preferred term were counted once within that preferred term in the patient's column. TEAEs are AEs that started or worsened on or after the date of first dose. Preferred terms were listed in order of descending frequency across all patients.
Source: Table 3 and Table 4, Sanchez Russo *et al.* (2024) (59); Table 58 and Table 65, PEACE CSR (84).

B.2.10.1.5. Adverse events of special interest

Hypersensitivity reactions, injection site reactions, and HACs were defined as AEs of special interest for PEACE as it was considered that collection of additional information across the entire study population would allow better characterisation of these events (84). An understanding of the favourable and predictable long-term tolerability profile of pegzilarginase is important given the need for chronic treatment and allow for at-home administration to reduce treatment burden on patients, caregivers, and healthcare systems.

a. Hypersensitivity reactions

In the double-blind portion of PEACE, two patients experienced hypersensitivity reactions. One patient in the pegzilarginase group experienced three AEs of hypersensitivity, which were mild to moderate in severity and resolved with standard treatment. Another patient treated with pegzilarginase had an event of swelling face that

was identified by the investigator as a potential hypersensitivity reaction and was assessed as possibly related to pegzilarginase although there was no interruption in study treatment as a result of the event, which was treated with oral cetirizine (59, 84). No additional hypersensitivity reactions occurred during the LTE period (84).

b. Injection site reactions

No patient experienced an injection site reaction in the double-blind period because no patient received SC administration of pegzilarginase or placebo in the double-blind period. During the LTE, injection site reactions were reported for [redacted] of patients ([redacted] of 20 patients) in the pegzilarginase/pegzilarginase group, and [redacted] in the placebo/pegzilarginase group. All incidences of injection site reactions were non-serious, mild, and either resolved spontaneously or resolved with standard medical care (84).

c. Hyperammonaemia events

HACs were prespecified in the protocol where ammonia levels were >100 µM, patients were symptomatic, patients required treatment in a hospital or emergency room, and are summarised by a sponsor-defined MedDRA query, which included the MedDRA preferred terms of hyperammonaemia, hyperammonaemic crisis, and hyperammonaemic encephalopathy that met these conditions (84).

Overall, 21.9% of patients (7 of 32 patients) experienced a HAC AE during the 24-week double-blind period, with fewer events in the pegzilarginase arm (3 of 21 patients, 14.3%) compared to the placebo group (4 of 11 patients, 36.4%) Table 23. Many of the reported events occurred in the context of potential precipitating factors, i.e., infection (59, 84). In the LTE, fewer patients experienced HACs in the pegzilarginase/pegzilarginase arm ([redacted] of 20 patients, [redacted]) compared to the placebo/pegzilarginase group ([redacted] of 11 patients, [redacted]). The hyperammonaemia TEAEs observed in PEACE occurred at rates consistent with those typically observed in patients with ARG1-D (11, 15). Hyperammonaemia was transient and manageable with standard care. A majority of patients had a potential history of hyperammonaemia and precipitating factors identified by the investigator (see Table 11, Section B.2.3.1.8).

Furthermore, for most of the LTE visits, all patients had normalised ammonia levels of ≤100 µM, with a large proportion of patients having values falling in the category of normal

(range: 0 to 35 µM) (84). Although it was not possible to quantitatively assess the change in HACs to understand the impact of pegzilarginase, [redacted] suggests a decline in HACs with pegzilarginase treatment (47).

B.2.10.1.6. Study drug discontinuation

No TEAEs led to the discontinuation of the study drug (59, 84).

B.2.10.1.7. Deaths

No deaths occurred in the PEACE study (59, 84).

B.2.10.2. Study 102A

The safety and tolerability of pegzilarginase was evaluated as the primary endpoint in Study 102A. Safety endpoints were evaluated using the FAS, which included all patients who received any study medication (96).

B.2.10.2.1. Exposure to pegzilarginase

As discussed in Section B.2.3.2.4, patients had the option of switching to SC administration of pegzilarginase from Week 25 onward. All patients switched to SC administration, with exception of one patient who withdrew and discontinued the study after 26 IV doses. Ten of 13 patients (76.9%) received SC administration by home healthcare. The median IV exposure was [redacted] weeks (range: [redacted] weeks), while median SC exposure was [redacted] weeks (range: [redacted]) (Table 25) (96).

All patients ttansitioning to SC treatment (n=13) were exposed to pegzilarginase for >144 weeks, out of which 10 patients (76.9%) were on treatment for more than 196 weeks. Overall, the median exposure to pegzilarginase in Study 102A (n=[redacted]) was [redacted] weeks (range: [redacted] weeks) (Table 25) (96).

Table 25: Pegzilarginase exposure (Study 102A; FAS)

	IV (n=14)	SC (n=13)	IV and SC (n=13)
Duration of exposure, weeks			
n	14	13	13
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Maximum duration of exposure, categories, n (%)			
≤4 weeks	0	0	0
>4 to ≤24 weeks	[redacted]	[redacted]	[redacted]
>24 weeks to ≤48 weeks	[redacted]	[redacted]	[redacted]
>48 weeks to ≤96 weeks	[redacted]	[redacted]	[redacted]
>96 weeks to ≤144 weeks	[redacted]	[redacted]	[redacted]
>144 weeks to ≤196 weeks	[redacted]	[redacted]	[redacted]
>196 weeks to ≤240 weeks	[redacted]	[redacted]	[redacted]
>240 weeks	[redacted]	[redacted]	[redacted]

Key: FAS: Full Analysis Set; IV: intravenous; SC: subcutaneous; SD: standard deviation.
Notes: The columns in this table represent patients on IV, patients who switched to SC, and patients who received both routes of administration. Note that one patient withdrew from the study prior to receiving SC; thus, 13 subjects were available for this analysis.
[a]Twelve of the 14 patients switched from IV to SC administration at Week 25. Five of these were captured in the >4 to ≤24 weeks row because they switched almost immediately after the Week 24 dose; six of these were captured in the >24 weeks to ≤48 weeks row because they switched a few days into Week 24. Two patients switched at Week 38, and one patient discontinued at Week 26.
Source: Table 43; Study 102A CSR (96).

B.2.10.2.2. Summary of adverse events

In total, [redacted] patients ([redacted]) had at least one TEAE, with [redacted] TEAE events reported in total. Most TEAEs were reported within the system organ class of gastrointestinal disorders. The most frequently reported TEAEs were cough, vomiting, headache, hyperammonaemia, nausea, upper abdominal pain, increased ammonia, nasopharyngitis and COVID-19. Most TEAEs were of mild to moderate severity, with only [redacted] TEAEs assessed as severe. No patients experienced TEAEs that required dose reduction, led to pegzilarginase discontinuation, or resulted in death (Table 26) (96).

Table 26: Overview of TEAEs by patient and event count (Study 102A; FAS)

Event	Total (n=14)	
	Patient, n (%)[a]	Counts of Events[b]
Patients with any TEAE	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Drug-related TEAE	[redacted]	[redacted]

TEAE requiring dose reduction	[redacted]	[redacted]
TEAE requiring dose interruption	[redacted]	[redacted]
TEAE leading to discontinuation of pegzilarginase	[redacted]	[redacted]
Drug-related TEAE leading to discontinuation of pegzilarginase	[redacted]	[redacted]
TEAE with fatal outcome	[redacted]	[redacted]
Patients with any SAE	[redacted]	[redacted]
Drug-related SAE	[redacted]	[redacted]

Key: FAS: Full Analysis Set; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Notes: Percentages are based on the number of subjects in the Full Analysis Set. Dose interruptions are identified based on a response of "Missed dose," "Dose held," or "Drug Interrupted" in the "Action taken with study treatment" field of the adverse event case report form. Adverse events are coded using Medical Dictionary for Regulatory Activities Version 24.0.
[a]Patients are only included in the category denoting the highest severity reported for all TEAEs in the study.
[b]Total study TEAEs for all patients included in the category for their corresponding severity.
Source: Table 46; Study 102A CSR (96).

B.2.10.2.3. Common adverse events

TEAEs that occurred in ≥15% of patients in the FAS are summarised below in Table 27 (96).

Table 27: TEAEs occurring in ≥15% of patients by preferred term (Study 102A; FAS)

Preferred Term	Total (n=14)
Patients with any TEAE, n (%)	[redacted]
Cough	[redacted]
Vomiting	[redacted]
Headache	[redacted]
Abdominal pain upper	[redacted]
Ammonia increased	[redacted]
COVID-19	[redacted]
Hyperammonaemia	[redacted]
Nasopharyngitis	[redacted]
Nausea	[redacted]
Constipation	[redacted]
Upper respiratory tract infection	[redacted]
Gastroenteritis	[redacted]
Pyrexia	[redacted]
Arthralgia	[redacted]
Decreased appetite	[redacted]
Diarrhoea	[redacted]
Fatigue	[redacted]
Oropharyngeal pain	[redacted]
Rhinorrhea	[redacted]
Transaminases increased	[redacted]

Key: FAS: Full Analysis Set; TEAE: treatment emergent adverse event.
Notes: Percentages are based on the number of subjects in the Full Analysis Set. Adverse events are coded using Medical Dictionary for Regulatory Activities Version 24.0.
Source: Table 47; Study 102A CSR (96).

B.2.10.2.4. Summary of serious adverse events

A total of [redacted] patients ([redacted]) experienced SAEs. SAEs were most frequently in the system organ classes of Metabolism and nutrition disorders, Infections and infestations, and Gastrointestinal disorders. The most frequently reported SAEs were hyperammonaemia ([redacted]), gastroenteritis ([redacted]), and respiratory syncytial virus infection ([redacted]). None of the SAEs were life-threatening or fatal (96).

[redacted] patients ([redacted]) experienced SAEs that were assessed by the investigator as related to pegzilarginase, comprising [redacted] SAEs of hyperammonaemia and [redacted] SAE of increased ammonia (96).

B.2.10.2.5. Study drug discontinuation

No TEAEs led to the discontinuation of the study drug (96).

B.2.10.2.6. Deaths

No deaths occurred in Study 102A (96).

B.2.10.3. Study 101A

The safety data for pegzilarginase from Study 101A is summarised in Appendix P.

B.2.11 Ongoing studies

The pegzilarginase ARG1-D clinical development programme currently consists of three studies: Study 101A, Study 102A, and PEACE, the latter of which forms the pivotal study informing the submission. All three studies are complete; final results from the double-blind period and LTE data up to Week 150 for PEACE and the final results from Study 102A are provided in Sections B.2.1 – B.2.7 of the submission, while results from Study 101A are provided in Appendix P.

One additional clinical study is currently under development; CAEB1102-301A (Study 301A). Study 301A is a planned Phase 3, open-label study of the safety, pharmacokinetics, and activity of weekly SC pegzilarginase in ARG1-D patients below two years of age. This study is due to begin in Q2 2024 and will fulfil the EMA Paediatric Committee Paediatric Investigation Plan requirements. Considering the population of patients in the decision problem for this appraisal concerns ARG1-D patients aged 2

years and older, evidence from this study is not considered to be relevant to this submission. Interpretation of clinical effectiveness and safety evidence.

B.2.12 Principal findings from the clinical evidence

As described in Section B.1.3, the treatment goal for patients with ARG1-D is to minimise exposure to the neurotoxic effects of elevated arginine and its metabolites, which is very rarely, if ever, achieved with the current IDM regimens. Therefore, successful demonstration of efficacy in pivotal clinical trials requires a statistically significant reduction in pArg in conjunction with a clinical response in mobility.

The efficacy and safety of pegzilarginase in ARG1-D patients aged 2 years and older is provided by an international, randomised, double-blind, pivotal Phase 3 study (PEACE) (59, 84), and a Phase 2, open-label, LTE study (Study 102A).

The pivotal Phase 3 PEACE study met its primary endpoint, demonstrating both a clinically and statistically significant reduction in pArg with pegzilarginase compared to placebo (estimated reduction relative to placebo: 76.7%; p<0.0001) after 24 weeks of treatment. PArg levels below guideline recommended target and within the normal range were achieved in 90.5% of pegzilarginase treated patients compared to 0% of the patients in the placebo arm (p<0.0001) (see Section B.2.6.1.1.a). Furthermore, continued administration of pegzilarginase via the SC route of administration in those who were randomised to pegzilarginase in the double-blind portion of the study resulted in similarly consistent and sustained reduction in pArg levels in the LTE period. Dietary excursions did not impact the ability of patients to maintain plasma arginine within the normal range (see Section B.2.3.1.5.c) (59, 84).

In addition, clinically relevant functional mobility improvements, as assessed by 2MWT, GMFM-E, and GMFM-D, were demonstrated with pegzilarginase treatment. Statistically significant and clinically meaningful improvement in GMFM-D was observed in patients treated with pegzilarginase compared to those treated with placebo at Week 24 (4.2 points; p=0.0208) (see Section B.2.6.1.1.c.ii). Furthermore, similar proportions of patients in the pegzilarginase group demonstrated clinically relevant and/or numerical increases in GMFM-E (11 of 20 patients, 55.0%) and 2MWT (10 of 20 patients, 50.0%) assessments (see Sections B.2.6.1.1.b.i [2MWT] and B.2.6.1.1.b.ii [GMFM-E]). For patients completing

the LTE, increases from baseline in 2MWT, GMFM-E, and GMFM-D continued to be observed in patients treated with pegzilarginase (59, 84), highlighting continued improvement with further therapy.

Overall, the majority (90.5%) of pegzilarginase-treated patients achieved a response by normalising pArg, while no patients treated with placebo were able to normalise pArg. For those evaluable patients meeting the clinical thresholds at the individual mobility assessments and at the composite level, the extent and the magnitude of response were greater in those patients treated with pegzilarginase compared to placebo (see Section B.2.6.1.1.d.i) (59, 84). This indicates a positive overall impact linking meaningful arginine reduction to clinical effect. This supports the demonstrated treatment effect of pegzilarginase in both reducing and normalising pArg and the benefit of clinical outcomes in patients with ARG1-D. Normalisation of pArg has not been achieved by IDM alone, and is a new milestone for a treatment of ARG1-D. Given the diversity of age, disability, and progression of disease, these data suggest that clinical improvements may be demonstrated regardless of the severity of underlying disease at presentation after the normalisation of pArg levels.

In Study 101A/102A, pegzilarginase demonstrated early, clinically meaningful, consistent, and sustained reduction in pArg to both therapeutic guidelines and normal levels, corresponding decreases in plasma GC levels, increases in ornithine levels, and clinically meaningful improvements in mobility as assessed by neuromotor function through up to 262 weeks of treatment with pegzilarginase.

The clinically meaningful improvements in mobility, including the magnitude of improvement in GMFM-E score and 6MWT observed at Weeks 24 and 48 were generally consistent with those observed during PEACE (see Sections B.2.6.2.3 [6MWT] and B.2.6.2.4.b [GMFM-E]). The consistency of the open-label Study 102A data with those of the PEACE double-blind period are unlikely to be due to a placebo effect, thereby supporting the credibility of long-term results observed in Study 102A. Clinically meaningful improvements in mobility as assessed by neuromotor function that were seen after 24 weeks were maintained or continued to improve through 144 weeks of treatment in Study 102A. These results are especially clinically relevant in a population that would

be expected to experience detectable disease progression, including decreased mobility, over time.

In summary, pegzilarginase demonstrated early, clinically meaningful, consistent, and sustained reduction in pArg to both therapeutic guidelines and normal levels, corresponding decreases in plasma GC levels, and increases in ornithine levels. Clinically meaningful improvements in mobility, as assessed by neuromotor function with up to 150 weeks of treatment in PEACE and up to 262 weeks of treatment in Study 102A, were demonstrated and were associated with the reductions in pArg.

B.2.12.1. Strengths and limitations of evidence base

B.2.12.1.1. Strengths of evidence base

A key clinical goal for patients with ARG1-D is to achieve pArg levels to meet the guideline recommended level (<200 µM) and ideally to normal levels (15, 80), although this is very rarely, if ever, achieved with current IDM regimens. As of the most recent data cut-off (24th March 2022), 100.0% of evaluable patients continuing treatment with pegzilarginase at LTE Week 24 (19 of 19 patients) achieved pArg levels below the clinical guideline target of <200 µM, and a large majority (88.2%) were within the normal range of ≥40 - ≤115 µM (see Section B.2.6.1.1.a). This occurred in a cohort of ARG1-D patients where, despite current IDM approaches, mean (SD) pArg at baseline was over double guideline recommended levels (402.0 [101.8]). By reducing and maintaining pArg to normal levels in the long-term, patients have the potential to halt the progression of manifestations, reduce the impact of prior disease progression, and improve functional mobility.

At study baseline in PEACE, patients randomised to pegzilarginase were of a slightly younger age, had lower pArg levels and suffered from less moderate/severe spasticity compared to those randomised to receive placebo (see Section B.2.3.1.8). The difference in baseline characteristics between the two treatment groups could be attributed to the 2:1 randomisation ratio and/or absence of stratification for age, pArg and level of spasticity covariates during randomisation. As patients randomised to pegzilarginase had less severe disease at baseline and were close to the upper limit of the scale, it was more challenging for pegzilarginase to demonstrate a significant benefit across clinical outcomes versus placebo. Despite suffering from less severe disease, patients treated with pegzilarginase demonstrated a statistically significant reduction in pArg from

baseline versus the placebo group. With regards to mobility outcomes, patients treated with pegzilarginase demonstrated a statistically significant and clinically meaningful improvement in GMFM-D versus placebo, while clinically relevant/numerical improvements in 2MWT and GMFM-E were also observed.

Furthermore, while the response to pArg to pegzilarginase was highly consistent across patients, functional mobility outcomes were more variable, likely reflecting a combination of differences in disease severity and duration, establishment of functional impairment, and/or baseline performance. A majority of recruited patients had near-normal gross motor function at baseline, with 43.8% of patients classified as GMFCS Level I (most functional) at study enrolment (see Section B.2.3.1.8) (59, 84). As a result, measurement of improvement in functional mobility assessments was limited by the upper boundary of the test, as some were close to or at the ceiling or upper boundary of response at baseline. This was observed for many patients who demonstrated an improvement in 2MWT, GMFM-D or GMFM-E. Many patients achieved normative distance or neared the maximum possible score but, because their baseline score limited the magnitude of possible effect size, they were unable to meet thresholds for clinical response. Despite this, patients at or near the ceiling of functional mobility scores at baseline improved to the upper limit of maintained their status without decline during the LTE period. Without disease-modifying treatment, these patients would otherwise follow the natural course of the disease and would be expected to experience a decline in their neuromotor function, amongst other outcomes, over time, despite IDM regimens (29).

In addition, although study sites were instructed to minimise dietary protein prescription changes, a higher proportion of patients on pegzilarginase (8 of 21 patients, 38.1%) than placebo (2 of 11 patients, 18.2%) consumed >15% of total calories/day at Week 24 of the double-blind period versus baseline. Similar was also noted for total consumed protein (including natural and EAA protein). Importantly, this did not impact the ability of patients treated with pegzilarginase to maintain normal pArg levels (≥40 - ≤115 μM) (59, 84). Furthermore, the consumed natural protein increased and consumed EAAs decreased over the LTE period (84). As highlighted in Sections B.1.3.1.2.a and B.1.3.1.3, current dietary restrictions are frequently described as unpalatable, difficult to comply with, and a contributor to poorer HRQoL amongst both patients and caregivers. Further real-world data could demonstrate the role of pegzilarginase in diet management of ARG1-D.

PEACE represents the largest group of prospectively evaluated patients and the first randomised, blinded, placebo-controlled trial in ARG1-D (59, 84). A placebo group was used to assist the interpretation of any observed effects of pArg and other efficacy endpoints that could have been impacted by improved compliance with any IDM components. However, as previously described in Section B.1.3.2.3, and demonstrated in the 24-week, double-blind period of PEACE in Section B.2.6.1.1, IDM doesn't alter the disease course of ARG1-D. In addition, the use of placebo assists in the interpretation of secondary endpoints and safety endpoints, which may have the potential to be influenced by patient or investigator knowledge of assigned study treatment.

B.2.12.1.2. Limitations of evidence base

As described in Section B.2.6.1, the double-blind and LTE portions of the PEACE study occurred during the COVID-19 pandemic, which required changes to the conduct of the study and stay-at-home measures to prevent the spread of the illness. This required the implementation of pauses on an individual patient level based on the study visit each patient was in when site closures occurred. The number of missed visits and assessments due to COVID-19 was small in comparison to the total number planned. Despite the pandemic, the study was well-executed, and patient safety and data integrity were maintained. Overall, the COVID-19 pandemic did not significantly impact the ability to monitor and manage patient safety, data integrity, or efficacy assessment.

In addition, the absence of significant results in motor function assessments between the pegzilarginase and placebo groups indicates that the 24-week placebo-controlled period of PEACE may have been too short to cover the optimal treatment effect on adaptive behaviour, neurocognition and memory, HRQoL, and mortality. However, continued treatment beyond 24 weeks resulted in increases in MCID responder rates for patients treated with pegzilarginase/pegzilarginase, while those treated with placebo/pegzilarginase demonstrated stabilisation or numerical improvements in functional mobility outcomes.

Early, consistent, sustained, and statistically significant decreases in plasma GC levels were observed in patients treated with pegzilarginase versus placebo during the double-blind period ($p=0.0059$ to $p<0.0001$). As highlighted in Section B.1.3.1.2.a.iii, elevated levels of plasma GCs may contribute to the occurrence of seizures in patients with ARG1-

D, although the exact mechanism is not fully understood. Despite the reduction in plasma GC levels, a statistically significant difference in the frequency of seizure events was not observed between the pegzilarginase and placebo treatment groups. At baseline, 33.3% of patients (7 of 21 patients) randomised to pegzilarginase had a history of seizures, with a mean (SD) of 0.1 (0.4) in the previous year, despite elevated GC levels, implying that seizures were well-controlled with current IDM. By contrast, although a similar proportion of patients randomised to placebo had a history of seizures (4 of 11 patients, 36.4%), patients reported a much greater mean (SD) number of seizure events in the previous year (17.5 [35.0]). In the double-blind portion of the study, no patients in the placebo arm suffered a seizure event, highlighting good adherence to IDM regimens, perhaps better than that seen in real world practice, although there is no evidence to support this. No seizure events were recorded for patients transitioning from placebo to pegzilarginase during the LTE portion of the study. Consequently, evidence on the link between a reduction in plasma GC levels and seizure events from PEACE is inconclusive.

B.2.12.2. Applicability of evidence to practice

B.2.12.2.1. Patient characteristics

Despite the strict exclusion criteria, including restrictions around IDM adherence and mobility requirements, 48 patients participated in the clinical studies of pegzilarginase, with PEACE representing the largest group of prospectively evaluated patients to-date (n=32) (2, 59, 96). PEACE represents ~7% of all estimated total ARG1-D cases amongst countries with clinical study sites (24, 59), including 20% of the known UK patient population (5 of ■ patients). This patient cohort was highly heterogenous; patients in PEACE and Study 102A varied in terms of age (2-32 years), duration of illness, and degree of manifestations of underlying disease. The diverse population of patients observed in PEACE and Study 102A is deemed to be generalisable to the broader population of ARG1-D patients observed in UK clinical practice.

For the 32 patients enrolled in the PEACE FAS, the median (range) age of patients at enrolment was 10.5 years (range: 2 – 29 years) (59, 84). This was slightly lower than the median age of patients enrolled onto the European BoI study (14 years [range: 0 – 49 years]) and those included in the UK-based study by Keshavan *et al*. (2022) (16.0 years [range: 12 – 28 years]) (30, 46).

The majority of patients (56.2%) in the FAS had gross motor functional impairment of GMFCS Level ≥II (59, 84), a proportion similar to that reported in Study 102A (50.0%) and the European BoI study (50.0%), which included six ARG1-D patients from the UK (50.0%) (Table 28) (46). In addition, the distribution of GMFCS levels observed in PEACE and the European BoI study was also largely consistent irrespective of the difference in sample size. Underlying disease characteristics were also comparable between PEACE, Study 102A and the European BoI study at baseline (Table 28).

Table 28: Comparison of patient demographics and baseline characteristics of PEACE, Study 102A and the European BoI study

	PEACE (n=32)	Study 102A (n=14)	European BoI (n=21)
Age at enrolment, years, mean (SD)	10.7 (6.5)	[redacted]	16.7 (1.7)
Age at onset of manifestations, years, mean (SD)	1.9 (2.4)	[redacted]	3.7 (2.1)
Spasticity, n (%)			
Lower-limb	13 (61.9)	[redacted]	12 (57.1)
Upper-limb	1 (4.8)	[redacted]	0 (0.0)
History of seizures, n (%)			
Yes	11 (34.4)	[redacted]	6 (28.6)
No	21 (65.6)	[redacted]	13 (61.9)
Missing	0	[redacted]	2 (9.5)
GMFCS Level (I – V), n (%)			
I	14 (43.8)	7 (50.0)	8 (50.0)
II	13 (40.6)	4 (28.6)	5 (31.3)
III	0	[redacted]	0
VI	5 (15.6)	[redacted]	2 (12.5)
V	0[a]	[redacted][a]	1 (6.3)
Missing	0	[redacted]	5 (23.8)

Key: BoI: burden of illness; GMFCS: Gross Motor Function Classification System; SD: standard deviation.
Notes: The GMFCS assigns gross motor function capabilities based on movements such as sitting, walking, and use of mobility devices with five categories ranging from I (most functional) to V (transported in wheelchair in all settings) (57).
[a]No patients at GMFCS Level V were enrolled due to inability to complete functional mobility assessments.
Source : Table 1, Sanchez Russo *et al*. (2024) (59); Table 14.1.5.1 and Table 14.1.5.2, PEACE CSR (84); Table 13, Study 102A CSR (96); Table 4 and 5, A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers (46).

In addition, patients with extreme mobility impairment (i.e., unable to complete assessments [GMFCS Level V]) were excluded from the clinical development programme of pegzilarginase in ARG1-D. Patients with GMFCS V have severely limited self-mobility even with the use of assistive technology (see Figure 6, Section B.1.3.1.2.a.iv), and were therefore unable to be assessed for measurable deficits in functional mobility outcomes in PEACE and Study 102A: 2MWT/6MWT, GMFM-D, or GMFM-E. However, the aforementioned clinical mobility assessments are not used for ARG1-D patients in UK

clinical practice. Considering the variety of progressive and debilitating manifestations associated with the disease, which may develop irrespective of GMFCS level, it is anticipated that all patients with ARG1-D could derive clinical benefit and be considered for treatment with pegzilarginase. In addition, minimal patients with GMFCS Level V are observed in clinical practice (Table 28). As highlighted in the Table 28 above, although the clinical studies of pegzilarginase excluded patients with GMFCS Level V, the observed distribution of patients across GMFCS levels in PEACE and Study 102A is largely representative of what is observed in clinical practice.

Furthermore, PEACE included five study sites from the UK, namely Birmingham Children's Hospital, University Hospital of Wales, Great Ormond Street Hospital for Children, Willink Biochemical Genetics Unit, and the Salford Royal Hospital. In total, four of the five study sites enrolled and treated patients. Five UK patients were enrolled and included in the PEACE FAS (5 of 32 patients, 15.6%). Three of five UK-recruited patients were randomised to receive treatment with pegzilarginase in the double-blind portion of the study (3 of 21 patients, 14.3%), while the remaining two patients were randomised to receive placebo before transitioning to pegzilarginase treatment in the LTE phase of the study (2 of 11 patients, 18.2%). Of note, none of the five UK patients were included in European BoI due to study exclusion criteria.

The majority of patients in the PEACE FAS were recruited from study sites in the US (14 of 32 patients, 43.8%), where newborn screening is used to routinely screen for ARG1-D. Outside of the US, Italy was the only additional country that enrolled patients in PEACE where newborn screening is currently available (3 of 32 patients, 9.4%). Early detection of these patients via newborn screening would likely cause these patients to be managed with IDM at an earlier age than would otherwise be observed in countries were newborn screening of ARG1-D is not routinely performed. In the UK, and the remainder of the PEACE study sites where newborn screening is not currently available (Austria, France, Germany, and Canada) (15 of 32 patients, 46.9%), patients with ARG1-D initiate IDM later on in life after diagnosis via molecular testing and/or sibling screening. Despite differences in diagnostic practice, once a patient is diagnosed, it is anticipated that the subsequent management and treatment of patients in ARG1-D across all study sites is to be aligned with guidelines issues by Häberle *et al*. (2019) (see Section B.1.3.2) (15).

In addition, when the PEACE cohort was stratified by region (US versus ex-US), there were no observable differences between the two groups at baseline in pArg, 2MWT, and GMFM-E (see Appendix E). As a result, the availability of newborn screening did not impact the generalisability of the overall baseline characteristics with UK clinical practice. Furthermore, this also highlights that despite early intervention, current IDM regimens are very rarely, if ever, successful at maintaining plasma arginine below guideline-recommended levels, resulting in continued disease progression.

B.2.12.2.2. Analysis sets

In consideration of the most appropriate analysis set for decision making, the FAS for PEACE (n=32) is presented, with data from the pegzilarginase group used in the subsequent cost-effectiveness analysis. As described in Section B.2.4.1, this analysis set includes all patients who were randomised and received at least one dose of blinded study treatment.

B.2.12.2.3. Service provision

Treatment with pegzilarginase should be initiated and supervised by a physician experienced in the management of patients with inherited metabolic diseases. Pegzilarginase is intended for IV infusion or SC injection and should be administered by a healthcare professional. If appropriate, SC home administration by the patient or caregiver can be considered after at least eight weeks, once a stable maintenance dose has been established and the risk for hypersensitivity reactions has been assessed as low. Before self-administration, the patient or caregiver should receive adequate training (1).

Furthermore, pegzilarginase will interfere with routine laboratory analysis, resulting in erroneous low measurements due to post-collection degradation of arginine. During clinical studies, nor-NOHA tubes were used to inhibit residual pegzilarginase activity and stabilise arginine in plasma samples. Tubes of nor-NOHA will be made available by Immedica upon the commercialisation of pegzilarginase in the UK (1).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

No cost effectiveness studies in the population of people with ARG1-D were identified in the SLR, therefore no results are presented.

B.3.2 Economic analysis

As no cost effectiveness studies in ARG1-D were identified in the SLR, a *de novo* model was conceptualised and constructed.

B.3.2.1. Patient population

The model population (GMFCS heath state distribution, age and gender distribution) is assumed to be as per the pooled PEACE (n=32), Phase 1/2 (Study 101A/102A, n=16) and European burden of illness (BoI) survey (IMM-PEG-001) who provided GMFCS data (n=16) study characteristics. This approach was chosen, firstly, because the larger data pool is likely to be more representative of clinical practice and more likely to include all GMFCS health states at baseline. In PEACE, for example, no patients were in GMFCS 3 at baseline. Secondly, pooled data from PEACE and the Phase 2 study were used for the majority of regression analyses informing the model. Logically, the model baseline characteristics should also be informed by the same dataset. Finally, the BoI survey included patients from the UK.

It should be noted that age, gender and GMFCS are modified independently in the model to allow exploration of the impact of each separately. Furthermore, it should be noted that the BoI characteristics used in the model differ from those reported in other sections of the submission as they are derived from the subgroup of patients who reported GMFCS scores (n=16), rather than the 21 patients in the BoI. The model cohort characteristics at entry are summarised in Table 30.

Table 29: Economic model baseline demographics

Characteristic	Value	Source
Baseline Age (mean)	Pooled (base case): [redacted] Comprising: PEACE: 10.7 Phase 1/2: [redacted] BoI: 15.63	Pooled PEACE (N=32) (Table 11), Phase 1/2 (N=16) (Table 15) and BoI (N=16) patients (total pooled N = 64).
% Female	Pooled (base case): [redacted] Comprising: PEACE: 41% Phase 1/2: [redacted] BoI: 75%	Pooled PEACE (Table 11), Phase 1/2 (Table 15) and BoI patients (total pooled N = 64).
Weight characteristics of pooled PEACE + and phase 1/2 patients.	Age 16 and below (N=39), average age [redacted] female: [redacted] Age 17 and above (N=9), average age [redacted] female: [redacted]	Pooled PEACE + and Phase 1/2 patients. (Table 11 and Table 15)
Expected general population weight given pooled PEACE + and phase 1/2 patients. baseline characteristics	Age 16 and below: 34.0 kg Age 17 and above: 77.0 kg	NHS Digital (107),
Weight ratio vs general population (paediatric, adults)	[redacted] (age 16 and below) [redacted] (age 17 and above)	Calculated. Ratio of actual weight in pooled PEACE and Phase 1/2 patients vs expected weight given same age and gender distribution.

Note: Demographics from the n=16 BoI patients in the economic analysis differ from the n=21 patients summarised in the BoI report.

Table 30: Economic model motor function at baseline

Baseline GMFCS category	Patient proportions				Source
	Pooled n=64 (base case)	PEACE (n=32)	Phase 1/2 (n=16)	BoI (n=16)	
GMFCS I	48.4%	43.8%	56.3%	50.0%	PEACE + Phase 1/2 and BoI patients
GMFCS II	34.4%	40.6%	25.0%	31.3%	PEACE + Phase 1/2 and BoI patients
GMFCS III	3.1%	0.0%	12.5%	0.0%	PEACE + Phase 1/2 and BoI patients

GMFCS IV	12.5%	15.6%	6.3%	12.5%	Pooled PEACE + phase 2 patients (N = 46).
GMFCS V	1.6%	0.0%	0.0%	6.3%	Pooled PEACE + phase 2 patients (N = 46).

Key: GMFCS: Gross Motor Function Classification System.

B.3.2.2. Model structure

As stated in Section B.3.1, no cost effectiveness studies have previously been conducted in ARG1-D, therefore a Markov cohort model was built in Microsoft Excel to evaluate the cost effectiveness of pegzilarginase + IDM (hereafter referred to simply as pegzilarginase) vs. IDM alone. The model has a lifetime horizon (87 years; calculated as 100 minus the baseline age) and a 13-week cycle time with a half-cycle correction. The model includes the ability to apply a flexible stopping rule (criteria to be defined by the user) at week 26, but none is applied in the model base case given that all patients in PEACE achieved the primary endpoint of change from baseline in pArg at week 24 (see Section B.2.6.1.1.a).

The cohort model captures the movement of patients over their lifetime through five mutually exclusive motor deficit health states, defined by GMFCS score (see Section B.1.3.1.2.a.iv for description) and death (see Figure 25), and further by level of intellectual disability, categorised into mild/normal, moderate or severe cognitive impairment. The GMFCS was considered the best option for categorising motor deficits as it is known that ARG1-D shares similar disease characteristics and symptoms with cerebral palsy (CP). A further reason was that GMFCS or GMFCS-like health states have formed the basis of other cost effectiveness models and/or utility studies in rare diseases with neurological decline, even if not due to the same underlying disease pathology (108). An SLR was therefore conducted where CP was used as a proxy disease for ARG1-D to explore data options for the health economic model (109). In this SLR, several studies were found that related utilities and resource utilization with different GMFCS levels that could be used to model the health economic consequences of ARG1-D disease progression. To complement the review in CP, during the conceptual modelling stage clinical experts were asked which other rare diseases might be most similar to ARG1-D in their clinical presentation, which led to the use of metachromatic leukodystrophy (MLD) and X-linked adrenoleukodystrophy (X-ALD) as alternative sources of costs and/or utility values.

While occupying any GMFCS and/or cognitive health state, the patients can experience hyperammonaemic crises (HACs) (defined as “an event in which a subject had an ammonia level ≥100 μM with one or more symptoms related to hyperammonaemia requiring hospitalization or emergency room management”, Section B.1.3.1.2.b.i). While the model is structured to be able to capture other disease-related acute events such as severe nausea and seizures, the former have not been included in the model due their possible overlap and double-counting with HACs and the latter not included due to their relative infrequency once stabilized on appropriate anti-epileptic medicine.

Patients are at risk of dying from disease-related mortality during every model cycle. During the conceptual modelling phase, [redacted] and an additional UK clinical expert stated that the main causes of mortality in ARG1-D patients were HACs, complications from infections/surgery, neurological damage and liver disease. Due to lack of data, death due to liver disease could not be modelled. The model therefore captures mortality via either an overall survival (OS) curve, which is independent of health state occupancy and reflects all-cause mortality, or by capturing GMFCS-specific mortality. In addition to GMFCS-specific mortality, patients have an instantaneous risk of death when they experience HAC, conditional on their peak ammonia level (see Section B.1.3.1.2.b.i).

In the pegzilarginase arm, patients start on weekly pegzilarginase treatment but can discontinue at any model cycle. Once they discontinue, patients, assume the progression rate of patients on IDM.

In both arms, the model captures the costs of IDM by health state, including medications, healthcare resource, essential amino acid (EAA) supplements, nursing care and social services support such as assisted schooling. The model captures the impact on health-related quality of life (HRQoL) of motor deficit, cognitive deficit, improved diet and HACs. Costs and outcomes are discounted at a rate of 3.5%.

A diagram of the model structure is presented in Figure 25.

Figure 25: Model structure diagram

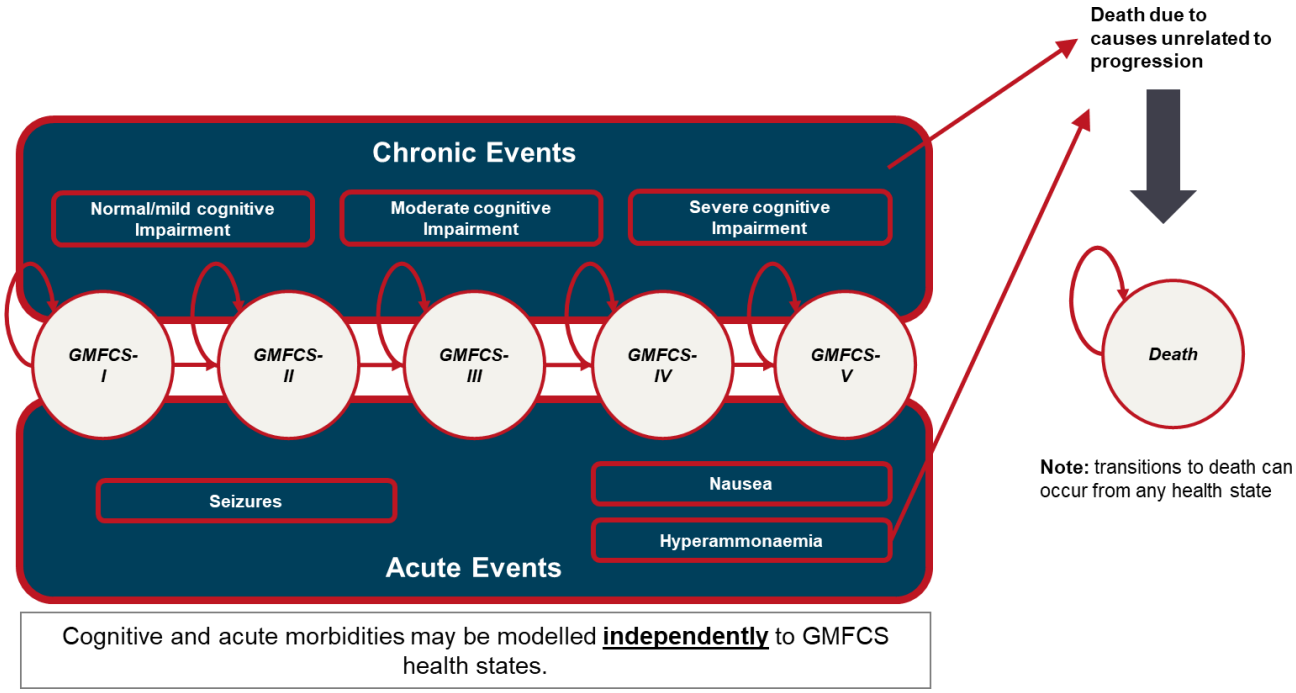


Table 31: Features of the economic analysis

	Current evaluation (no past evaluations in ARG1-D)	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime (87 years)	ARG1-D is a chronic disease. Pegzilarginase can impact outcomes over the patients' lifetime.
Waning of treatment effect	No waning of treatment effect is assumed in the base case. A scenario is included whereby some ongoing progression is modelled following initial improvement.	Pegzilarginase is a recombinant human enzyme. There is potential for immunogenicity to pegylated therapeutic proteins (PEG), however across all clinical trials in the pegzilarginase ARG1-D development program, 12 of 48 subjects (25%) tested positive for anti-drug antibodies (ADAs) against PEG and/or the protein moiety of pegzilarginase, with the majority detected early after the first dose. There was no assay available for detecting neutralising antibodies during the clinical development programme. The ADAs were transient in nature and resolved during continued treatment. The presence of ADAs was associated with transient changes in the pharmacokinetics (PK) and pharmacodynamics (PD) of pegzilarginase in patients with ARG1-D.
Source of	EQ-5D-5L responses from	The NICE reference case prefers health

utilities	ARG1-D patients and their carers were obtained from the BoI and mapped to 3L utilities using the van Hout algorithm (46). Cognitive deficit decrements from a vignette study in metachromatic leukodystrophy (MLD) are added (see HST18) (110, 111). A utility gain from improved diet was included, from a vignette study in patients with a restricted diet.	state utility values to be obtained from patients (or their carers) on the EQ-5D. Given the small sample size, the EQ-5D values collected will not represent the heterogeneity of cognitive deficits experienced by different patients. It would also fail to reflect HRQoL gains in patients who do not change GMFCS health state but experience an improvement in cognitive function when taking pegzilarginase. The restricted diet was considered to have a negative impact on HRQoL as reported by patients, their carers (46), and interviewed clinicians. In PEACE, more patients on pegzilarginase showed an increase in consumption of dietary protein.
Source of costs	Costs are obtained from the BoI study of patients and carers of patients with ARG1-D (including patients from the UK, France, Spain and Portugal). Due to missing data or low sample size for some health states, data are supplemented with health state cost data from MLD.	The NICE reference case prefers costs from UK patients. Where there was a paucity of data, notably in more severe GMFCS health states, the ARG1-D cost data were supplemented with cost data from MLD (HST18) as patients with this condition also suffer from motor and cognitive decline.

Key: ARG1-D: arginase 1 deficiency; BoI: burden of illness; EQ-5D: EuroQol 5-Dimensions; GMFCS: Gross Motor Function Classification System.
Note: There have been no past NICE appraisals in ARG1-D. Therefore, only the 'Current evaluation' columns are populated.

B.3.2.3. Intervention technology and comparators

The intervention is weekly pegzilarginase in combination with IDM (referred to as pegzilarginase within Section B.3 for simplicity). Pegzilarginase is intended to substitute for the deficient human arginase 1 enzyme activity in patients with ARG1-D. Pegzilarginase rapidly and sustainably reduces plasma arginine and converts it to urea and ornithine. This prevents disease manifestations and clinical symptoms.

The comparator is IDM alone.

B.3.3 Clinical parameters and variables

B.3.3.1. Progression through GMFCS health states

B.3.3.1.1. Initial disease progression

As stated in the Model Structure section, the model captures change in motor function on the GMFCS. The GMFCS was captured at baseline for the purpose of defining response criteria and defining subgroups and at the same follow-up timepoints as the GMFM D and E (GMFM D&E). GMFCS is not analysed or reported in the CSR. The observed change in GMFCS score in PEACE between two follow up timepoints was therefore utilised to generate a single model transition matrix for each arm.

- The change in GMFCS score between baseline and week 24 in the placebo arm was utilised to generate a single transition matrix, which was applied in the model from week 0 to week 26 for the IDM arm.

- The change in GMFCS score between baseline and week 96 in the pegzilarginase arm was utilised to generate a single transition matrix, which was applied in the model from week 0 to month 36 in the pegzilarginase arm. This means that the observed transitions between baseline and week 96 are extrapolated for a period of approximately one year in the pegzilarginase arm of the model. There is the flexibility to further extrapolate these observed transition probabilities up to 48 months (given some patients continued to show improvement in GMFM D&E score for up to 4 years).

The phase 2 data were not included, as this began as a dose escalation study and patients did not initially receive dosing consistent with the SmPC, which poses challenges to defining a baseline timepoint equivalent to that of PEACE.

As described above, a single transition matrix was generated for each arm from the patient movements from baseline to either week 24 (for IDM) or week 96 (for pegzilarginase). Given the slow nature of changes in GMFCS, this avoids generating multiple transition matrices capturing very few patient movements. These transitions were adjusted to model cycle length and applied to the model over the initial period (up to week

26 for IDM, up to month 36 for pegzilarginase), assuming a constant rate of transition, as described below:

In the IDM arm, the observed patient transitions from baseline to week 24 were used to generate a single transition matrix. Transition probabilities were adjusted to the model cycle length (13 weeks; 0.25 years), using the conversion:

$$Probability_{13\ weeks} = 1-(1-probability_{24\ weeks})^{0.25/(24/weeks\ in\ year)}$$

Note that this is mathematically the same as converting to a rate using the formula -LN(1-probability), adjusting to cycle length and reconverting to a probability as per the standard method in Drummond et al (112).

In the pegzilarginase arm, the observed patient transitions from baseline to week 96 were used to generate a transition matrix. Transition probabilities were adjusted to the model cycle length (13 weeks; 0.25 years) using the conversion:

$$Probability13\ weeks = 1-(1-probability24\ weeks)^{0.25/(96/weeks\ in\ year)}$$

Note that, due to missing data, several assumptions had to be made regarding transition probabilities:

- Where a GMFCS score was missing, the last observation carried forward (LOCF) approach was used to impute missing values at week 96. This is considered a conservative approach, as no deterioration in GMFM D&E score was seen in any observed data in the pegzilarginase arm, whereas some patients showed improvement.

- There were no movements from GMFCS III to II observed in the pegzilarginase arm. This is unrealistic given that there was movement from GMFCS IV to III. Therefore, the average of the transition probabilities from GMFCS IV->III and GMFCS II to I were used to populate the transition probability of GMFCS III->II. This is not for the IDM arm as, although some patients improved GMFCS health state, other measures of mobility such as GMFM D&E and/or 6-MWT did not demonstrate improvement or worsened and GMFCS is not expected to improve over the longer term.

- There were no patients in GMFCS V throughout the trial follow-up period. Therefore, in the pegzilarginase arm half of the transition probability from GMFCS IV->III was applied to populate the transition probability of GMFCS V->IV.

The cycle-adjusted transition matrices applied in the model up to week 26 (IDM) and month 36 (pegzilarginase + IDM) are shown in Table 32 and Table 33 below. All patient counts informing these matrices can be found in the "**GMFCS patient counts**" sheet.

After this initial phase whereby observed GMFCS transitions are utilised, the model thereafter uses regressions to predict change in GMFM D&E score over time, as well as GMFCS occupancy conditional on GMFM D&E score (see Sections B.3.3.1.2.c and B.3.3.1.2.d below).

Table 32: 13-week transition probabilities, IDM arm

From/To	GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
GMFCS I	100%	0%	0%	0%	0%
GMFCS II	14%	71%	0%	14%	0%
GMFCS III	0%	0%	100%	0%	0%
GMFCS IV	0%	0%	31%	69%	0%
GMFCS V	0%	0%	0%	0%	100%

Key: GMFCS: Gross Motor Function Classification System.

Table 33: 13-week transition probabilities, pegzilarginase + IDM arm

From/To	GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
GMFCS I	100%	0%	0%	0%	0%
GMFCS II	8%	92%	0%	0%	0%
GMFCS III	0%	10%	90%	0%	0%
GMFCS IV	0%	0%	14%	86%	0%
GMFCS V	0%	0%	0%	5%	95%

Key: GMFCS: Gross Motor Function Classification System

B.3.3.1.2. Extrapolated disease progression

Following the initial period during which transition matrices are applied, IDM patients are assumed to progress whereas in the base case pegzilarginase patients are assumed to remain in the health state they occupied at the end of the initial 36 months. Continued progression of pegzilarginase patients, but at a reduced rate compared with IDM (implemented using a hazard ratio) is considered in scenario analyses.

It would be unrealistic to extrapolate the observed GMFCS movements in the IDM arm over the course of the model given that over this very short follow up time, only a few patients changed GMFCS health state, including a few transitions to an improved GMFCS health state, which would not be realistic over longer term. Therefore, an alternative method of modelling transitions past the observed period was required.

In the PEACE clinical trial and studies 101A/102A several outcome measures related to disease progression were collected (see Sections B.2.3.1.6 and B.2.3.2.6):

- Plasma arginine levels (pArg)
- Gross Motor Function Measure (GMFM D and GMFM E)
- 2-Minute and 6-Minute Walk Test (2MWT; 6MWT)
- Ornithine and guanidino compounds (GCs)
- Vineland Adaptive Behaviour Scales (VABS-II)
- Modified Ashworth Scale (MAS)
- Neurocognition and memory (BSID-III and Wechsler intelligence batteries)
- HRQoL (Paediatric Quality of Life Inventory [PedsQL], 36-Item Short Form Health Survey, and Short-Form Zarit Burden Interview [ZBI-12])

Out of these outcome measures, reduction in pArg was statistically significant and GMFM D&E showed meaningful improvement at study endpoint compared with baseline values in the pegzilarginase arm. For both of these, data were available from the long-term follow up study. In the PEACE trial, a numerical improvement in the pegzilarginase arm was seen in the 2MWT (70% at week 24 from baseline). However, since walking ability is largely correlated with age it would be difficult to model a lifetime disease progression only based on study 2MWT data. Another limitation with 2MWT is that it does not capture other motor functions such as the ability to sit or run which is of importance to classify patient's mobility. Moreover, there was also a lack of data to relate different walking ability intervals with appropriate HRQoL and costs. The final rationalisation for using either pArg or GMFM D&E for modelling GMFCS disease progression are outlined below.

a. Arginine levels

A logical modelling choice would be to use pArg-response levels (<200 μM or normal pArg level), as a surrogate to predict GMFCS occupancy, given that high pArg, whether as the primary driver or proximal causal component of downstream toxicity, is believed to be the key driver of global developmental delay and progressive spasticity (31, 32). Despite the established harmful effects of high pARG, little data exists to establish a long term, linear relationship between pARG levels and symptoms of disease. Therefore, we did not use pARG as a surrogate for disease progression despite knowing that pARG levels is the main driver for disease in these patients. Also, since all patients treated per protocol with pegzilarginase in PEACE FAS reached guideline recommendations (<200 μM) pArg at week 24 (none in the placebo group) (see Section B.2.6.1.1.a), which were then maintained in the long-term extension study, it was not possible to link individual change in symptoms over time to pArg level. Of note, as highlighted in Section B.2.6.1.1.a, there were reasons why two patients (9.5%) did not achieve guideline recommended levels of pArg at week 24; one patient discontinued from the study at Day 36, whilst another patient received the incorrect treatment allocation at week 23. Therefore, all patients who received the correct treatment course throughout the 24-week double-blind period achieved guideline-recommended pArg levels.

Although external data sources such as the UCDC study found that cumulative arginine exposure is correlated with the deterioration in select neuropsychological outcomes in patients with ARG1-D (60), the outcome data from the UCDC registry did not provide the required information to be able to allocate patients to GMFCS health states. This was confirmed by showing clinical experts extracts of patient reports from the registry and querying whether it was possible to allocate individual patients to specific GMFCS health states based on their longitudinal data. Because no data source was available to extrapolate pArg levels to GMFCS, pArg levels are not used to predict clinical outcomes in the model.

b. GMFM D&E scores

Apart from pArg, data on GMFM D and GMFM E (the former a secondary endpoint), were available in the PEACE trial for the placebo arm for up to six months and up to 36 months for the pegzilarginase arm. A description of these scores and their range can be found in Sections B.2.6.1.1.b.ii and B.2.6.1.1.c.ii. GMFM D&E, being a continuous score, changes

faster over time than GMFCS and is also known to correlate with GMFCS in CP (113). Changes in GMFM D&E could therefore act as an intermediary score to capture disease progression over time from the trial where the follow-up time was too short to capture changes in GMFCS. It should be noted that in CP, substantial within-stratum variation was found in gross motor development (113). A further analysis in CP generated reference percentiles, providing for normative interpretation of GMFM-66 scores within GMFCS levels (114). One analysis demonstrated correlations between the GMFM D and GMFM E domains and GMFCS score, but no predictive algorithms were provided and only GMFCS I-III were included (115).

Therefore, outside sources were explored to establish a relationship between GMFM D&E score and GMFCS, including the aforementioned UCDC registry and the burden of illness study (46). As explained in Section B.3.3.1.2.a , outcomes from the UCDC registry were not in a format suitable to track change in GMFCS (or GMFM D&E) over time. The BoI was not suitable as the GMFM D&E was not collected, and data were cross-sectional rather than longitudinal, which left the Phase 2 and PEACE data as the only source of data to establish a relationship between GMFM D&E and GMFCS.

c. Progression in GMFM D&E over time

Given the lack of material change in motor scores in the IDM arm over the 24-week double-blind period, a potential relationship between age and motor function in the data was explored in order to predict progression for patients on IDM. While no relationship was found between baseline GMFCS and age at baseline, a correlation between total GMFM D&E score at baseline and age at baseline was observed (Figure 26). This is to be expected, as GMFCS being a categorical score encompassing only 5 levels, changes more slowly with age whereas GMFM D&E is a continuous score with a larger range in the observed data, making it easier to generate a slope from a regression of a small number of observations.

An ordinary least squares (OLS) regression was therefore fitted to the baseline patient data from the PEACE and Phase 1/2 studies in order to enable prediction of GMFM D&E score given a particular age (Table 34). When all available subjects were considered (N=45), the decline per year of age was statistically significant, at -1.4 per annum

(p=0.031). The regression is used to predict both the GMFM D&E score at baseline and the score as the cohort ages in the IDM arm.

Figure 26: Plot of GMFM D&E score vs age (natural scale)

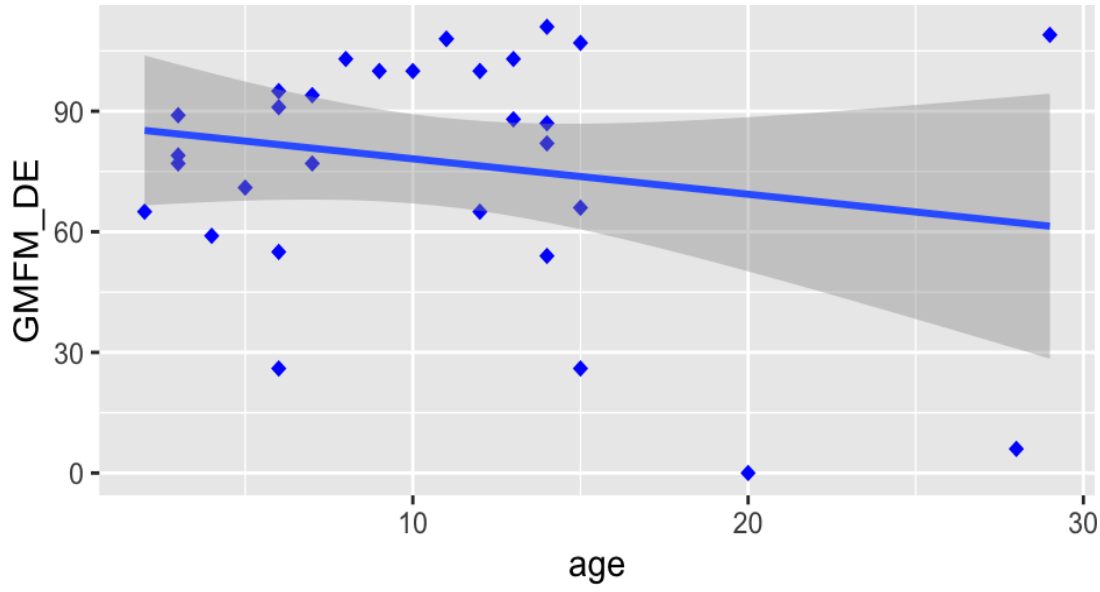


Table 34: OLS regression of GMFM D&E score vs. age

Predictors	Estimates	CI	p
(Intercept)	94.6712	76.8648 – 112.4777	<0.001
age	-1.4379	-2.7376 – -0.1381	0.031
Observations	45		
R^2 / R^2 adjusted	0.104 / 0.083		

Note: Two patients in the phase Ia trial and one patient in PEACE had missing baseline GMFM D&E.

d. Predicting GMFCS from GMFM D&E score

Figure 27 and Figure 28 below depict the relationship between GMFCS and GMFM D&E for the baseline only and in the longitudinal samples. There is some consistency between the two, suggesting that a repeated measures model was appropriate despite high levels of missing data and censoring. Appropriate to a dependent variable (GMFCS) with more than two levels, cumulative logistic regression was carried out using a random effects model for repeated measures, with the continuous variable GMFM D&E total score as the predictor as shown in Table 28. The model was informed by both PEACE and Phase 1/2 data combined, contributing 436 observations over 48 subjects to the analysis. A non-mixed regression is included in the economic model as a sensitivity analysis, which led

to a very minor increase in the ICER (not reported in the scenario analyses given ~1% impact).

An important assumption underpinning ordered logistic regression is the presence of proportional odds. That is, constant intervals between dependent variable and the probability of being in the predicted category. In CP, there is some suggestion that this may not hold true for the relationship between GMFM-66 score and GMFCS, but cumulative logistic regression is an approach previously used for predicting GMFCS from GMFM D&E score in CP (115).

Note that there is no estimate for the cut between GMFCS IV and V, as there were no observations of GMFCS V in the study data (and very few GMFCS IV). The available literature also tends to exclude prediction of GMFCS IV and V, given that GMFM D&E may already be at zero for some GMFCS III patients (115). This is a key weakness of the model, as it leads to very few patients in GMFCS V, which clearly reduces the potential of the model to capture mortality related to neurological progression as well as the very poor quality of life experienced by patients in the worst GMFCS health states.

Figure 27: GMFCS at baseline by GMFM D&E

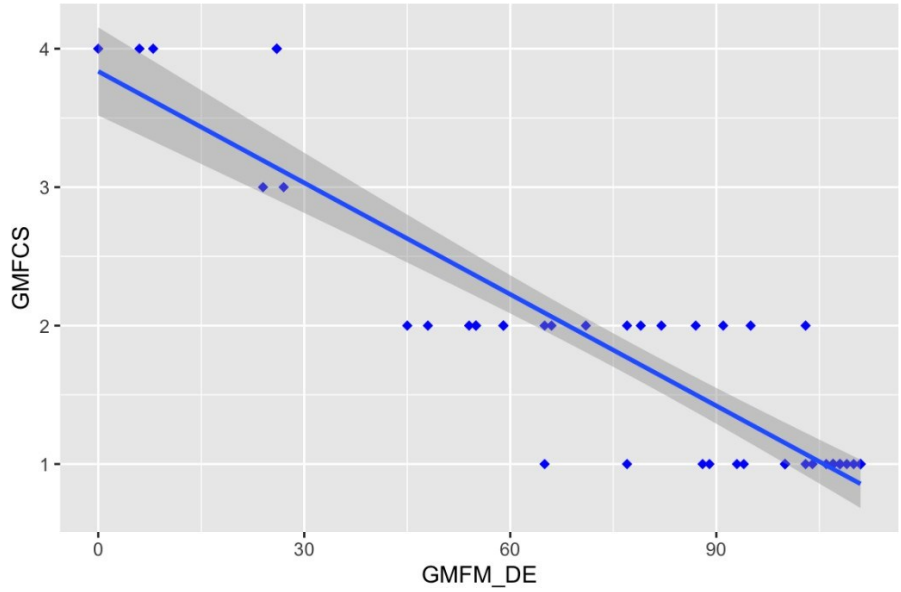


Figure 28: GMFCS over study by GMFM D&E

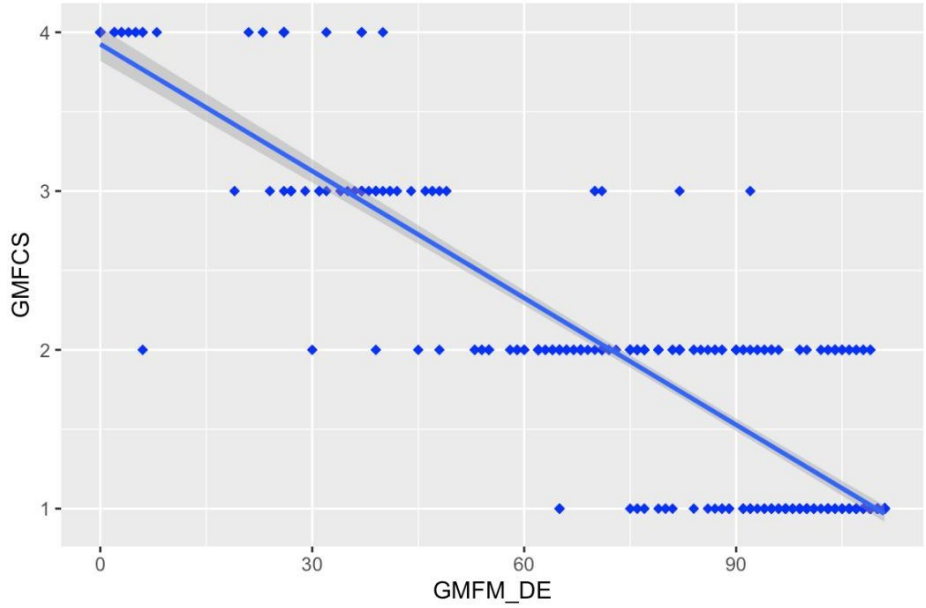


Table 35: Ordered logistic model of GMFCS vs. GMFM D&E score

Predictors	Log-Odds	CI	P value
GMFCS 1 and lower	-17.2355	-26.5581 to -7.9129	
GMFCS 2 and lower	-7.9108	-13.8577 to -1.9639	
GMFCS 3 and lower	-2.7166	-7.2684 to 1.8352	
GMFM D&E	-0.1951	-0.3003 to -0.0899	0
Observations (Groups)	436 (48)		

Key: CI, confidence interval; GMFCS: Gross Motor Function Classification System.

e. Generation of GMFCS transition probabilities from the ordered logit model

The derivation of transition probabilities for IDM from the ordered logit model is carried out in 3 steps:

1. Calculate the cumulative probability of being in a GMFCS state conditional on GMFM D&E score at a given cycle.

   The cumulative probability of being in each GMFCS health state, conditional on GMFM D&E score at a given cycle, is calculated from the ordered logit model in Table 35 (which generates coefficients on the log odds scale) as follows, using GMFCS I as an example:

*EXP(-17.2355-GMFM D&E score*0.1951)/(1+EXP(-17.2355-GMFM D&E score*0.1951)*

2. Calculate the probability of moving to the next heath state, based on the cumulative probability of being in GMFCS state X at time *t+1* vs. time *t*.

   Transition probability(cycle t->t+1) = 1-cumulative probability(cycle t)/cumulative probability(cycle t+1)

   This relies on the assumption that patients can only move one health state per cycle.

3. Adjust the probability of moving to the next health state by the probability of being alive; conditional on age and GMFCS-specific mortality rates and instantaneous mortality from HAC.

As described in Section B.3.3.1.1, during the short-term 36-month period, pegzilarginase patients could transition to better GMFCS health states based on the observed data. Following this period, a hazard ratio (HR) is applied to the IDM progression rates. In the base case, this HR is assumed to be zero, which results in no disease progression for patients receiving pegzilarginase. This is considered reasonable, given that pArg levels are controlled in these patients, and the underlying disease pathology leading to motor deficits has been paused.

B.3.3.2. Neurocognitive deficits

As well as motor deficits, patients with ARG1-D can experience cognitive disability, as explained in Section B.1.3.1.2.a.i. During model conceptualisation, clinical experts were questioned regarding whether cognitive deficits correlated with motor deficits in ARG1-D. Clinical experts were divided on this aspect, with one expert stating that worse GMFCS health states were generally associated with higher incidence of cognitive deficit, the others stating that this was independent and tended to be associated with metabolic decompensation events and hyperammonaemia. In the BoI study (46), there was no clear correlation between GMFCS level and cognitive score, although all patients with GMFCS levels IV-V had relatively high (worse) cognitive scores.

Given that cognitive deficit does not necessarily correlate with motor deficit and that patients might achieve improvement in cognitive performance without changing GMFCS health state, it is important to capture the impact of treatment on neurocognitive outcomes. In HST18, atidarsagene autotemcel (Libmeldy®) for treating MLD, an attempt was made to capture the impact of cognitive deficit on patient and carer HRQoL (111).

In the pegzilarginase clinical studies, the Vineland Adaptive Behaviour Scales (VABS II) was used to capture changes in adaptive behaviour. The VABS-II contains 4 domains: communication, daily living skills, socialization, and motor skills and is considered the most appropriate instrument for capturing neurocognitive changes used in the trials. However, a means of generating utility values from the VABS-II is required. A literature search did not identify any means of mapping to utility from the VABS-II. Therefore, other means of assigning utility were sought. One option included in the model is to use the approach used in HST18, whereby patients were assigned to cognitive deficit categories and disutilities by category applied. This was achieved via a real-world study in which cognitive deficit was measured on the Development Quotient (DQ) scale, which captures the ratio between a patient's developmental age and their chronological age.

We therefore looked to the BoI study (46) to see whether patients could be assigned to the MLD cognitive function categories, given that disutilities were available from HST18, and BoI study included a rating of cognitive function. Figure 4 from the study report shows the distribution of cognitive scores by GMFCS. No cut offs were defined for the total score (only subdomain scores) for mild, moderate or severe cognitive disability. However, there were 13 questions in total, in which "no/some problems" scored <2, "moderate" 2 and "severe/cannot do at all" ≥3. Multiplying these individual question scores by 13, we therefore assumed that scores of 0-26 denoted normal/mild dysfunction, 27-39 was moderate dysfunction and >40 was severe dysfunction. It can be seen in Table 36 below that there is lack of a clear pattern given the very small sample size of 14, which is insufficient to cover the total number of cognitive health states available.

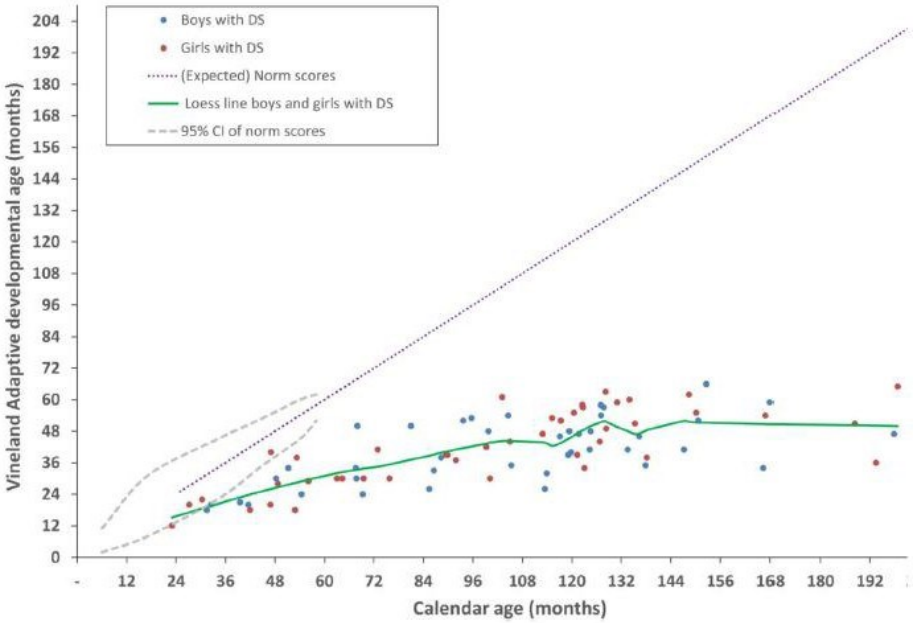
Table 36: Assignment of patients from BoI study Figure 4 to cognitive health states

Health State	Normal/Mild Cognitive Function	Moderate Cognitive Impairment	Severe Cognitive Impairment
GMFCS-I	5		1
GMFCS-II	1	3	1
GMFCS-III			
GMFCS-IV	1	1	
GMFCS-V			1

Key: GMFCS: Gross Motor Function Classification System.
Note: It was assumed that scores of 0-26 denoted normal/mild dysfunction, 27-39 was moderate dysfunction and >39 was severe dysfunction.

Given that we did not have a large enough patient sample size to allocate ARG1-D patients from BoI study to generate a reasonable distribution of cognitive deficit severity states health states, we explored whether it might be possible to assign patients to cognitive deficit severity states using the VABS-II. A study in Down syndrome provides an illustration of how this might be achieved (see Figure 29) (116). In this study, it was demonstrated that in the general population, Vineland score generally correlates with calendar age, whereas Down syndrome participants tended to score far below the line. An attempt was therefore made to repeat this process in ARG1-D; that is, assess whether the patients' Vineland score tended to be lower than the expected score given their calendar age. No correlation could be found with GMFCS, with patient scores lying both above and below the expected score line.

Figure 29: Plot of expected vineland score vs. that of Down's syndrome patients



Key: Adaptive developmental age as estimated by their adaptive behaviour in the Vineland-S, as a function of calendar age in 83 children with Down Syndrome (DS). Note that all scores fell below the norm (identity line; n = 979, age range 1–72 months; Sparrow et al.15,16). According to the measurement focus of the Vineland-S, the norm scores of typically developing children equal their calendar age. Blue bullets: Measured boys with DS (n = 40). Red bullets: Measured girls with DS (n = 43). Solid green line: Loess line fitted to the data of the children with DS pooled across boys and girls. Dotted purple line: (Expected) norm scores (mean) of typically developing children pooled across boys and girls. Grey dashed lines: upper and lower bound of the 95% confidence interval of norm scores of typically developing children.

Given that it was not possible to capture improvement in cognitive function via any of the methods outlines, for IDM the model applies the proportions of patients with different levels of cognitive deficit from MLD, which assumes that cognitive deficit correlates with motor deficit, apart from GMFCS I (Table 37). In GMFCS I it was assumed that 5% of patients would occupy moderate and severe disability health states, respectively (one patient in BoI study was in the severe state, and it is therefore likely that some might be in the moderate state given larger sample size). For the pegzilarginase arm (Table 38), an assumption was made that in GMFCS health states I-III, there is a small benefit from treatment with pegzilarginase, given the small improvement in VABS-II scores observed in the clinical studies. Cognitive deficit was assumed to correlate with motor deficit in GMFCS-IV and V, with no incremental benefit from treatment (given that these patients are further in their disease course and that an improvement in GMFCS state would, by definition, lead to a reduction in cognitive deficit. The different substate distribution for pegzilarginase was applied in the model after 1 year. Other than this switch, these substates are static by GMFCS health state over time.

Table 37: Cognitive deficit by GMFCS health state in the IDM arm

Health State	Normal/Mild Cognitive Function	Moderate Cognitive Impairment	Severe Cognitive Impairment	Source
GMFCS-I	90.00%	5.00%	5.00%	Assumption
GMFCS-II	53.00%	38.00%	9.00%	MLD cognitive impairment health states from HST18 (111)
GMFCS-III	33.00%	42.00%	25.00%	MLD cognitive impairment health states from HST18 (111)
GMFCS-IV	17.00%	28.00%	55.00%	MLD cognitive impairment health states from HST18 (111)
GMFCS-V	4.00%	17.50%	78.50%	MLD cognitive impairment health states from HST18 (111)

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

Table 38: Cognitive deficit by GMFCS health state in the pegzilarginase arm

Health State	Normal/Mild Cognitive Function	Moderate Cognitive Impairment	Severe Cognitive Impairment	Source
GMFCS-I	100.00%	0.00%	0.00%	Assumption: all patients with cognitive impairment move to mild.
GMFCS-II	70.00%	25.00%	5.00%	Assumption: 13% of moderate impairment patients move to mild and 4% of severe move to mild.
GMFCS-III	43.00%	32.00%	25.00%	Assumption: 10% of moderate impairment patients move to mild.
GMFCS-IV	17.00%	28.00%	55.00%	MLD cognitive deficit health states from HST18 (111).
GMFCS-V	4.00%	17.50%	78.50%	MLD cognitive deficit health states from HST18 (111).

Key: GMFCS: Gross Motor Function Classification System; MLD: metachromatic leukodystrophy.

B.3.3.3. Treatment stopping rule

Inclusion of treatment stopping rules can improve cost effectiveness by assuming that patients who do not achieve specific clinical thresholds are discontinued in clinical practice, leaving patients with the best clinical outcomes and QALY gains on treatment.

Although a number of pArg thresholds were evaluated in PEACE (achievement of <200 μM; achieving between 40 to 115 μM [normal levels]) there was no pre-specified arginine threshold that might define a desired level of efficacy and/or treatment continuation rule in clinical practice. Therefore, UK clinical experts were asked regarding a continuation rule that might be applicable to pegzilarginase. Clinical experts were divided regarding this question, with one expert stating that % reduction from baseline in pArg (50%) would be more appropriate than a threshold, while others considered that evidence of clinical deterioration was more appropriate. One expert stated that, were a threshold to be applied in the economic model, 40 to 115 μM (normal levels) was seen as strict, with <200 μM cited as a more realistic threshold.

Given the lack of consensus on a stopping rule and the preference for decision making based on disease progression, no stopping rule considering arginine levels was included in the model.

As some clinicians cited clinical deterioration as a reason for stopping treatment, the model has an optional stopping rule whereby patients who progress to GMFCS V. This option is not assumed in the base case, but it would have no impact, as patients on pegzilarginase are assumed not to progress, but it would affect a very small proportion of patients in scenarios where a low level of ongoing progression occurs.

B.3.3.4. General treatment discontinuation

In the PEACE study, one patient in the pegzilarginase treatment group discontinued the study during the double-blind period “for personal reasons” and all 31 patients who completed the double-blind period continued onto the LTE portion of the study and completed the study. Although the single discontinuation in the pegzilarginase arm equates to 4.8% of the cohort, we have assumed a low (1%) annual discontinuation rate in the model, as the patient who discontinued pegzilarginase did so early on in the study, when they were receiving pegzilarginase by infusion in hospital. The administrative burden on patients would be lower in practice as patients can receive SC injections from treatment initiation and can rapidly move to home-based administration, with no need for the regular trial assessments patients underwent in PEACE.

B.3.3.5. Frequency of HACs

Although HACs are less frequent in ARG1-D than in other UCDs, [redacted] and an additional UK clinical expert still cited HACs as a significant source of mortality and contribution to morbidity and progression. HACs are therefore included in the model to capture their impact on costs, HRQoL and mortality. To model HACs, we use the definition of a hyperammonaemic episode from PEACE: "an event in which a subject had an ammonia level ≥100 µM with one or more symptoms related to hyperammonaemia requiring hospitalization or emergency room management".

Four serious HACs were experienced by three patients in the PEACE placebo arm. Given the small placebo sample size and follow-up time and the protocolised exclusion of patients without stable ammonia scavenger doses, the PEACE data were supplemented with data from ARG1-D patients in the UCDC registry. The data from both sources were pooled and used to estimate a rate of [redacted] HACs per patient/year for IDM (see Table 39). In the model, this was adjusted to a rate per model cycle before converting to a probability of [redacted] per cycle.

Table 39: Calculation of HAC rate per year for IDM

	Number of events	Number of patients	Total patient-years	Rate per patient-year
UCDC registry	[redacted]	[redacted]	[redacted]	[redacted]
PEACE placebo	[redacted]	[redacted]	[redacted]	[redacted]
Total IDM	[redacted]	[redacted]	[redacted]	[redacted]

Key: HAC: hyperammonaemic crisis; IDM: individualised disease management; UCDC: Urea Cycle Disorders Consortium.

To generate a HAC rate on pegzilarginase, a rate ratio was applied to the rate per patient-year on IDM. The rate ratio was generated by comparing the number of events in the pegzilarginase LTE arm (patients originally randomised to pegzilarginase, mean follow-up time per patient [redacted] days), versus the number of events in patients on placebo (mean follow-up time per patient [redacted] days) (see Table 40). Only the event rate from the LTE phase was used for the pegzilarginase arm (the double-blind period was excluded), as by this timepoint patients would have benefitted from the full treatment effect of pegzilarginase and its downstream metabolic impact. This approach generated a rate ratio of 0.075 for pegzilarginase vs IDM.

Table 40: Number of HAC events informing rate ratio estimate

	PEACE placebo arm	PEACE pegzilarginase arm LTE phase
Total patients	11	21
Mean days of follow up	[redacted]	[redacted]
Total patient-years of follow up	[redacted]	[redacted]
Number of patients with events	[redacted]	[redacted]
Number of events	[redacted]	[redacted]
Rate ratio		0.075

Key: HAC: hyperammonaemic crisis; LTE: long-term extension.

B.3.3.6. Mortality

Little evidence regarding overall survival in ARG1-D is available in the literature and mortality data were not available from the UCDC registry. The only estimate available comes from an SLR in ARG1-D, in which the median age at death of patients in the case studies considered was 17 years; half died before 1 year of age, half between age 17-39 and one at 60 yrs. The median age of patients who were not reported dead was 16, the oldest alive was 37 and second oldest 31 (29). Immedica is not aware of many patients over the age of 40 in any of the centres it is in contact with throughout Europe (only one patient aged 49 in the BoI study). [redacted] and an additional UK clinical expert stated the key causes of mortality in ARG1-D patients to be HACs, complications from infections/surgery, neurological damage and liver disease. Economic models in other rare diseases have either captured mortality using overall survival (OS) curves generated from registries and/or applied standardised mortality ratios (SMRs) to general population mortality from the literature, stratified by GMFCS health state. Unfortunately, given the absence of data, neither of these options is available in ARG1-D. Two options are therefore available in the model for modelling of mortality, described in sections B.3.3.6.1 and B.3.3.6.2. These different options can be applied independently by arm.

B.3.3.6.1. Mortality based on unspecified ARG1-D disease symptoms and HACs

In the clinical setting, few patients will survive to adulthood and most patients will die before the age of 30-40 years, though there is insufficient data to be able to allocate

specific sources of excess mortality in a quantitative manner. One approach might therefore be to calibrate the model such that all patients are dead by a specific age. To ensure that mortality estimates account for both age and neuro-disability, SMRs were applied to general population mortality. As this would only capture the impact of neuro-disability, mortality from HAC was captured as an instantaneous risk, conditional on experiencing the HACs modelled in Section B.3.3.5.

a. ARG1-D calibrated SMRs

Given the lack of data to inform SMRs in ARG-1, a starting point for SMR weightings was those applied in MLD to capture the impact of neuro-disability (which we understand were CP SMRs, sourced from the CLN 2 HST12 by the EAG) (111). As there were two more MLD health states than GMFCS, clinical experts were asked during the conceptual modelling phase which GMFC-MLD health states could be collapsed into ARG1-D GMFCS health states. A multiplier was applied to these SMRs and the Excel 'Goal seek' function was used to calculate the SMR multiplier that led to all patients being dead by age 35 (noting that this mortality was inclusive of instantaneous mortality from HAC events, see B.3.3.6.1.b below). A logical approach for this would be to start all patients at age 0 and assign them all to GMFCS I, but the generated SMRs led to an unrealistically low survival due to the higher general population mortality rates in the first years of life. Patients were therefore set to age 4 for the calibration, the age at which general population mortality drops substantially. A cohort of patients aged 4 would logically not be expected to have the same distribution as a cohort aged 13 (the baseline age of the model). Thus, when seeking the SMR multiplier, the baseline GMFCS distribution is set to 66.7% in GMFCS I and 33.3% in GMFCS II, which was the baseline distribution of patients aged under 5 in the pooled PEACE, Phase 1/2 and BoI datasets. The goal seek function is then used to generate the SMR multiplier. This approach led to a median survival of 18 years with nearly all patients dead by age 35. The required multiplier was 554.94. As discussed in Section B.3.3.1.2.d, a key weakness of the model was the lack of observations in the trial data in GMFCS V and few in GMFCS IV, which substantially reduces the patient movements to health states associated with high excess mortality. This may explain why such high SMRs were required to predict realistic mortality for ARG1-D patients using the model.

In the pegzilarginase arm, the MLD SMRs were applied without a multiplier. This retains past committee assumptions of residual mortality due to neurological disability while removing the excess mortality from other undefined causes such as liver disease. Mortality from HACs is also retained in the pegzilarginase arm, but their contribution is lower than in the IDM arm both due to reduced incidence (see Section B.3.3.5) and reduced mortality rates (see Section B.3.3.6.1.b). The SMRs applied in the model are presented in Table 41.

Table 41: SMRs applied in the model

Health State	Unweighted MLD SMRs (pegzilarginase arm)	ARG1-D SMR (IDM arm)	Source
SMR multiplier (applied to IDM arm)	-	554.94	Obtained via model calibration: SMRs that lead to nearly all patients dead by age 35.
GMFCS-I	1.16	643.73	HST18 committee papers (111). Average of GMFC MLD 0 and 1
GMFCS-II	1.32	732.51	HST18 committee papers (111). GMFC MLD 2
GMFCS-III	1.80	998.88	HST18 committee papers (111). GMFC MLD 3
GMFCS-IV	1.80	998.88	HST18 committee papers (111). GMFC MLD 4
GMFCS-V	8.14	4514.95	HST18 committee papers (111). Average of GMFC MLD 5 and 6

Key: GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; SMR: standardised mortality ratio.
Note: these were the SMRs applied to patients treated with Libmeldy® in HST18, but we have removed the 1.25 SMR that was added to account for toxicity of the gene therapy delivery procedure by dividing all MLD SMRs by 1.25.

b. Mortality from HAC

As stated above, the survival calibration generated the SMRs that predicted all patients to be dead by age 35, inclusive of any deaths from HAC. While the frequency of HAC estimated in B.3.3.5. came specifically from ARG1-D patients, no data are available for mortality rate from HAC specific to ARG1-D. We therefore made use of the available literature on mortality from HAC in UCD, which demonstrated that the risk of mortality in UCD is correlated with the peak ammonia levels during the HAC admission (61). In this study, the mortality rate in 299 patients with 1,181 HACs over 25 years and association

with patient age and peak ammonia levels was examined. Table 4 of the publication stratifies patients into age bands and into the following peak ammonia groups:

- ≤200 µmol/liter
- >200-500 µmol/liter
- >500-1000 µmol/liter
- >1000 µmol/liter

Mortality rates from the >2 years to 12 years (305 episodes) cohort and age >12 years (325 episodes) were relevant to the model (as pegzilarginase is only licensed for age 2 and above).

To apply these mortality data to ARG1-D patients, the peak ammonia levels by HAC episode in ARG1-D was required. This was available from the HAC events in the pegzilarginase studies, but given the small patient numbers, was supplemented with two sources: (1) individual case reports of hospitalised HACs in the Bin Sawad SLR (29) (2) individual patient reports in the UCDC registry (60).

For patient receiving pegzilarginase, aligned with our approach to deriving a treatment effect on HAC rate (see Section B.3.3.5), we restricted the analysis to patients who had received treatment with pegzilarginase for at least 24 weeks. However, in contrast to the approach for HAC rate ratio, which considered a randomized comparison, we consider peak ammonia levels for all HAC events experienced by patients who had received pegzilarginase for at least 24 weeks, regardless of the initial treatment allocation. The rationale for this is that peak ammonia levels can vary by admission even in the same patients and secondly to increase sample size. In the pegzilarginase LTE arm, peak ammonia levels were only available from [redacted] events; [redacted] were associated with peak ammonia levels under 200 µmol/Liter and [redacted] with peak ammonia levels 200-500 µmol/Liter. A tabulation of these data is provided in Table 42 below.

Table 42: Counts of peak ammonia distribution from ARG1-D patients

	IDM			Pegzilarginase
Peak ammonia level	**SLR**	**PEACE placebo**	**UCDC registry**	**PEACE pegzilarginase LTE**
≤200 µmol/Liter	25	[redacted]	[redacted]	[redacted]
>200-500 µmol/Liter	14	[redacted]	[redacted]	[redacted]
>500-1000 µmol/Liter	4	[redacted]	[redacted]	[redacted]
>1000 µmol/Liter	4	[redacted]	[redacted]	[redacted]
Total	**47**	[redacted]	[redacted]	[redacted]

Key: IDM: individualised disease management; SLR: systematic literature review; LTE: long-term extension; UCDC: Urea Cycle Disorders Consortium.

The mortality rate by age and by peak ammonia level was combined with the distribution of peak ammonia to generate a mortality rate due to HACs for patients in the model aged 12 and below and >12 as presented in Table 43. These rates were multiplied by the risk of having a HAC per model cycle (as described in Section B.3.3.5) on IDM vs. pegzilarginase.

Table 43: Calculation of mortality rates from HAC

			Distribution of peak ammonia level in HACs	
Peak ammonia level	**Mortality rate age 2-12**	**Mortality rate age >12**	**PEACE placebo**	**PEACE pegzilarginase**
≤200 µmol/liter	2.1%	0.7%	[redacted]	[redacted]
>200-500 µmol/liter	2.3%	0.6%	[redacted]	[redacted]
>500-1000 µmol/liter	17.9%	6.3%	[redacted]	[redacted]
>1000 µmol/liter	100.0%	50.0%	[redacted]	[redacted]
	IDM			**Pegzilarginase**
Mortality rate in age 2-12	**5.9%**			[redacted]
Mortality rate in age >12	**2.4%**			[redacted]

Key: HAC: hyperammonaemic crisis.

B.3.3.6.2. Mortality based on median survival

An alternative approach to that outlined in B.3.3.6.1 is to model overall survival based a user-specified median. When running this scenario, the survival estimate of 17 years from

a literature review by Diaz et al.(45) is used as an initial value. In this approach, the model is set to generate a median OS of age 17 by applying an exponential survival distribution. For example, given an age at baseline of 12 in the model, median OS is estimated as 17-12 = 5 years. A constant annual mortality rate (exponential survival curve) is then estimated using the following formula:

Annual mortality rate = -LN(0.5)/median OS

Were this mortality rate to be applied unrestricted, it could lead to the unrealistic situation of a lower mortality rate than the general population and/or than that might be expected for a patient with existing neuro-disability. To avoid this situation, the model includes SMRs by GMFCS health state, applied to general population mortality. When the constant mortality rate estimated using the median OS of age 17 falls below that of the SMR-weighted general population, the model applies the latter mortality rate (noting that this restriction never needs to be applied if the median OS is very young). Given the lack of data to inform SMRs in ARG-1, SMRs from MLD are applied in the base case (see the unweighted SMRs in Table 41) (111).

B.3.3.6.3. Alternative SMRs

An alternative source of SMRs is available from a study in cerebral palsy (117). In the latter study, it should be emphasised that the SMRs are not stratified by GMFCS, but rather by a measure called the overall disability score (DISAB), which has range between 1 and 12. While obviously correlated it is not possible to draw one to one correlations between GMFCS and DISAB and the SMRs assigned to each GMFCS health state is based on assumptions. Therefore, while providing an alternative source of mortality SMRs, these are not applied in the model base case.

Health State	SMR	Source
GMFCS-I	1.62	Mean if DISAB 1-5 (117)
GMFCS-II	6.43	Mean if DISAB 6-7 (117)
GMFCS-III	11.6	DISAB 8 (117)
GMFCS-IV	27.5	DISAB 9 (117)
GMFCS-V	41.2	DISAB 10 (117)

Key: DISAB: overall disability score; GMFCS: Gross Motor Function Classification System; SMR: standardised mortality ratio.

B.3.3.7. Treatment-related adverse events

Overall, the majority of TEAEs recorded in PEACE were mild in severity, with a similar incidence of mild TEAEs observed across both treatment groups, (47.6% of patients [10 of 21 patients] in the pegzilarginase group versus 45.5% of patients [5 of 11 patients] in the placebo group) during the double-blind portion of the study. No patient in the pegzilarginase arm experienced TEAEs requiring dose reduction or TEAEs leading to discontinuation (see Section B.2.10.1) (59, 84). Therefore, no TEAEs were included in the model.

B.3.4 Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

No preference-based HRQoL instruments were administered in the PEACE or Phase 2 studies.

B.3.4.2. Mapping

The PedsQL and SF-36 were administered to patients in PEACE, but as only 3 patients were aged over 18, SF-36 values were not mapped to the EQ-5D.

The only algorithm we were able to identify which maps the PedsQL onto the EQ-5D was one by Khan et al (118). This algorithm had poor predictive ability for poorer health states (utility <0.6) and was stated to be robust for populations comparable to that used to generate the algorithm; that is, children aged 11-15 years in attendance at secondary school. Given the substantial difference between the Khan population and ARG1-D patients, both in terms of age but also morbidity, no attempts were made to map using this algorithm.

A published algorithm that maps the PedsQL onto Child Health Utility-9 Dimensions (CHU-9D) utilities was explored (119). This algorithm was developed in a sample of children and young people of a wide age range (0 to 16 years of age) and with chronic conditions. The mapping was conducted at the item level on baseline GMFCS data. As no numerical trend by GMFCS health state was observed using simple summary statistics (Table 44), which clearly lacks face validity, no attempt at utility regressions was made and mapped values from the trial are not used in the economic model.

Table 44: Utility mapped from the PedsQL

Health State	N	CHU-9D Utility
GMFCS-I	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]
GMFCS-III	[redacted]	[redacted]
GMFCS-IV	[redacted]	[redacted]

Key: CHU-9D: Child Health Utility-9 Dimensions; GMFCS: Gross Motor Function Classification System; PedsQL: Paediatric Quality of Life Inventory.
Note: These values are not used in the economic model.

B.3.4.3. Health-related quality-of-life studies

The SLR identified one publication which reported HRQoL scores in a cohort of Chinese patients with ARG1-D (82), and two publications that report HRQoL data UCDs (120, 121) (see Appendix H). No published preference-based HRQoL values that could inform utility values in ARG1-D patients were identified in the SLR.

B.3.4.3.1. Patient utility values

The European BoI study (46), collected utility data from ARG1-D patients on the EQ-5D-5L and used the van Hout algorithm to generate 3L utility values (Table 45) (we are aware that Fernandez-Alava has since superseded van Hout as NICE's preferred algorithm but have not been able to update the analyses) (68). The sample providing both GMFCS and EQ-5D comprised 16 patients, ranging from age 3 to 49. 14 of the patients were not able to respond themselves and responses were provided by caregivers, including caregivers of two adult patients. The patient utility values collected in the European BoI study are presented in Table 45.

Table 45: Patient utility values from the burden of illness study

Health State	ARG1-D Health State Utilities	Standard error	Source
GMFCS-I	0.783	0.081	European BoI study (46)
GMFCS-II	0.598	0.123	European BoI study (46)
GMFCS-III	0.344	0.069	The average of GMFCS 2 and 4. European BoI study (46)
GMFCS-IV	0.090	0.061	European BoI study (46)
GMFCS-V	0.028	0.006	European BoI study (46)

Key: ARG1-D: arginase 1 deficiency; BoI: burden of illness; GMFCS: Gross Motor Function Classification System;
Note: van Hout crosswalked values

When data is limited, one strategy is to use a proxy disease. It is known that ARG1-D shares similar disease characteristics and symptoms with CP. A systematic literature review was therefore conducted where CP was used as a proxy disease for ARG1-D to explore data options for the health economic model (109). In this SLR, several studies were found that related utilities with different GMFCS levels. Although CP has similarities in disease presentation to ARG1-D (e.g. occurrence of spasticity), unlike ARG1-D, CP is not a progressive disease and therefore estimation of utilities may be misleading when basing the analysis on utilities derived from a CP population. For a progressive disease, patients do not have the possibility to adapt to the situation. They know the disease will progress and there might be a further reduction in HRQoL due to the fear of more severe symptoms and due to the risk of early mortality. Nevertheless, two options using utility values from CP are included in the model for comparison purposes. These are from a Swedish study that collected the EuroQol-5 Dimensions 5-Levels (EQ-5D-5L) and used the UK tariff and a UK study which captured values on the EuroQol- 5 Dimensions (EQ-5D-Youth) (using adult UK tariff) and CHU-9D instruments (122, 123).

Table 46: Utility values from cerebral palsy

Health State	EQ-5D-3L Jarl et al., 2019	EQ-5D-Y Ryan et al., 2020	Source
GMFCS-I	0.80	0.82	Jarl *et al*. (2019) (122); Ryan *et al* (2020) (123)
GMFCS-II	0.58	0.75	Jarl *et al*. (2019) (122); Ryan *et al* (2020) (123)
GMFCS-III	0.48	0.39	Jarl *et al*. (2019) (122); Ryan *et al* (2020) (123)
GMFCS-IV	0.17	0.14	Not in Ryan *et al*. (2020): used ratio of 4 vs 3 from Jarl *et al* (2019) (122)
GMFCS-V	0.04	0.03	Not in Ryan *et al*. (2020): used ratio of 5 vs 4 from Jarl *et al* (2019) (122)

Key: EQ-5D-3L: EuroQol-3 Dimensions-3 Levels; EQ-5D-Y: EurolQol-5 Dimensions-Youth; GMFCS: Gross Motor Function Measure.

As discussed in B.3.2.2, there are other rare diseases that are characterized by both neuromotor and neurocognitive progression, including MLD and X-ALD, which have published utility values for GMFCS-like health states. Of these two, clinical experts considered X-ALD to be the most similar to ARG1-D in severity. Therefore, the model also includes the option to use utility values from MLD (values used by ICER group as

NICE's accepted values redacted) and X-ALD cost effectiveness studies (noting that in the X-ALD analysis, we believe that the values originated from multiple sclerosis) (Table 47) (124, 125). As there were two more MLD health states than GMFCS, clinical experts were asked during the conceptual modelling phase which GMFC-MLD health states could be collapsed into ARG1-D health states. It should be noted that the utility in GMFCS V for MLD, being negative, is substantially lower than those in any of the other indications for which scenarios are included.

Table 47: Utility values from MLD and X-ALD

Health State	MLD utilities	Source	X-ALD utilities	Source
GMFCS-I	0.93	Average of GMFC-MLD 0 and 1 (125)	0.96	General population utility of 12-year old
GMFCS-II	0.84	GMFC-MLD 2 (125)	0.68	ALD-DRS I (124)
GMFCS-III	0.38	GMFC-MLD 3 (125)	0.59	ALD-DRS II (124)
GMFCS-IV	0.00	GMFC-MLD 4 (125)	0.11	ALD-DRS III (124)
GMFCS-V	-0.11	Average of GMFC-MLD 5 and 6 (125)	0.03	ALD-DRS IV (124)

Key: Gross Motor Function Measure; MLD: metachromatic leukodystrophy; X-ALD: x-linked adrenoleukodystrophy.

B.3.4.3.2. Cognitive sub-state disutilities

As well as motor deficits, patients with ARG1-D can experience cognitive disability, as explained in Section B.1.3.1.2.a.i. Given that cognitive deficit does not necessarily correlate with motor deficit and that patients might achieve improvement in cognitive performance without changing GMFCS health state, it is important to capture the impact of treatment on neurocognitive outcomes.

It could be argued that the ARG1-D utility values captured in the patient survey might already include the impact of cognitive deficit, but several arguments can be made against this. Firstly, capturing the impact of cognitive deficits on HRQoL is challenging; the EQ-5D does not have a cognitive domain and as patients' cognitive performance declines, their ability to capture the impact of this decline on HRQoL instruments logically becomes more challenging. Secondly, the sample size in the ARG1-D patient survey was very small and therefore unlikely to capture the full range of potential scores and impacts of cognitive function on HRQoL by health state. Finally, without further cognitive

disutilities, no benefit would be captured in those patients who improved cognitive performance but did not change GMFCS health state while receiving pegzilarginase.

The mean utility values of patients with vs without cognitive limitations in the BoI study were 0.453 vs 0.727, respectively. However, as stated in B.3.3.2, patients in the most severe health states also tended to have more severe cognitive deficits and there is no means of applying the disutility value generated by this difference differentially across health states.

In HST18, an attempt was made to capture the impact of cognitive function on patient and carer HRQoL and the impact of Libmeldy® (111). While the magnitude of the benefit was a point of debate, a utility benefit from the improved cognitive function resulting from treatment was accepted by the appraisal committee. We therefore include the possibility to add additional decrements to the GMFCS health states in order to capture the changes in cognitive function modelled in Section B.3.3.2 on patient HRQoL. The disutilities from MLD are applied (Table 48), calculated by subtracting the difference between the utility values of the mild/normal cognitive function health states and the moderate and severe cognitive function health states. As the 'negativity' of the resultant health states in MLD was a significant topic of debate, but the final values accepted by NICE committee are unknown, the model applies a limit such that no health state utility value can fall beneath a user-defined threshold, -0.25 in the base case.

Table 48: Cognitive substate disutilities from MLD

Health State	Moderate Impairment	Severe Impairment	Source
GMFCS-I	-0.24	-0.53	Average of GMFC-MLD 0 and 1 (125)
GMFCS-II	-0.28	-0.57	GMFC-MLD 2 and 1 (125)
GMFCS-III	-0.28	-0.49	GMFC-MLD 3 and 1 (125)
GMFCS-IV	-0.16	-0.33	GMFC-MLD 4 and 1 (125)
GMFCS-V	-0.17	-0.28*	Average of GMFC-MLD 5 and 6 (125)

Note: Values were redacted in HST18, therefore we apply the utility values reported in the ICER group evaluation of Libmeldy®.*Original value -0.33; 0.28 after application of minimum utility restriction.

B.3.4.3.3. Caregiver disutilities

In the BoI survey, utility values if caregivers were elicited and stratified by GMFCS (Table 49). Caregivers reported few limitations on the EQ-5D-5L. Anxiety/depression was the

dimension where most caregivers reported problems, 25% of the caregivers experienced moderate anxiety/depression. Responses on the (cross-walked) EQ-5D led to a U-shape patter, with higher values in GMFCS I and V (Table 49). There were no caregivers with patients in GMFCS III. To generate disutilties, the caregiver utilities by GMFCS were subtracted from the general population utility norm for the caregiver sample (mean age 44 years, 66% female), which was 0.882. As the caregiver utility for GMFCS V was 1 (only one observation), we instead assumed it was the same disutility as GMFCS IV.

Table 49: ARG1-D caregiver disutility values from the BoI study

Health State	Utility	Disutility	Source
GMFCS-I	0.821	-0.13	Difference between population norm and carer utility. (46)
GMFCS-II	0.732	-0.22	Difference between population norm and carer utility. (46)
GMFCS-III	0.599	-0.35	The average of GMFCS II and GMFCS IV
GMFCS-IV	0.465	-0.49	Difference between population norm and carer utility. (46)
GMFCS-V	1.000	-0.49	Assumed equal to GMFCS IV
Population norm	0.882		Ara and Brazier, aged 44, 66% female (126)

Key: ARG1-D: arginase 1 deficiency; BoI: burden of illness; GMFCS: Gross Motor Function Measure Classification System.

The caregiver disutility values generated from the ARG1-D survey were very high when compared with, for example, caregiver disutilities for MLD in HST18, which lacks face validity given the relative severity of the diseases. In the absence of a reasonable alternative, the model base case therefore applies the disutilities from HST18. GMFC-MLD health states were collapsed into GMFCS health states according to clinical expert feedback, the same way as was done for the patient utility values (Table 50). Patients were assumed to have 2 caregivers up to age 16 and 1 thereafter, with no upper age limit.

Table 50: Caregiver disutility values from MLD (HST18)

Health State	Disutility	Source
GMFCS-I	0.00	Average of GMFC-MLD 0 and 1(111)
GMFCS-II	-0.02	GMFC-MLD 2(111)
GMFCS-III	-0.03	GMFC-MLD 3(111)
GMFCS-IV	-0.09	GMFC-MLD 4(111)
GMFCS-V	-0.16	Average of GMFC-MLD 5 and 6(111)

Key: GMFCS: Gross Motor Function Classification System; MLD: metachromatic leukodystrophy.

B.3.4.3.4. Utility gain from improved diet

Patents with ARG1-D have to follow a severe protein-restricted diet, which poses a significant burden on both patients and caregivers, impacting HRQoL more than medication in some cases (11-13, 46). In the PEACE study, although sites were instructed to minimize dietary protein prescription changes, by week 24, a higher proportion of subjects increased their total protein consumption by more than 15% in the pegzilarginase group compared to placebo (42.9% versus 18.2%). Importantly, dietary excursions did not impact ability to maintain pArg within therapeutic range (59).

A utility gain for the impact on HRQoL of improved diet was therefore included in the model. The utility decrement associated with a severely restricted diet was sourced from HST13 (Waylivra for treating familial chylomicronaemia syndrome (FCS) in adults) and specifically, a vignette study by Matza et al. that was used to generate utility values in this indication (127, 128). Patients with FCS, like patients with ARG1-D, have to follow a strict diet, except that FCS patients have to restrict their dietary fat levels instead of protein. The Matza vignette with the highest utility value was chosen as the reference point, as this represents patients whose triglycerides (TGs) are well controlled but who still have to follow a strict diet. The difference in utility value between this vignette and the general population utility of a person aged 46 (the average age of the patients recruited to the FCS clinical study) and proportion female in the model (56%) was assumed to represent the utility decrement of a severely restricted diet (Table 51). As patients in the PEACE trial had an improved diet (as opposed to no restricted diet) half of the utility gain was applied. The utility gain was applied to the difference between pegzilarginase and placebo in the proportion of patients who had a >15% increase in their % of total calorie consumption that was protein at week 24 (calculated as 24.7%).

Table 51: Calculation of utility gain from improved diet

Parameter	Utility value	Source
Utility of controlled patient on strict diet	0.80	Utility of low TG, AP naïve health state Matza et al (127)
General population utility value	0.88	General population utility of 46-yr old, 41% female (126)
Difference in utility between no diet and severely restricted	0.08	Difference in utility value between the above two values
Difference in utility between improved diet and severely restricted	0.04	Assumed to be half the decrement of fully restricted diet
% of patients with utility gain from improved diet	24.7%	In PEACE, 42.9% on pegzilarginase compared to 18.2% on placebo consumed >15% of calories as total protein (59).

Key: TG, triglycerides; AP, acute pancreatitis.

B.3.4.3.5. Disutility of ageing

Throughout the model time horizon, a utility decrement is applied multiplicatively to the GMFCS utility and cognitive substate disutility values, using the Ara and Brazier algorithm for population norms (126).

B.3.4.4. Adverse events

B.3.4.4.1. Disease-related adverse events

The HAC events modelled in Section B.3.3.5 were assumed to incur a disutility. No utility values could be identified in the literature for hyperammonaemia or metabolic decompensation, therefore the disutility of epilepsy/convulsions was applied (129). The disutility was assumed to last for 7 days (Table 1Table 52).

Table 52: Disutility of HACs

Parameter	Value	Source
Annual QALY loss	0.067	Disutility of epilepsy/convulsions (129)
Duration of HAC (days)	7.00	Assumption

Key: HAC: hyperammonaemic crisis; QALY: quality-adjusted life year.

B.3.4.4.1. Treatment-related adverse events

No patient in the pegzilarginase arm experienced TEAEs requiring dose reduction or TEAEs leading to discontinuation (see Section B.2.10.1) (59, 84). Therefore, no TEAEs events were included in the model.

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

The core motor disability health state in the model are defined by GMFCS score (see Section B.1.3.1.2.a.iv for description of each health state). Cognisant of the NICE reference case, we have used the ARG1-D patient survey utility values for GMFCS health states in the base case as they were collected in ARG1-D patients and/or their carers using the EQ-5D. However, it should be noted that very few patients in the IDM arm transition to the GMFCS IV and V and their low utility values. This almost certainly leads to an overprediction of QALYs in the IDM arm. Furthermore, it should be noted that the ARG1-D utility values are similar to those of poorer GMFCS-like health states in other rare diseases such as MLD and X-ALD, while being substantially lower in GMFCS I. There is no obvious reason why this should be the case, other than some disutility due the restrictive diet. Therefore, we have addressed this face validity issue by assuming that utility in the GMFCS I health state is the average of the general population aged 13 years and 56% female (as per model baseline characteristics) and the BoI GMFCS I value of 0.78.

We include scenario analyses whereby the utility values from X-ALD and MLD are applied, as these substantially reduce the ICER. It is also possible to select utilities for CP in the model, but these will not be representative of the HRQoL of ARG1-D patients, who additionally can experience symptoms of metabolic disturbance and liver disease such as nausea.

Table 53: Summary of annual utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
GMFCS I	0.87 (0.08)	0.67 - 0.98	B.3.4.3.1 (page 158)	NICE reference case prefers EQ-5D utility values from

				patients. GMFCS I adjusted upward to be more representative.
GMFCS II	0.60 (0.12)	0.35 - 0.82	B.3.4.3.1 (page 158)	As above
GMFCS III	0.34 (0.07)	0.22 - 0.48	B.3.4.3.1 (page 158)	As above
GMFCS IV	0.09 (0.06)	0.01 - 0.24	B.3.4.3.1 (page 158)	As above
GMFCS V	0.03 (0.01)	0.02 - 0.04	B.3.4.3.1 (page 158)	As above
GMFCS I - Cognitive disutility - Moderate impairment	-0.24 (0.05)	0.15 - 0.34	B.3.4.3.2 (page 160)	No cognitive domain on EQ-5D; patients may have improved cognition on pegzilarginase and not change health state.
GMFCS II - Cognitive disutility - Moderate impairment	-0.28 (0.06)	0.18 - 0.40	B.3.4.3.2 (page 160)	As above
GMFCS III - Cognitive disutility - Moderate impairment	-0.28 (0.06)	0.18 - 0.40	B.3.4.3.2 (page 160)	As above
GMFCS IV - Cognitive disutility - Moderate impairment	-0.16 (0.03)	0.10 - 0.23	B.3.4.3.2 (page 160)	As above
GMFCS V - Cognitive disutility - Moderate impairment	-0.17 (0.03)	0.11 - 0.23	B.3.4.3.2 (page 160)	As above
GMFCS I - Carer disutility	-0.01 (0.002)	-0.006 - -0.014	B.3.4.3.3 (page 161)	Insufficient sample size in ARG1-D BoI study to capture change by GMFCS. Values from MLD used as proxy, given MLD also impacts both motor and cognitive function.
GMFCS II - Carer disutility	-0.03 (0.01)	-0.02 - -0.04	B.3.4.3.3 (page 161)	As above
GMFCS III - Carer disutility	-0.07 (0.01)	-0.04 - -0.10	B.3.4.3.3 (page 161)	As above
GMFCS IV - Carer disutility	-0.11 (0.02)	-0.07 - -0.15	B.3.4.3.3 (page 161)	As above

GMFCS V - Carer disutility	-0.16 (0.03)	-0.10 - -0.23	B.3.4.3.3 (page 161)	As above
HAC disutility	-0.07 (0.01) -0.001 per event after adjustment for duration of 7 days.	-0.04 - -0.10	B.3.4.4.1 (page 164)	No disutility of HAC could be found in the literature; assumed same as seizure/convulsions.
Utility gain from full cessation of diet (50% of value assumed for relaxation)	0.08 (0.02)	-0.05 - -0.11	B.3.4.3.4 (page 163)	Clinicians and patients cited the restrictive diet as having important impact on HRQoL. Patients in PEACE demonstrated increased consumption of overall protein vs. placebo.

Key: ARG1-D: arginase 1 deficiency; EQ-5D: EuroQol 5-Dimensions; GMFCS: Gross Motor Function Measure Classification System; HAC: hyperammonaemic crisis; HRQoL: health-related quality of life.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

No published sources of healthcare resource use (HCRU) and costs were identified in the literature. The primary source of HCRU used in the model is the BoI patient survey (46).

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Pegzilarginase acquisition costs

Pegzilarginase can be administered via intravenous (IV) infusion or subcutaneous injection (SC) by a healthcare professional in an outpatient setting upon initiation of treatment. After eight weeks, and if deemed appropriate, SC home administration by the patient or caregiver may be considered (1). The recommended initial dose of pegzilarginase is 0.1 mg/kg per week, but dosing of pegzilarginase is individualised and the dose may be increased or decreased in 0.05 mg/kg increments to achieve therapeutic goals. In the PEACE study, dose optimization took place in the double-blind period, with patients continuing their optimized dose in the LTE.

For the purposes of the model, dosing was therefore split into 12-week periods and a random effects model fitted to the pegzilarginase dosing data in mg/kg. The analysis

considered dose data for 20 subjects, as one subject had no post baseline visit data (as they discontinued at week 6 for personal reasons unrelated to treatment). Patient characteristics such as weight and gender were not found to be significant covariates, nor was the initial 12-week period vs 12-24 weeks, therefore the final random effects model included only a covariate for >24 weeks treatment (vs ≤24 weeks as reference) (Table 54). This predicted a dose per patient of 0.15mg/kg in the first 24 weeks and 0.16mg/kg thereafter. In the probabilistic analysis, dose was capped at 0.2 mg/kg per week as doses above this were not studied in the pegzilarginase clinical trials.

Table 54: Random effects model for pegzilarginase dose

Predictors	Estimates	Confidence Interval	P value
Intercept	0.1474	0.1250 – 0.1698	<0.001
time [weeks > 24]	0.0155	0.0050 – 0.0261	0.004
Random Effects			
N_{subjid}	20		
Observations	142		
Marginal R^2 / Conditional R^2	0.016 / 0.744		

Pegzilarginase is licensed for ARG1-D patients aged 2 up to adulthood, thus the age and hence the weight of the cohort receiving treatment varies as the patient ages. The patient weight therefore needed to calculate for each model cycle. Mean weight by age and gender for the UK general population is available from NHS Digital (107), but the fact that ARG1-D patients have to follow a restricted diet should be taken into consideration, as well as their diminished growth. Comparing the mean weight of patients recruited to the Phase 2 and PEACE studies, patients aged 16 and below were 9% lighter than the age and gender-matched population norm and adults were 23% lower (noting that the latter comprised only a small proportion of patients). Therefore, patient weight as the cohort ages is assumed to be 9% lower than the population norm up until age 16 and 23% thereafter. Although we acknowledge the uncertainty in dealing with such small patient numbers, the weight ratio is dynamically calculated and any variation in this ratio is captured within the probabilistic analysis.

B.3.5.1.2. Weight-based dosing estimates

Three options for weight-based dosing are included in the model:

a. Vial wastage, based on distribution of patient weight

Having estimated the mean (multiplier adjusted) ARG1-D patient weight, a normal distribution of patient weight for each age was assumed. Based on this, the proportion of patients requiring 1, 2, 3 whole vials etc. was calculated based on the weight cut-offs for requiring a given number of whole vials (method of moments approach). E.g. the maximum patient weight possible to only require one 2mg vial at a dose of 0.15mg/kg is 2/0.15 = 13.6kg. 31% of patients aged 2 are expected to weigh less than 13.6kg, assuming a normal distribution around a mean weight of 14.8kg and standard error of 2.5kg. The remaining 69% would require 2 vials.

b. No wastage, based on point estimate of patient weight

Having estimated the mean (multiplier adjusted) ARG1-D patient weight, this is multiplied by the dose in mg/kg.

c. Dose banding, based on point estimate of patient weight

This approach represents a compromise between the full wastage and no wastage approaches and was selected as the base case. Weight cut-offs for requiring a given number of whole vials were calculated, but assuming a margin of 10%. E.g., the maximum patient weight possible to only require one 2mg vial at a dose of 0.15mg/kg is 2/0.15 = 13.6kg, but we assume that a patient can weigh up to 10% more than this; that is, 14.9kg, before requiring an additional vial.

In all the above approaches, drug costs were calculated by multiplying the drug cost per mg, including PAS (Table 55), by the average or weighted average number of mgs per age band.

Table 55: Pegzilarginase acquisition cost

Parameter	Unit cost
Cost of 2mg vial including PAS	[redacted]
Cost per mg	[redacted]

For IDM, which applies to both model arms, no costs were explicitly calculated in the base case as the costs of medication such as ammonia scavengers, anti-epileptics and/or the cost of dietary supplements were already captured within the health state costs described in Section B.3.5.2.

In the event that alternative health state costs from proxy diseases are modelled, the model can apply the costs of EAA diet and ammonia scavengers separately. Anti-epileptics are not costed separately for these scenarios as these are also often used in the proxy diseases, being a common feature of more severe neuromotor dysfunction. Not forming part of the base case, these are not described here but information on costing can be provided on request.

B.3.5.1.1. Pegzilarginase administration costs

According to the license, pegzilarginase can be administered in either the outpatient (either IV or SC) or home setting. In the clinical trials, treatment was initiated as intravenous administration with subsequent transition to subcutaneous administration after 8 weeks. It was assumed that 100% of administrations would occur in the hospital setting for the first two months and that 90% of hospital administrations would be SC and 10% IV. After the first two months, 90% of patients would switch to home-based SC administration, for which no cost is assumed. For those continuing to receive treatment in hospital after two months, 100% of administrations were assumed to be SC, as it was assumed that the only reason a patient would continue to receive their doses in hospital was due to requiring IV administration. The pegzilarginase administration costs are summarized in Table 56. Note that due to the model cycle length of 3 months, the actual switch in costs takes place after 3 months, rather than 2 months.

Table 56: Pegzilarginase administration costs

First 8 weeks	Value	Source
Proportion administered in hospital	100.00%	Assumption
Proportion administered at home	0.00%	Assumption
Proportion of hospital administrations that are IV	10.00%	Assumption
Proportion of hospital administrations that are SC	90.00%	Assumption
9 weeks onwards	**Value**	**Source**
Proportion administered in hospital	10.00%	Assumption
Proportion administered SC at home	90.00%	Assumption

Proportion of hospital administrations that are IV	0%	Assumption. Patients will be either in hospital due to a hospitalisation or because they require help with administering SC injection.
Unit costs	**Value**	**Source**
IV administration in hospital	£51.50	1 hour of a band 5-6 nurse's time (130). 30 minute infusion in CSR, then adding extra prep and observation time.
SC administration in hospital	£12.88	15 minutes of a band 5-6 nurse's time (130)
Doses per year	52.2	Pegzilarginase is administered weekly

Key: IV: intravenous; SC: subcutaneous.

B.3.5.1.2. Pegzilarginase monitoring costs

The ARG1-D health state costs by GMFCS described in Section B.3.5.2. include monitoring of pArg levels on IDM, as well as outpatient appointments with the NHS metabolic services. As we assume that there will be no change in the frequency of monitoring and clinician appointments (the frequency of which is determined by disease control) no separate monitoring costs are included.

B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. ARG1-D health state HCRU and costs

No sources of UK health state costs in ARG1-D were identified in the SLR. The only article identified was a US study which did not stratify resource use by GMFCS (75). The primary source of HCRU used in the model is the BoI patient survey (46). The HCRU elicitation and costing methods are described within the standalone report and will not be discussed in more detail here. Notable gaps were the absence of data for GMFCS III, as there were no patients in GMFCS III within the sample. Secondly, only one patient was in GMFCS V, and their costs were lower than those GMFCS IV. Unexpected patterns in the data almost certainly results from the very low sample size (GMFCS I n=8, GMFCS II n=5, GMFCS III n=0, GMFCS IV n=2, GMFCS V n=1). The cost and HCRU data collected in the survey were therefore amended using a number of assumptions:

- The costs of GMFCS III is assumed to have the average of the costs of GMFCS II and IV.

- GMFCS V is assumed to incur the average of the costs from HST18 MLD health states 5 and 6, plus the cost of diet from ARG1-D GMFCS IV.
- The cost of family caregiving is excluded from the base case as this would not be a cost incurred by the NHS or Personal Social Services.
- Special schooling costs were only applied up to age 17 in the model.
- In the societal costs scenario analysis, family caregiving and caregiver production costs were only applied up to age 17 in the model.
- In the societal costs scenario analysis, patient production loss was only applied from age 18 in the model.

The annual health state costs assumed in the model as presented in Table 57. Costs which diverge from the BoI patient survey and which have been replaced with assumptions due to the very small sample size are highlighted in grey boxes. The costs include societal costs, which can be included as a scenario analysis but are not included within the model base case.

Table 57: Annual ARG1-D health state costs

Cost category	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS III (n=0)	GMFCS IV (n=2)	GMFCS V (n=1)
Health care costs	£6,228	£5,525	£9,591	£13,657	£71,456[1]
Medication costs	£10,369	£5,972	£13,568	£21,164	£21,164[2]
Diet costs	£9,067	£7,253	£8,160	£9,067	£9,067[2]
Professional caregiving costs	£195	£4,992	£4,992	£4,992	£0[3]
Wheelchair costs	£0.00	£26	£60	£93	£1,092[4]
Special schooling costs	£3,261	£11,668	£10,991	£10,314	£46,680[5]
Societal costs (not included in base case)					
Family caregiving costs	£995	£3,713	£4,951	£6,188	£0
Production loss patient	£7,480	£11,968	£20,944	£29,920	£59,840
Production loss caregiver	£11,220	£17,952	£23,936	£29,920	£59,840
Total NHS and PSS costs	**£29,120**	**£35,436**	**£47,362**	**£59,287**	**£149,459**
Total societal costs	**£19,695**	**£33,633**	**£49,831**	**£66,028**	**£119,680**

Key: GMFCS: Gross Motor Function Measure Classification System.
Notes: Source: BoI study Table 16 (46). [1]Assumed the sum of MLD costs of Medical tests, Medical visits and procedures, Hospitalisation and Emergency. [2]Assumed the same as ARG1-D GMFCS IV. [3]Assumed same as MLD costs of respite care. [4]Assumed same as MLD cost of healthcare equipment. [5]Assumed the same as MLD cost of social services.

B.3.5.3. Adverse reaction unit costs and resource use

B.3.5.3.1. Disease-related adverse events

The HACs modelled in Section B.3.3.5 are assumed to incur a cost of hospitalisation. No costs corresponding to a hyperammonaemia event were identified in either the literature or NHS reference costs. Each HAC event was therefore assumed to incur the cost of an inpatient admission for Paediatric Metabolic Disorders, calculated as the weighted average of non-elective long stay and short stay admissions PK72A, PK72B, PK2C. No equivalent adult HRG code was available, therefore the paediatric code was used for all events £5,984. Note that this HRG code will not capture the not insignificant proportion of paediatric patients who are admitted to ICU.

B.3.5.3.2. Treatment-related adverse events

As explained in Section B.3.3.7, no serous TEAEs were observed for patients receiving pegzilarginase, therefore no costs are modelled.

B.3.5.3.3. Miscellaneous unit costs and resource use

It is anticipated that pegzilarginase will be delivered as part of the existing specialised service provision.. As per the license, pegzilarginase is anticipated to be delivered in the outpatient setting for the first 8 weeks, as either an IV infusion or SC injections, after which we believe the majority of patients will take their SC injections at home. There are already homecare delivery arrangements in place for medications as part of metabolic services and it is anticipated that pegzilarginase will be delivered as part of this.

Potential savings not explicitly captured in the model include the reduction in incidence of seizures and requirement for medication. Guanidino compounds (GCs) increase in the plasma and cerebrospinal fluid as a result of elevated pArg and may contribute to the susceptibility of seizures amongst patients with ARG1-D (16, 21, 31, 55). In reducing pArg levels, pegzilarginase may consequently reduce susceptibility to seizures.

The model does not capture the impact of ARG1-D on liver disease, liver malignancy and requirement for liver transplantation. No data were available to inform the cost savings and/or QALY benefits of avoiding liver disease and its treatment. It is anticipated that the need for liver transplant in these patients will be reduced with the introduction of pegzilarginase (Immedica is aware of at least one patient where this is the case).

While the health state costs will by definition include the costs of treating spasticity, there may be within-GMFCS improvements in spasticity that are not captured within the model. That is, GMFCS may not be granular enough to capture the benefits of treatment on incidence of spasticity.

B.3.6 Uncertainty

The majority of issues of uncertainty are due to the rarity of ARG1-D, which comprises a very small subset of already rare UCDs, limiting the data available from past and current registry studies that could inform natural history to complement the very short double-blind period.

Key areas of uncertainty impacting the cost effectiveness results are the health state utilities in ARG1-D, the rate of natural history disease progression and mortality and to what extent pegzilarginase reduces or prevents this. The PEACE study included only a very short double-blind period insufficient for capturing the natural history of such an ultra-rare condition with often a prolonged disease course. Immedica has made every effort to identify external sources of data which could inform disease progression, including an SLR of case reports (29) and exploration of the UCDC registry (32). Neither of these resources included key trial outcomes such as GMFM D&E and/or GMFCS scores that would permit population of the IDM arm of the economic model with their data.

The regression models used to inform the economic model, specifically (1) the prediction of GMFM D&E score from age and (2) the prediction of GMFCS score from GMFM D&E score, were generated from very small samples and, in the case of the GMFCS regression, did not include any observations in GMFCS V and very few in GMFCS IV. This likely leads to underprediction of patient movements to more severe health states and a potential over prediction of QALYs in the IDM arm.

To estimate short-term transition probabilities for pegzilarginase, GMFCS data from the LTE of PEACE were used. However, since patients contributed data for different lengths of follow up, LOCF was used to generate the same follow-up time between baseline and week 96. This will, most probably, underestimate the true long term effect of pegzilarginase.

B.3.7 Managed access proposal

No managed access scheme is anticipated.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

The summary table of base case analysis inputs can be found in Appendix Q (see Table 107).

Table 58 below outlines the key assumptions applied in the cost effectiveness model.

Table 58: List of model assumptions

Assumption	Justification
GMFM D&E score is assumed to worsen with age	In a regression of baseline GMFM D&E score vs age, age was statistically significant.
GMFM D&E score is predictive of GMFCS category	A relationship between GMFM-66 score and GMFCS score has been demonstrated in the CP literature, though this did not include all GMFCS health states (113-115)
All patients with ARG1-D are expected to die before the age of 35 on IDM alone.	Immedica is aware of very few patients aged above their early thirties across European treatment centres.
Mortality from HAC is conditional on peak ammonia levels.	The available literature on mortality from HAC in UCD, demonstrates that the risk of mortality in UCD is correlated with the peak ammonia levels during the HAC admission (61). It is known that patients with ARG1-D are less prone to fatal HACs than other types of UCD, but this is already captured in the model, as the incidence of HACs and their peak ammonia levels have been obtained from ARG1-D patients.
Patients receiving pegzilarginase can improve GMFCS for up to 3 years post-treatment initiation.	In the clinical trials, some patients' GMFM D&E scores were still improving up to 4 years post treatment initiation.
Following 3 years of treatment, patients receiving pegzilarginase remain in their GMFCS health state.	Once pArg levels are controlled, the underlying disease pathogenesis is controlled and there is no reason for patients to progress. Patients cannot become 'resistant' to pegzilarginase; Anti-drug antibodies were only observed early during treatment and resolved following long-term treatment(1).
Pegzilarginase reduces mortality from HACs, by reducing both incidence of HACs and	A positive relationship is observed between arginine and ammonia levels, with markedly

peak ammonia levels.	elevated pArg typically coinciding with peak ammonia levels and metabolic decompensation events (30). [redacted] and additional UK clinical experts in consultation with Immedica confirmed that elevated levels of pArg are the triggering factor for hyperammonaemia events and metabolic decompensation. Incidence of HACs was reduced in the pegzilarginase arm of PEACE and few patients experienced peak ammonia levels above 100µM.
Pegzilarginase reduces all other causes of excess mortality, apart from neuro-disability.	Once pArg levels are controlled, the underlying disease pathogenesis is controlled and there is no reason for patients to progress or develop the morbidities that lead to mortality such as liver disease.
The excess mortality due to neuro-disability is the same as in MLD.	The committee selected SMRs for patients treated with Libmeldy from HST12 (CLN2), which originally used SMRs from multiple sclerosis. It therefore appears to be *de facto* accepted that mortality rates are dependent on GMFCS state but independent of disease pathology.

B.3.9 Base-case results

B.3.9.1. Base-case incremental cost-effectiveness analysis resultsN

The base-case cost-effectiveness results are provided in Table 59, below. Pegzilarginase + IDM is estimated to yield substantially more discounted QALYs and LYs compared to IDM alone, with an incremental gain of [redacted] QALYs and [redacted] LYs. The ICER for Pegzilarginase + IDM is £871,279 with no HST QALY weighting applied. Pegzilarginase + IDM meets the criteria for the application of a QALY modifier as it is associated with more than 10 undiscounted QALYs (29.18). The QALY weighting applicable to the intervention was calculated by dividing the total undiscounted QALYs by 10, resulting in a QALY weighting of [redacted]. Multiplying the incremental QALYs associated with Pegzilarginase + IDM ([redacted]) by the QALY weighting results in a total of [redacted] weighted QALYs, which leads to a weighted ICER of £298,565 per QALY. The weighted QALY results are shown in Table 60. Disaggregated cost-effectiveness model results are provided in Appendix J.

The results from the net-health benefit (NHB) analysis are presented in Table 60. At the current HST WTP threshold of £100,000 per QALY, the weighted NHB associated with Pegzilarginase + IDM is [redacted].

Table 59: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pegzilarginase + IDM	[redacted]	21.528	[redacted]	-	-	-	-
IDM	[redacted]	5.087	[redacted]	[redacted]	16.440	[redacted]	£871,279

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 60, Base-case results with QALY modifier applied

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Undiscounted incremental QALYs	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Pegzilarginase + IDM	[redacted]	16.440	[redacted]	29.182	[redacted]	[redacted]	£298,565

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 61: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Weighted incremental QALYs	NHB at £100,000	NHB at £100,000 (with QALY weighting)
Pegzilarginase + IDM	[redacted]	[redacted]	-	-	-	-	-
IDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.10 Exploring uncertainty

B.3.10.1. Probabilistic sensitivity analysis (PSA)

A probabilistic sensitivity analysis (PSA) was conducted to explore the uncertainty around key model parameters. Parameters were simultaneously varied using appropriate distributions around their confidence intervals (see Appendix Q), based on the available data. A standard error of the mean of 20% was assumed where no uncertainty estimates were available. Although 1000 simulations were conducted, 500 iterations were sufficient to establish a stable rolling average ICER. Probabilistic results are presented in Table 62. The unweighted PSA ICER of £883,259 lies very closely to the deterministic ICER of £871,279, demonstrating stability of the results when uncertainty is captured. This was also the case for the weighted PSA and base-case ICERs which were £314,942 and £298,565, respectively. Outputs from the probabilistic sensitivity analysis iterations are presented as scatter points on the cost effectiveness plane in Figure 30 and Figure 31, below, which show the PSA with and without the QALY modifier. It is important to note here that with the exclusion of the QALY modifier, resulted in a narrower distribution of the incremental QALYs. This can be explained as inclusion of the QALY modifier results in a variation in the QALY weighting that is applied to the incremental QALYs for each of the 1000 iterations.

Figure 30: Scatter Plot of Simulations on Cost-Effectiveness (Pegzilarginase + IDM vs IDM; weighted QALY)

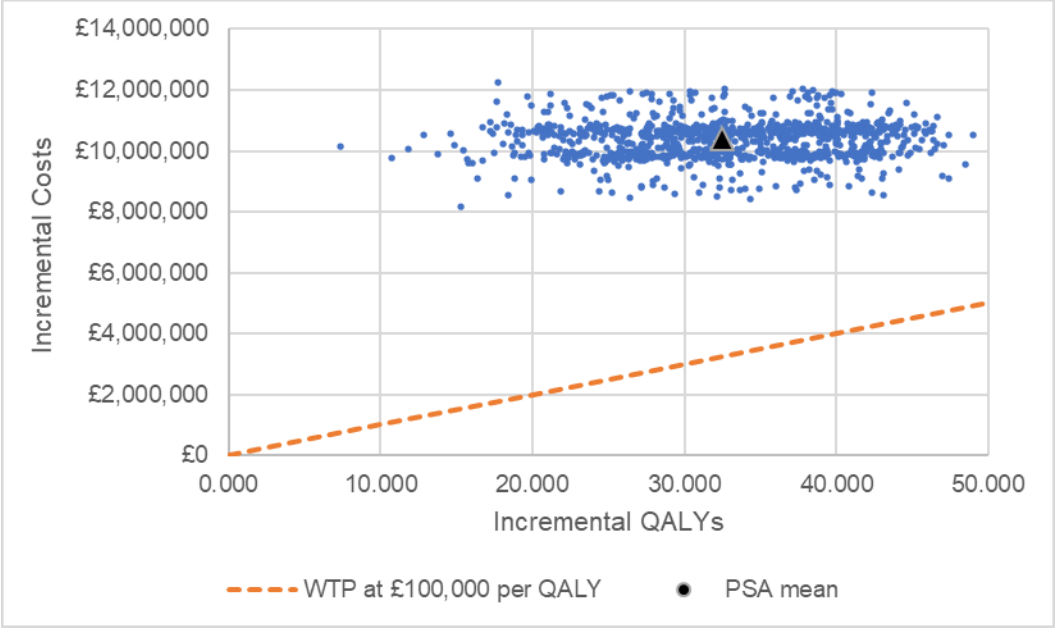
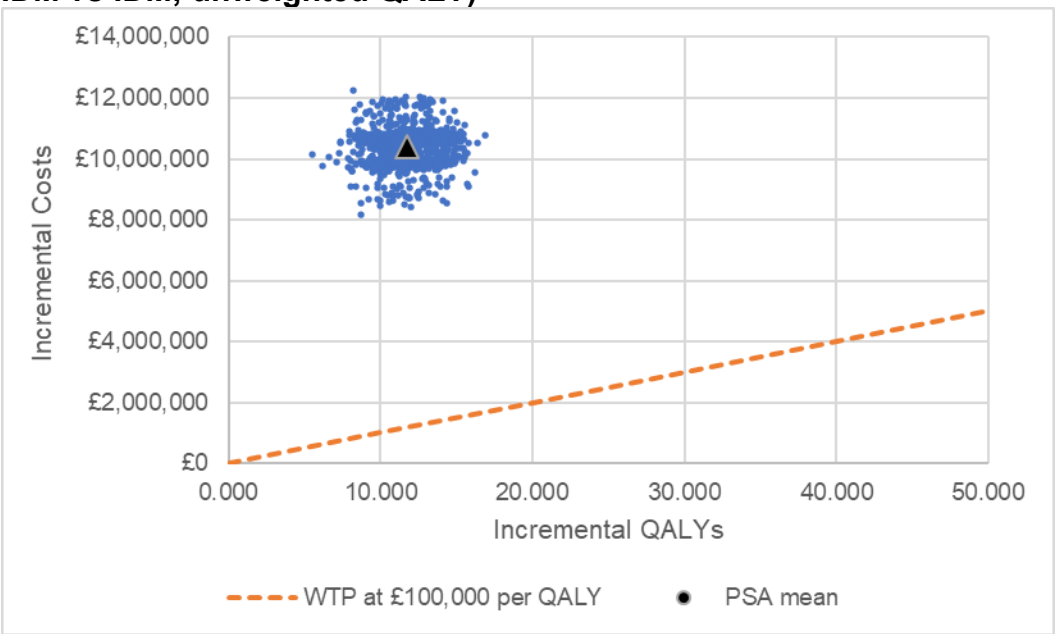


Figure 31: Scatter Plot of Simulations on Cost-Effectiveness (pegzilarginase + IDM vs IDM; unweighted QALY)



The probabilistic sensitivity analyses results were also plotted in the form of a cost-effectiveness acceptability curve (CEAC), as shown in Figure 32. The CEAC shows the probability of cost effectiveness for pegzilarginase + IDM and IDM, given varying willingness to pay thresholds for a QALY. According to the CEAC, the probability of pegzilarginase + IDM being cost-effective is 0% at a willingness to pay of £100,000 and

£300,000/QALY, compared to IDM which has a probability of 100% at both thresholds (Figure 32).

Figure 32: Cost effectiveness acceptability curve (CEAC) (Pegzilarginase + IDM vs IDM)

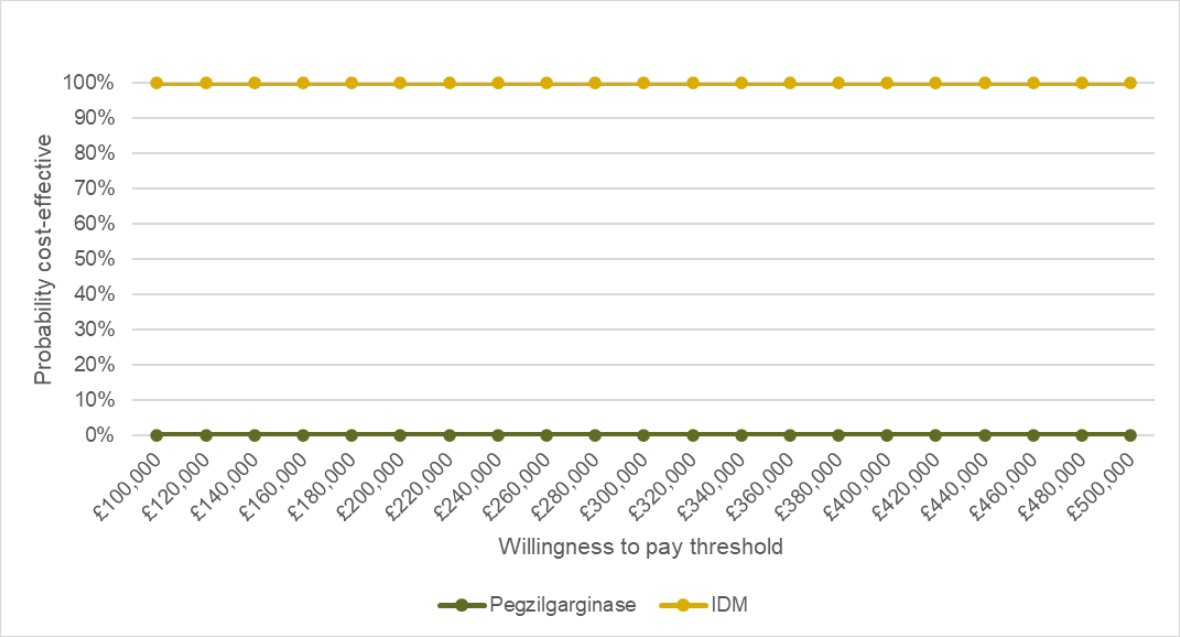


Table 62: Probabilistic cost-effectiveness model results

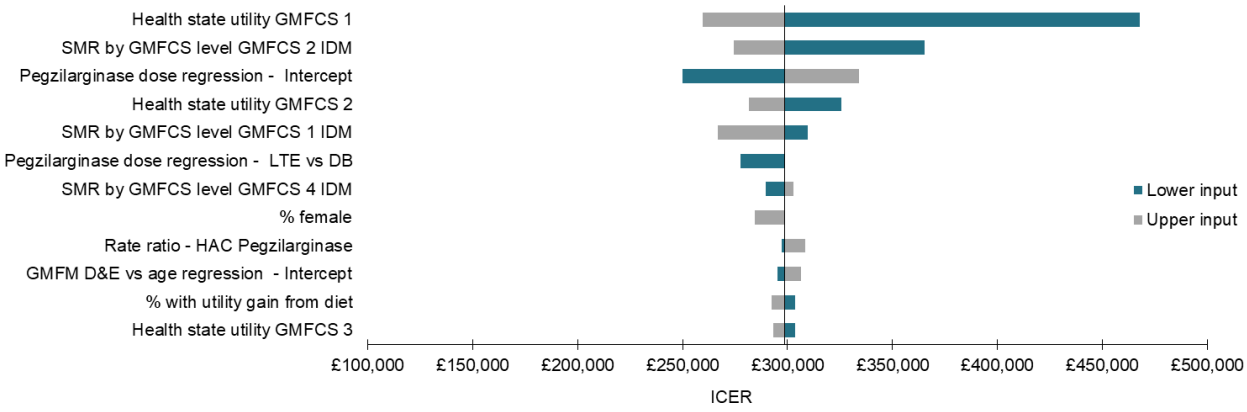
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)	ICER incremental (£/QALY)
Pegzilarginase + IDM	[redacted]	[redacted]	-	-	-	-	-
IDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio;; QALYs, quality-adjusted life years

B.3.10.2. Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates for parameter values. Parameters were varied individually around their confidence intervals, based on the available data, and/or assuming an appropriate distribution around the standard error of the mean of 20% where no uncertainty estimates were available. The results from the OWSA are presented in the form of a tornado diagram where the 12 parameters with the largest influence on the cost-effectiveness results are presented in Figure 33. The most sensitive parameters were health state utility for the GMFCS I health state, standardised mortality ratio in the GMFCS II IDM arm, the intercept value in the pegzilarginase dose regression and the intercept value in the GMFM D&E regression vs age. The ICER difference between the lower and upper input values for the first three most sensitive parameters in the deterministic sensitivity analysis ranged between £207,914 and £84,087.

Figure 33: Tornado diagram of pegzilarginase + IDM vs. IDM



B.3.10.3. Scenario analysis

A range of scenario analyses were conducted to further explore the sensitivity of the model to changes in key parameters and assumptions. The results of the scenario analyses are presented in Table 63. The most impactful scenarios were including assumptions that pegziarginase patients progress (that is, assuming some treatment effect waning after the initial improvement/stabilisation in GMFCS state). Assuming either an 80 or 90% reduction in GMFCS progression substantially decreases the QALYs in the pegzilarginase arm and hence the overall QALY gain (as GMFCS utility is a major driver

of the ICER, as shown in seen in Figure 33, and more severe GMFCS health states have higher mortality rates). This was followed by assuming that all ARG1-D patients were dead by age 55 (given there were patients aged 49 in the BoI study). This scenario generates higher life years in the IDM arm and hence reduced life years gained fpr pegzilarginase. The model was also sensitive to the weight ratio of ARG1-D patients vs the general population (which was changed to assume the same weight as the general population) as this determines the total dose of pegzilarginase required and hence the drug costs.

The aforementioned scenarios increase the weighted ICER by 19 to 131%. The remaining scenario analyses impacted the weighted ICER by less than 14%.

B.3.11 Subgroup analysis

No subgroups were specified within the final NICE scope, therefore none are presented here.

Table 63: Results of scenario analyses

Scenario	Base case setting	Scenario setting	Incremental costs	Incremental QALYs	QALY weight	Weighted incremental QALYs	ICER	Weighted ICER
Base case			[redacted]	[redacted]	[redacted]	[redacted]	**£871,279**	**£298,565**
Baseline GMFCS distribution and age	PEACE + Phase I/2 + BoI pooled (and age 13)	Phase I/2 (and age 15.1)	[redacted]	[redacted]	[redacted]	[redacted]	£822,972	£274,591
Duration of improvement in GMFCS	36 months	24 months	[redacted]	[redacted]	[redacted]	[redacted]	£925,891	£336,568
		48 months	[redacted]	[redacted]	[redacted]	[redacted]	£833,737	£277,912
Long-term GMFCS progression rate	No progression	90% reduction in GMFCS progression	[redacted]	[redacted]	[redacted]	[redacted]	£1,037,472	£476,586
		80% reduction in GMFCS progression	[redacted]	[redacted]	[redacted]	[redacted]	£1,186,973	£690,643
Weight ratio of ARG1-D patient vs general population	[redacted] for paediatric, [redacted] for adult	Same as general population	[redacted]	[redacted]	[redacted]	[redacted]	£1,035,480	£354,833
GMFCS health state utility values	ARG-1D patient survey	X-ALD	[redacted]	[redacted]	[redacted]	[redacted]	£790,203	£263,401
		MLD	[redacted]	[redacted]	[redacted]	[redacted]	£790,630	£263,543
Cognitive decline disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	£859,017	£286,599
Carer disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	£853,548	£285,149
Utility gain from improved diet	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	£885,391	£308,156

Drug costs	Dose banding	Wastage	[redacted]	[redacted]	[redacted]	[redacted]	£923,317	£316,397
Perspective	NHS and PSS	Societal	[redacted]	[redacted]	[redacted]	[redacted]	£883,762	£302,843
Age at which all IDM patients are dead	All IDM patients are dead by age 35	All IDM patients are dead by age 55	[redacted]	[redacted]	[redacted]	[redacted]	£987,963	£367,553

B.3.12 Benefits not captured in the QALY calculation

Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health

Patients with ARG1-D, being physically and/or mentally disabled, are not anticipated to achieve the employment rates of the general population. There are therefore significant productivity losses than can be offset by offering ARG1-D patients a treatment which may prevent disability and permit a normal working lifestyle.

The costs (or cost savings) to government bodies other than the NHS

Patients with ARG1-D can suffer from neuromotor and/or neurocognitive disability. This may lead to the requirement for schooling tailored to children with special needs, with additional staffing requirements and/or equipment. In the BoI survey (46), 9 patients (43%) had received or did receive specialized schooling (which has been captured within the health state costs in Section B.3.5.2.1).

The costs borne by patients that are not reimbursed by the NHS

Out of pocket expenses might include mobility equipment, home adaptations, transportation, supportive therapy such as speech therapy, extensive physiotherapy and counselling.

Estimates of time spent by family members providing care. Describe and justify the valuation methods used

In the BoI survey (46), seven out of 16 caregivers (44%) were employed, whereof three (43%) full-time and four (57%) part-time. Four caregivers (25%) had reduced their employment and three (19%) had stopped working due to caregiving. Only one of the caregivers who had reduced or stopped working due to caregiving reported that their child received professional caregiving. The symptom severity was high among patients to caregivers who had stopped working. Two caregivers (12.5%) had taken time off from work due to caregiving during the last four weeks. The mean impact on productivity while at work (presenteeism) was reported as 2.7 on average on a scale

from 0 (no impact) to 10 (full impact). The mean impact on daily activities was slightly higher, with 3.8 on average.

Production losses of caregivers were estimated in the BoI survey using the human capital approach, i.e., value according to gross wage and payroll taxes. Production loss calculation for patients was primarily based on data on sick-leave or early retirement. For caregivers, production loss was calculated based on data on time taken off from work or stopped/reduced employment. The calculations were based on an assumption that the caregivers would have worked full time if the patients did not have ARG1-D. Family caregiving was valued according to the opportunity cost approach where value of lost leisure time was assumed to correspond to the net wage. Family caregiver expenses were estimated to range between £995 and £6,188 per patient by GMFCS state and caregiver production losses were estimated to range between £11,220 to £59,840 by GMFCS state.

The impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area, including any planned or ongoing research initiatives relating to the treatment or disease area

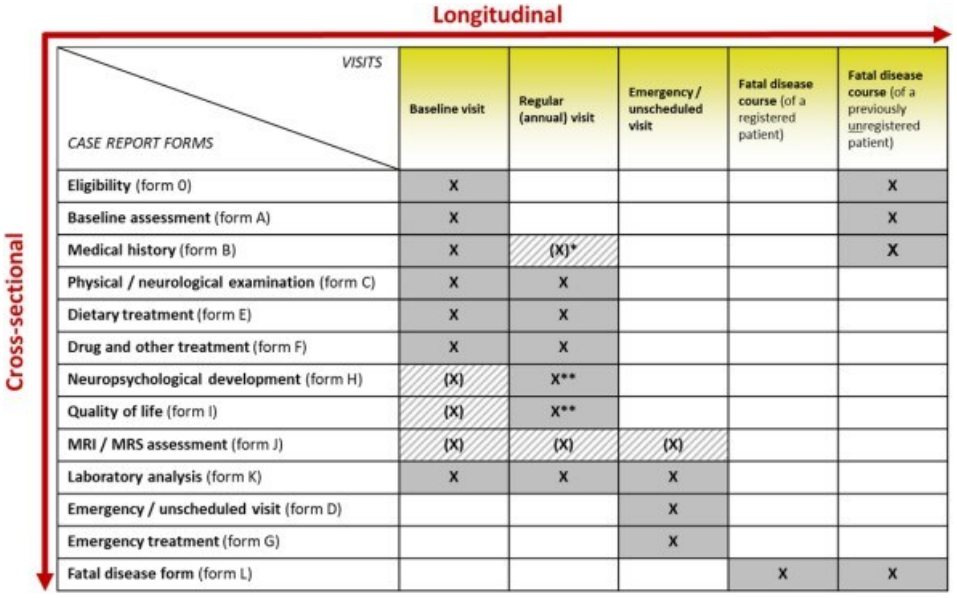
As an ultra-rare disease, little data exists regarding natural history, The PEACE trial double-blind period, being very short, can contribute little to natural history knowledge base, but follow-up of patients treated with pegzilarginase was, conversely, extensive, with some patients having nearly 4 years of follow-up data.

Any plans for creating a patient registry (if one does not currently exist) or collection of clinical effectiveness data over the next 5 years and how this will be reviewed

Post launch, real-world-data on ARG1-D patients and treatment with pegzilarginase will be collected within the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD). The E-IMD is an established patient-based registry including patients with organic acidurias and urea cycle disorders. Immedica has a pre-existing collaboration with the E-IMD and has initiated discussions with the E-IMD on collaboration with regards to a project on ARG1-D and pegzilarginase. The E-IMD registry comprises collection of a substantial amount of non-interventional disease

related data and allows for cross-sectional as well as longitudinal analyses (see Figure 34). Pegzilarginase will be added to the E-IMD registry's list of collected variables, facilitating real-world data collection in ARG1-D.

Figure 34: Schematic overview of the E-IMD registry design



VISITS / CASE REPORT FORMS	Baseline visit	Regular (annual) visit	Emergency / unscheduled visit	Fatal disease course (of a registered patient)	Fatal disease course (of a previously unregistered patient)
Eligibility (form 0)	X				X
Baseline assessment (form A)	X				X
Medical history (form B)	X	(X)*			X
Physical / neurological examination (form C)	X	X			
Dietary treatment (form E)	X	X			
Drug and other treatment (form F)	X	X			
Neuropsychological development (form H)	(X)	X**			
Quality of life (form I)	(X)	X**			
MRI / MRS assessment (form J)	(X)	(X)	(X)		
Laboratory analysis (form K)	X	X	X		
Emergency / unscheduled visit (form D)			X		
Emergency treatment (form G)			X		
Fatal disease form (form L)				X	X

* only if update is required; ** at least once during the course of the project; In brackets, optional tasks for visits

The expertise and additional infrastructure required to ensure safe and effective use of the technology and equiable access for all patients

No additional expertise of infrastructure is anticipated to be required; treatment with pegzilarginase can be integrated seamlessly into the existing metabolic disease specialised service, including homecare delivery of some prescribed medicines.

B.3.13 Validation

B.3.13.1. Validation of cost-effectiveness analysis

The model functionality and calculations were verified by a senior health economist not involved in constructing the pegzilarginase project, through use of an internal model quality control (QC) checklist (which can be provided on request).

Clinical validation of the model results poses enormous challenges with such a rare disease. As previously explained, no published or unpublished natural history data were available to inform model progression rates or mortality and our only clear point

of reference is that few ARG1-D patients over the age of 40 appear to be alive in Europe.

During the conceptual modelling stage, 3 clinicians were asked to validate the proposed model structure; 2 clinicians managed paediatric patients and one managed adult patients. The number of patients under their care ranged from none currently (but 10-12 in the last 10 years) to 9. It was apparent during conceptual model validation that clinician opinion varied widely, reflecting the heterogeneity in symptoms and progression of this disease. For example, some clinicians stated that children were at higher risk of mortality from hyperammonaemia whereas others stated that adults were more susceptible. Another example is lack of agreement regarding the speed of progression from one GMFCS health state to another (see Table 64 below). If we set our model such that 100% of patients begin in GMFCS I, 3.0 years are spent in GMFCS I, 3.2 in GMFCS II, and less than 1 in other health states on IDM. Thus, this lies within the bounds of the shortest progression times cited by the clinical experts. However, given so much range between responses, due to the rarity and heterogeneity of the disease, it is unclear to what extent clinician opinion can contribute to model validation.

Regarding overall survival, our economic model was calibrated such that nearly all patients were dead by age 40, which aligns with the observation in practice and with the age of patients recruited to PEACE (which had no upper age limit).

Table 64: Clinician elicitation regarding speed of progression

Clinician	Clinician patient cohort	Shortest time period to progress from GMFCS I to V	Longest time period to progress from GMFCS I to V
Clinician 1	Adult	Patients can progress from using handheld devices to limited self-mobility within 2-3 years (GMFCS 2 to GMFCS 4). For the remainder of the health states (GMFCS 3 to GMFCS 5), a speed of progression of 3-4 years between each stage is possible.	A slow decline was considered to be 5-6 years.
Clinician 2	Paediatric	Shortest time period was cited as 6-7 years.	Longest time period was cited as 20-25 years.
Clinician 3	Paediatric	Shortest time period was cited as 'a few years', without quantification.	Longest time period was cited as 'decades' and referred to Patient A who is 17 and is still able to walk without any mobility aids.

B.3.14 Interpretation and conclusions of economic evidence

This *de novo* economic analysis was required as there were no published cost effectiveness analyses, in any jurisdiction that we are aware of, in ARG1-D.

As discussed in Section B.1.3.1, the population in England is anticipated to be approximately [redacted] paediatric and [redacted] adult, which contrasts with 80% under 17 in our base case. A scenario analysis implemented in Section B.3.10.3, whereby the Phase I/2 trial characteristics were modelled (56% under 17) had a substantial impact on the ICER, but this was primarily a result of the change in GMFCS state distribution used in this scenario rather than the increased age (15 years old in Phase 1/2 vs 13 years old in the pooled base case), which had minimal impact when changed on its own. The GMFCS health state of the prevalent patients in England is unknown, thus it is unclear exactly what the cost effectiveness of pegzilarginase would be in this population. Notwithstanding this, we believe the analysis to be relevant and applicable to all patient groups likely to be offered pegzilarginase in clinical practice.

Key strengths of the analysis include a robust randomised placebo-controlled clinical study with significant follow-up time for patients receiving pegzilarginase, which

contributed significant data to the longer-term assumption that patient mobility and cognitive scores improved and/or stabilise through treatment with pegzilarginase. Clinical trial data were supplemented with registry data for the modelling of HACs, a key cause of mortality in pegzilarginase patients.

Limitations of the analysis include the lack of availability of a natural history study to inform progression rates on IDM. We employed a pragmatic approach using all the available baseline data to demonstrate a relationship between GMFM D&E score and age, and using all the available baseline and follow-up data to demonstrate a relationship between GMFM D&E score and GMFCS health state, the latter being consistent with the available evidence in CP (113-115). The progression predictions resulting from this approach fell within the bounds of estimates of time to progression from GMFCS I to GMFCS V provided by clinicians.

A further limitation was a lack of observations in GMFCS V to inform the ordered logistic regression of GMFCS vs. GMFC. This results in an extremely low rate of movement to the worst GMFCS health states and their low HRQoL and mortality. Cognisant of the NICE reference case, we have used the ARG1-D patient survey utility values for GMFCS states in the base case. However, as discussed in section B.3.3.1.2.d, very few patients in the IDM arm transition to GMFCS V and its low utility values. Furthermore, it should be noted that the ARG1-D utility values for poorer health states are higher than those of GMFCS-like health states in other rare diseases such as MLD and X-ALD. This almost certainly leads to an overprediction of QALYs in the IDM arm and an inflation of the ICER.

While mortality data in ARG1-D were sparse, perhaps the most compelling evidence of early mortality is the absence of any patient over the age of 50 in the BoI and trial cohorts and very few patients over the age of 30. We used a method which incorporated SMRs, the known distribution of patients alive and mortality from HACs to predict mortality of ARG1-D patients, which applied calibrated SMR weights to general population mortality rates. However, we believe that this approach was necessitated because, as discussed in section B.3.3.1.2.d, a key weakness of the analysis was the lack of observations in the trial data in GMFCS V and few in GMFCS IV, which substantially reduces the patient movements to health states associated with

high excess mortality. This may explain why such high SMRs were required to predict realistic mortality for ARG1-D patients. This calibration method predicted a median survival of approximately 18 years, which is slightly higher than that reported in the available literature (45), and results in nearly all patients being dead by age 35. We believe this to be the most robust method of estimating survival in the absence of data in ARG1-D patients.

B.3.15 Cost to the NHS and Personal Social Services

A total of [redacted] patients are estimated to be eligible for treatment with pegzilarginase in England. Due to the ultra-rare nature of ARG1-D, the number of eligible patients is not expected to grow over a 5-year period. Given the scarcity of treatment options available to patients with ARG1-D, the expected uptake of pegzilarginase is high, estimated to be 60% in year 1, 70% in year 2 and 80% in years 3 to 5. The estimated budget impact (with PAS applied) of pegzilarginase is [redacted] in year 1, rising slightly each year as patient uptake increases, to [redacted] in year 5.

A detailed breakdown of the technology costs and all resource implications associated with pegzilarginase is provided in the stand-alone budget impact assessment document that has been submitted as part of this appraisal.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: PEACE summary data tables

Appendix N: Placebo/pegzilarginase LTE results

Appendix O: Study 102A summary data tables

Appendix P: Study 101A clinical effectiveness and safety

Appendix Q: Summary of all the base case values in the cost effectiveness analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Summary of Information for Patients (SIP)

March 2024

File name	Version	Contains confidential information	Date
ID4029 Pegzilarginase vi. NICE SIP [noCON]_27.03.2024	1.0	Yes	27/03/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Pegzilarginase (Loargys®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Arginase 1 deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Pegzilarginase received marketing authorisation from the Medicines and Healthcare products Regulatory Agency on 20th December 2023 (PLGB 53487/0007) (1). Further details can be found in Section B1.2 of the company evidence submission. https://mhraproducts4853.blob.core.windows.net/docs/bc42347f14c6799e0e1fbf27c4668a9e5b3dbda1

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Immedica Pharma UK provide financial support to Metabolic Support UK in the form of an annual grant to cover ongoing running costs and the organisation of their annual UK conference.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

ARG1-D is an ultra-rare and debilitating metabolic disease that worsens over time. ARG1-D is caused by a fault in a gene that limits the body's ability to break down arginine, resulting in persistently high levels in the blood (2). Arginine is a vital amino acid that plays an important role in the body, but elevated arginine levels can have a devastating and progressive impact on a patient's ability to complete daily activities (2-4).

The excessive accumulation of arginine in the blood and cerebrospinal fluid (the clear fluid that surrounds the brain and spinal cord of all vertebrates) causes the development of key disease manifestations including:

- progressive spasticity (stiff or rigid muscles that can interfere with walking, movement, speech, and many other activities of daily living),
- developmental delay (not reaching developmental milestones at the expected age, affecting one or more areas of growth, such as cognitive, motor, social or emotional development),
- seizures (a sudden, uncontrolled burse of electrical activity in the brain),
- and potential early death (2-4).

While the way that patients experience the symptoms of ARG1-D varies, symptoms usually become apparent within the first five years of life, and worsen over time with increasing exposure to high blood arginine and its metabolites over time (5, 6).

The most common feature of ARG1-D is prominent and progressive lower-limb spasticity seen in early childhood, leading to gait abnormalities, difficulty walking and climbing stairs, and the need for assistive devices (2, 7). Patients typically have some form of lower-limb spasticity, with approximately 60-75% of patients having spasticity at initial presentation, which increases with extended follow-up (8). Most patients ultimately develop impairment of gross motor function and mobility, which may lead to them not being able to walk or becoming reliant on a wheelchair (9, 10). Patients may require substantial levels of assistance in their home by caregivers (11).

In England and Wales, there are 22 known patients living with ARG1-D (12). These patients are at a greater risk of dying earlier compared to the general population. Few patients are described in the literature who survive far into adulthood.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

A diagnosis of ARG1-D can be made with molecular genetic testing, which will require a blood test. Patients may have a genetic test earlier if they have a family history or ARG1-D. Patients will not need to have any extra diagnostic tests to be treated with pegzilarginase.

Delays in diagnosis of ARG1-D often occur due to similarities in clinical profile with other developmental diseases, including cerebral palsy and hereditary spastic diplegia, and a lack of disease awareness. An average delay in diagnosis of 6.1 years was reported in a UK-based study of six patients with ARG1-D (13).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are no UK-specific clinical guidelines for the diagnosis and management of ARG1-D. Current international guidelines for ARG1-D focus on reduction of blood arginine to levels of <200 µM, and ideally to within the normal range (≥40 -≤115 µM), as the main treatment goal (14). However, there are no approved treatments that specifically reduce arginine levels in patients with ARG1-D, and long-term outcomes are poor.

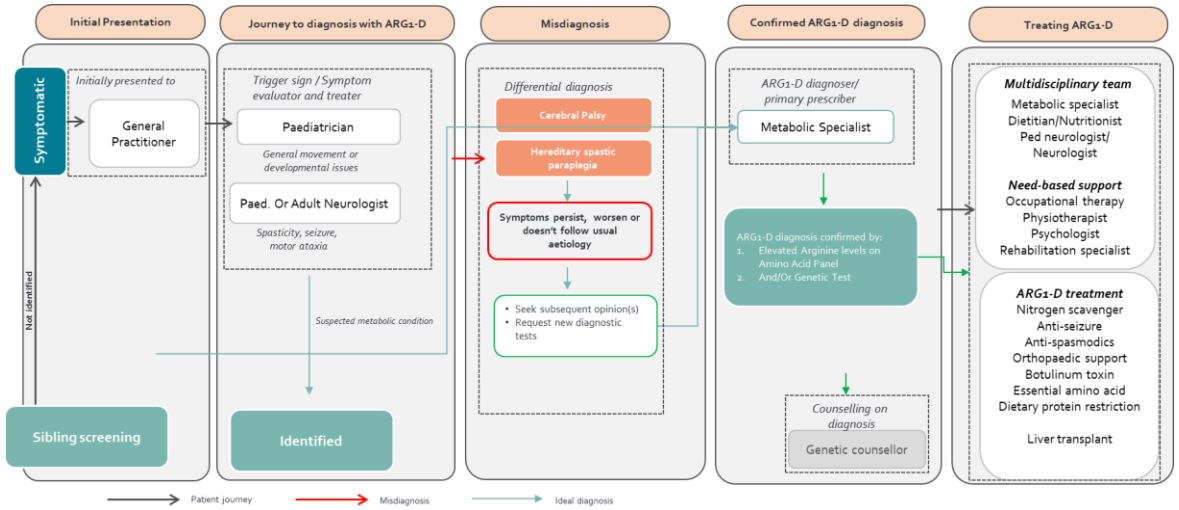
Current management approaches for ARG1-D include individualised disease management, which consists of individualised combinations of dietary protein restriction, amino acid supplementation, and symptomatic treatments to manage other clinical symptoms of the disease such as ammonia scavenging treatments to help control ammonia levels (14).

Dietary restriction can produce modest reductions in blood arginine levels, however reducing blood arginine to the guideline-recommended level is rarely achieved, partly because a substantial proportion of arginine is produced by the body itself (15, 16). In addition, the low protein diet is often difficult to maintain and manage, especially in growing children, resulting in poor compliance (13). Liver transplantation has been reported to achieve disease normalisation in some patients (17); however, transplantation is available only to a small fraction of patients and carries a significant risk of further medical problems and death. There is also no evidence that liver transplantation will reverse symptoms and the underlying damage that has already taken place.

Patients with ARG1-D require a range of continuous therapies and ongoing monitoring to manage manifestations, and often require surgery to manage muscular issues (13).

Other common medications include anti-epileptics for seizure control, anti-spasmodics for spasticity, and medical foods to aid nutritional status. The use of medical devices including ankle-foot orthoses, arm crutches, canes, walkers, and wheelchairs is common (9, 10).

Given the diversity of symptoms associated with ARG1-D, patients require support from a varied team of specialists, including metabolic specialists, paediatricians, dieticians, and neurologists (18).



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Immedica conducted a descriptive survey in a cohort of current ARG1-D patients to estimate the burden of illness in Europe from a societal perspective. Since ARG1-D is an ultra-rare disease, the study included all patients and caregivers who across participating clinics in the UK, France, Portugal and Spain. The questionnaire included questions on demographic variables, disease-related symptoms, healthcare resource use, and sick-leave (adult patients only) during the last 12 months, measures of caregiver burden, and health-related quality of life using the EQ-5D-5L (11).

Key findings from the survey are listed below:

- Cognitive abilities varied amongst patients; few patients had severe problems or no ability across several dimensions, including reading and writing, play and leisure, stressful situations and dimensions related to the ability to learn, think, and solve problems.
- Regarding diet adherence, a majority of patients could follow dietary guidelines at most or all of their meals, but many found the low protein diet difficult to follow. Some patients had problems with self-feeding.
- Family caregivers spent substantial amounts of time assisting with daily activities and transportation the most common types of assistance provided. Some patients also

received professional assistance to aid with daily activities and transportation, amongst others.

- Just under half of patients used aids or devices to assist mobility, whereof some patients were using a wheelchair.
- Most ARG1-D patients experienced problems with the ability to conduct daily activities, mobility, and pain/discomfort.
- Many paediatric patients don't attend mainstream education; just under half of paediatric patients had received/did receive specialised education.
- None of the adult patients were employed, highlighting a substantial loss of productivity associated with adult ARG1-D patients.
- With regards to caregivers, half were unemployed, with one-third stopping work due to caregiving. Of the caregivers who were still employed, over half had to reduce work hours in order to be a caregiver.
- Most ARG1-D caregivers experienced problems with anxiety/depression, pain/discomfort, and the ability to conduct daily activities, albeit the number of observations was small.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Patients with ARG1-D have low or absent levels of an enzyme called arginase. Arginase is one of six enzymes that play a role in the breakdown and removal of nitrogen from the body, a process known as the urea cycle. This enzyme helps the body control levels of arginine. If arginine is not controlled, it can build up in the body and cause damage to the brain and other organs.

The active substance in Loargys, pegzilarginase, acts similarly to the natural enzyme arginase-1, which is lacking or not working properly in patients with ARG1D-D. Treatment with pegzilarginase has been shown to rapidly and sustainably lower levels of arginine and its toxic metabolites, potentially preventing toxic effects to the brain and other organs. It is the first and only disease modifying treatment for patients with ARG1-D.

Patient Information Leaflet:
https://mhraproducts4853.blob.core.windows.net/docs/84fd0a0cd5029bdd3d0b810e60e836b39731674e

Summary of Product Characteristics:
https://mhraproducts4853.blob.core.windows.net/docs/bc42347f14c6799e0e1fbf27c4668a9e5b3dbda1

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Pegzilarginase is to be used in combination with other ways to manage the disease, which may vary from patient to patient. These may include:

- A diet that is low in protein
- Dietary supplements with essential amino acids
- Medicines to manage other symptoms of the disease, including medicines that lower levels of ammonia in your body (collectively known as ammonia scavenger therapies), control seizures (collectively known as anti-epileptics), and reduce spasticity (collectively known as anti-spasmodics)

ARG1-D treatment is highly individualised, and will depend on the range and severity of symptoms of the presenting patient. This is true with and without pegzilarginase as an option, and the pegzilarginase trial includes the use of individualised disease management in its design.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Pegzilarginase is intended for the long-term management of ARG1-D, to be used along with other ways to manage the disease, including a diet that is low in protein, dietary supplements with essential amino acids and medicines to manage symptoms of the disease, such as medicines that lower the levels of ammonia. Treatment with pegzilarginase will be started and supervised by a healthcare professional experienced in the management of patients with inherited metabolic diseases (1).

Pegzilarginase is administered as an infusion (drip) or as an injection under the skin, as considered appropriate by a healthcare professional. The recommended initial dose of pegzilarginase is 0.1 mg/kg per week, although the dose may be increased or decreased by 0.05 mg/kg increments to keep blood arginine levels under control, if deemed appropriate by a healthcare professional. Blood arginine levels will be monitored through regular blood tests alongside standard clinical monitoring visits, with intervals no longer than 3-6 months (1).

If deemed appropriate by a healthcare professional, pegzilarginase may be administered at home as an injection under the skin. Flexibility with regards to the mode and setting of administration allows for treatment to be tailored according to the requirements of the patient and/or caregiver. Furthermore, for patients who are able to do so (in the opinion of a healthcare professional), patients and/or their caregivers may be able to inject pegzilarginase themselves after training from a healthcare professional. This can minimise disruption to day-to-day routines through avoiding hospital attendance for drug administration, thereby improving patient and caregiver satisfaction (1).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
PEACE (otherwise known as CAEB1102-300A) was the pivotal trial that assessed the safety and efficacy of pegzilarginase with individualised disease management, compared to individualised disease management alone, in ARG1-D patients aged 2 years and above. Key inclusion criteria were: • patients aged ≥2 years; • documented ARG1-D diagnosis; • blood arginine ≥250 µM, and impairment on any secondary functional mobility assessment. Key exclusion criteria included: • symptomatic hyperammonaemia (ammonia ≥100 µM requiring acute care or hospitalisation) within 6 weeks before first pegzilarginase dose; • extreme mobility impairment (i.e., unable to complete assessments); • medical conditions or comorbidities that would preclude study compliance or data interpretation (e.g., severe intellectual disability); • prior liver or hematopoietic transplant; • or participation in prior pegzilarginase study. The study included 32 patients and took place in 19 study sites across the USA, UK, France, Austria, Canada, Germany and Italy. The study consisted of three distinct periods: • A 3-4 week screening period, which collected all necessary information to ensure that enrolled patients met the study eligibility criteria • A randomised, double-blind period of 24 weeks, during which patients were randomly assigned to treatment with pegzilarginase or placebo (a dummy treatment). Randomisation occurred in a 2:1 ratio, meaning that 2/3 of eligible patients were allocated treatment with pegzilarginase with individualised disease management, with the remainder allocated to placebo plus individualised disease management. Patients and trial staff were unaware of what treatment was being provided, hence the study is described as 'double-blinded'. • An open-label period of approximately 150 weeks, in which all patients received pegzilarginase. Patients previously randomised to receive placebo transitioned to treatment with pegzilarginase, while those initially randomised to pegzilarginase continued treatment until the end of the study. The last patient visit was on February 1st 2023. Further information about the PEACE study, including the final analysis of the 24-week double-blind period, and interim results from the long-term open-label period up to Week 24, can be accessed here (data cut-off date: March 24th 2022): https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00582-5/fulltext In addition, Study 102A (otherwise known as CAEB1102-102A) was an open-label trial that evaluated the long-term safety and efficacy of pegzilarginase in conjunction with individualised disease management for up to 4 years in patients with ARG1-D. Eligible patients were ≥2 years old with a documented diagnosis of ARG1-D, and completed participation in the parent study (Study 101A; CAEB1102-101A) without experiencing any significant adverse event. The study included 14 patients and took place in 8 study sites across the US, UK, Portugal and Canada. Study 102A was

an open-label, single-arm study, meaning patients and staff were aware of the treatment that was being administered and all patients received pegzilarginase. Study 102A was completed on December 15th 2022.

Further information about Study 102A, including interim results up to Week 96 of the study, can be accessed here: https://www.gimopen.org/article/S2949-7744(23)00009-2/pdf

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the pivotal PEACE study, pegzilarginase was compared with placebo in a study of 32 adults and children with ARG1-D. The main measure of effectiveness was the change in the level of arginine in the blood (plasma arginine) after 24 weeks of treatment. The study showed that pegzilarginase significantly reduced plasma arginine after 24 weeks of treatment, improving levels to better than those recommended in the guidelines in 90.5% of patients. These levels were achieved and maintained at normal levels (≥40 -≤115 µM). By contrast, no patient treated with placebo achieved the guideline-recommended levels of plasma arginine (<200 µM) (see Company Evidence Submission, Section B.2.6.1.1.a, page 75) (19).

Furthermore, patients treated with pegzilarginase met or exceeded pre-defined and literature-based thresholds for minimum clinically important differences, suggesting clinically meaningful improvements in functional mobility. Importantly, considering the progressive nature of ARG1-D, these improvements continued to increase in magnitude with long-term treatment. At Week 24, 47.1% of assessed patients treated with pegzilarginase met the criteria for response in response in ≥ 2 neuromotor function assessments along with normalisation of plasma arginine levels, with 6 of the responders having no worsening in any assessments. Without treatment with pegzilarginase, no patients met clinical response criteria in 2 or more clinical outcomes (see Company Evidence Submission, Section B.2.6.1.1.d.i, page 85) (19).

During the open-label extension, patients who previously received pegzilarginase demonstrated sustained improvements in plasma arginine levels and functional mobility assessments. Patients initially randomised to placebo who transitioned to pegzilarginase in the open-label extension period also showed similar reductions in mean plasma arginine levels (19).

In Study 102A, treatment with weekly pegzilarginase resulted in pronounced plasma arginine reduction and clinically meaningful improvements in functional mobility. After 2 years of treatment, 100% of patients had plasma arginine levels below guideline-recommended levels (<200 µM), while 77% normalised plasma arginine levels (≥40 -≤115 µM) (See Company Evidence Submission, Section B.2.6.2.1, page 95) (20). Clinically important response criteria were met or exceeded on assessments of functional mobility tasks involving aided walking, running, jumping, sitting and standing. The magnitude of improvement increased with longer duration of treatment. At an individual patient level, 10 of 12 evaluable patients met or exceeded the thresholds of clinically important response on ≥1 mobility assessment after 2 years. The remaining were clinically stable and did not decline in functional mobility (see Company Evidence Submission, Section B.2.6.2.6, page 102) (20).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient quality of life was measured using the Paediatric Quality of Life Inventory (PedsQL), a survey which measures the health-related quality of life across four different items: physical functioning, emotional functioning, social functioning, and school functioning). For each item, a score of 0-100 is generated, with higher values indicating a better quality of life.

At Week 24 of the double-blind period, patients achieved a minimal clinically important difference in emotional functioning, whilst a numerical improvement in social functioning was also observed. By contrast, patients treated with placebo observed a decrease in emotional functioning and social functioning scores. Across both treatment groups, a decrease in physical functioning and school functioning scores were observed, albeit the decline was more pronounced in patients treated with placebo versus pegzilarginase (see Company Evidence Submission, Section B.2.6.1.1.d.iv, page 88) (21).

Caregiver quality of life was also measured, and a small numerical reduction in ZBI-12 scores was observed in the pegzilarginase group at Week 24 of the double-blind period, indicating slight improvement in caregiver burden (see Company Evidence Submission, Section B.2.6.1.1.d.vi, page 89) (21).

Data on patient health-related quality of life was limited in Study 102A, with no obvious trends observed over time in the Patient-Reported Outcomes Measurement Information System (PROMIS) and PedsQL scores (see Company Evidence Submission, Sections B.2.6.2.9 & B.2.6.2.10, page 104). Caregiver burden scores, as measured by ZBI-12, remained similar over time through Week 96 (see Company Evidence Submission, Section B.2.6.1.11, page 105) (22).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Pegzilarginase was well-tolerated, with side-effects being mostly short-lived, mild/moderate in severity, and either self-limiting or manageable with standard medical care.

In the 24-week double-blind period of the study, the most common side effects reported were vomiting (29%), cough (19%), and pyrexia (19%). By contrast, nausea (36%), hyperammonaemia (27%), vomiting (27%) and abdominal pain (27%) were the most frequently reported side-effects amongst patients receiving treatment with placebo (19). More side-effects were reported during the open-label extension, however this was expected given the longer period of observation (see Company Evidence Submission, Section B.2.10.1.3, page 112) (21).

During the double-blind period, one patient experienced a serious adverse event related to pezilarginase. The event of hyperammonaemic encephalopathy in the pegzilarginase arm

occurred during concurrent urinary tract infection and constipation, was moderate in severity, not life-threatening, and was resolved within one week (19).

Unlike other enzyme replacement therapies, hypersensitivity reactions and injection site reactions were infrequently reported. During the double-blind period, 10% of patients treated with pegzilarginase experienced non-serious, mild/moderate hypersensitivity reactions that were managed with antihistamines. These occurred within the first 8 weeks of the study, and no additional events were recorded thereafter (19). Injection site reactions were reported for few patients in the open-label long-term extension. All incidences of injection site reactions were mild and resolved with without dose change (see Company Evidence Submission, Section B.2.10.1.5, page 114) (21).

After 2 years of treatment in Study 102A, the most common side-effects for patients treated with pegzilarginase were cough (57%), vomiting (57%), and headache (50%). Side effects were generally mild/moderate, non-serious, short-lived, and manageable. No hypersensitivity reactions were reported, while three patients experienced mild injection site reactions. Hyperammonaemia was reported for 6 patients; 4 of 6 patients had a history of hyperammonaemia (20).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Pegzilarginase demonstrates rapid, statistically significant, and sustained efficacy in plasma arginine levels, allowing greatly improved control of arginine levels relative to what can be achieved with current treatment options.
- Pegzilarginase is the only disease-modifying treatment to normalise plasma arginine levels in the management of ARG1-D. Normalisation of plasma arginine was previously unachievable with current individualised disease management, as reflected by the multiple-fold elevation of plasma arginine in the trial cohort at baseline and extensive documentation in the literature.
- Patients treated with pegzilarginase were able to increase their caloric intake, as well as total consumed protein, without an impact on their ability to maintain normal pArg levels (≥40 - ≤115 μM). Given that current dietary restrictions are frequently described as unpalatable, difficult to comply with, and a contributor to poorer quality of life among patients and caregivers, this could translate to a benefit in the treatment of ARG1-D.
- Pegzilarginase produced meaningful clinical improvements in functional mobility. With long-term treatment, the size of improvements increased and surpassed thresholds for clinically important response (substantially for some patients). The increasing improvement with longer-term treatment suggests potential to stop progression of manifestations, reduce impact of prior disease progression, and improve functional mobility.
- Pegzilarginase can be administered via intravenous infusion or subcutaneous injection, in a hospital or home setting (if deemed appropriate), allowing treatment to be tailored according to the requirements of the patient and/or caregiver. For patients and/or caregivers who are deemed appropriate to do so, the self-administration of pegzilarginase could minimise disruption to day-to-day routines through avoiding hospital attendance.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments
• Pegzilarginase addresses the underlying cause of the disease by normalising arginine levels, but does not treat symptoms of ARG1-D. Hence, individualised disease management, which may include a low protein diet, dietary supplements with essential amino acids, and ammonia scavenger therapies, may still be required alongside pegzilarginase treatment. • Pegzilarginase is intended for administration by infusion (drip) or an injection under the skin by a healthcare professional, which will require an additional hospital visit, in addition to standard clinical monitoring visits, for at least the first 8 weeks of treatment. As a result, during this period, treatment with pegzilarginase will initially involve more visits to hospital.

3i) Value and economic considerations

Introduction for patients: Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model. In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on: • The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?) • If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)? • How the condition, taking the new treatment compared with current treatments affects your quality of life.
The manufacturer of pegzilarginase built an economic model in Microsoft Excel to explore the cost-effectiveness of pegzilarginase when compared with individualised disease management in adults, adolescents, and children aged 2 years and older, with Arginase 1 deficiency (ARG1-D). The economic model shows the different ways in which a patient's health can change after treatment. It compared the total costs (drugs and healthcare resource use) generated by pegzilarginase and individualised disease management as well as the survival and quality of life over their lifetime. The last two are combined to produce a measure called the quality-adjusted life year (QALY). One QALY is equal to one year of life in perfect health. The model used data from the PEACE and 101A/102A trials, and the key input was response to treatment measured through the Gross Motor Function Classification System (GMFCS) score. The GMFCS is a five-level classification that was developed for use with children with cerebral palsy, which presents with many similar motor issues as ARG1-D. The GMFCS assigns gross motor function capabilities based on movements such as sitting, walking, and use of mobility devices

with five categories ranging from I (most functional) to V (transported in wheelchair in all settings). The model also included factors such as hyperammonaemic crises (abnormally high levels of ammonia), seizures, nausea, and mortality.

The results of the economic model showed that pegzilarginase is associated with increased QALYs compared with individualised disease management, but with a higher cost. Patients receiving pegzilarginase had a mean increase in survival of 42.5 years, with an incremental cost effectiveness ratio was approximately £298,000.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

A key clinical goal, rarely obtainable with the current individualised management treatment approach, is to achieve guideline-recommended levels of plasma arginine, and ideally to normal levels, although this has generally not been attainable in this patient population to date. Consequently, patients continue to experience disease progression and succumb to early mortality.

Currently, patients with ARG1-D are not anticipated to achieve the employment rates of the general population, or may suffer from neuromotor and or/neurocognitive disability leading to requirement for tailored schooling and equipment. In addition, caregivers may also need to stop or reduce their employment.

Pegzilarginase represents the first and only disease-modifying treatment to normalise plasma arginine levels in the management of ARG1-D. By lowering and maintaining plasma arginine levels at normal levels in the long-term, patients have the potential to halt the progression of disease manifestations, reduce the impact of prior disease progression, and improve functional mobility.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

ARG1-D predominantly affects individuals from ethnic minority background in the UK. Immedica estimate that majority of patients managed in UK clinical practice are from ethnic minorities. A 20-year retrospective review of patient medical records at Great Ormond Street Hospital identified six patients from three unrelated families, all of whom were of Somali or Pakistani ethnicity.

Furthermore, ARG1-D is inherited autosomal recessive disease, meaning two copies of an abnormal gene must be present in order for the disease or trait to develop. Given the nature of the disease, the birth and population prevalence of the condition is highest in countries with a high prevalence of consanguineous parents (i.e., parents of the same blood origin). By contrast, countries with predominantly homogenous white European population and very low

consanguinity have the lowest birth and population prevalence rate of ARG1-D (23). Consanguinity was observed in two of three families included in the aforementioned study by Great Ormond Street Hospital (13).

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on the product characteristics and clinical effectiveness data for pegzilarginase:

- Summary of Product Characteristics: https://mhraproducts4853.blob.core.windows.net/docs/bc42347f14c6799e0e1fbf27c4668a9e5b3dbda1
- Patient Information Leaflet https://mhraproducts4853.blob.core.windows.net/docs/84fd0a0cd5029bdd3d0b810e60e836b39731674e
- UK Public Assessment Report: https://mhraproducts4853.blob.core.windows.net/docs/210d7d61f0fb614aba979d0ae124caa48ffdf6d9
- European Medicines Agency: https://www.ema.europa.eu/en/medicines/human/EPAR/loargys
- Efficacy and safety of pegzilarginase in arginase 1 deficiency (PEACE): a phase 3, randomized, double-blind, placebo-controlled, multi-centre trial: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00582-5
- Pegzilarginase demonstrates long-term, clinically meaningful improvements in functional mobility in ARG1-D: patient-level analysis from the Phase 3 PEACE trial: https://onlinelibrary.wiley.com/doi/10.1002/jimd.12668
- Clinical effect and safety profile of pegzilarginase in patients with arginase 1 deficiency: https://onlinelibrary.wiley.com/doi/10.1002/jimd.12343
- Long-term efficacy and safety of pegzilarginase for arginase 1 deficiency: 2 years of experience in the phase 2 extension study: https://www.sciencedirect.com/science/article/pii/S2949774423000092

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/

- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

2-Minute Walk Test (2MWT): Evaluates the distance travelled on a flat surface in two minutes (with bracing or assistive devices)

Argininase-1: Enzyme that catalyses the conversion of arginine to urea and ornithine in the final step of the urea cycle

Consanguinity: Kinship with a relative who is descended from a common ancestor

EQ-5D-5L: A survey that asks patients to mark how they are – generic, preference-based measure of health-related quality of life in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Gross Motor Function Classification System (GMFCS): Evaluates self-initiated movement with emphasis on sitting, walking, ascending stairs, and wheeled mobility, and classifies impairment from Level 1 to 5

Gross Motor Function, Part D (GMFM-D): Evaluates the level of unaided mobility with regards to sitting and standing (possible scores range from 0-39)

Gross Motor Function, Part E (GMFM-E): Evaluates the level of unaided mobility with regards to walking, running, and jumping (possible scores range from 0-72)

Hyperammonaemia: Ammonia ≥100 µM requiring acute care or hospitalisation

Hypersensitivity reaction: An allergic reaction

Paediatric Quality of Life Inventory (PedsQL): Brief measure of health-related quality of life in children and young people in 4 domains: emotional functioning, physical functioning, school functioning, and social functioning

Patient-Reported Outcomes Measurement Information System (PROMIS): A set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children living with chronic conditions

Pyrexia: Elevation of an individual's core temperature above 38C

Zarit Burden Interview Short 12 Items (ZBI-12): Evaluates health-related quality of life after a period of time of caregiving for patients with chronic disease

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Medicines and Healthcare products Regulatory Agency. Loargys | Summary of Product Characteristics 2023 [Available from: https://mhraproducts4853.blob.core.windows.net/docs/72ef9201a40c63d480c8c06ec3ce85dd931f57e2.

2. Sun A, Crombez EA, Wong D. Arginase Deficiency. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle

3. Iyer R, Jenkinson CP, Vockley JG, Kern RM, Grody WW, Cederbaum S. The human arginases and arginase deficiency. J Inherit Metab Dis. 1998;21 Suppl 1:86-100.

4. Sin YY, Baron G, Schulze A, Funk CD. Arginase-1 deficiency. J Mol Med (Berl). 2015;93(12):1287-96.

5. Carvalho DR, Brum JM, Speck-Martins CE, Ventura FD, Navarro MM, Coelho KE, et al. Clinical features and neurologic progression of hyperargininemia. Pediatr Neurol. 2012;46(6):369-74.

6. Huemer M, Carvalho DR, Brum JM, Ünal Ö, Coskun T, Weisfeld-Adams JD, et al. Clinical phenotype, biochemical profile, and treatment in 19 patients with arginase 1 deficiency. J Inherit Metab Dis. 2016;39(3):331-40.

7. Diez-Fernandez C, Rüfenacht V, Gemperle C, Fingerhut R, Häberle J. Mutations and common variants in the human arginase 1 (ARG1) gene: Impact on patients, diagnostics, and protein structure considerations. Hum Mutat. 2018;39(8):1029-50.

8. European Medicines Agency. Loargys | European Public Assessment Report 2023 [Available from: https://www.ema.europa.eu/en/documents/assessment-report/loargys-epar-public-assessment-report_en.pdf.

9. Brockstedt M, Smit LM, de Grauw AJ, van der Klei-van Moorsel JM, Jakobs C. A new case of hyperargininaemia: neurological and biochemical findings prior to and during dietary treatment. Eur J Pediatr. 1990;149(5):341-3.

10. Cederbaum SD, Moedjono SJ, Shaw KN, Carter M, Naylor E, Walzer M. Treatment of hyperargininaemia due to arginase deficiency with a chemically defined diet. J Inherit Metab Dis. 1982;5(2):95-9.

11. Immedica Pharma AB. Data on File - A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers 2023.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID4029 Pegzilarginase EAG clarification letter response [CON]_08.08.24	2.0	Yes	08/08/2024

Section A: Clarification on effectiveness data

Statistical questions

A1. Priority: Clarify why all patients are assumed to start with the same GMFM_DE score (75.9) when it is clear from Figure 26 of the company submission document B (CS doc B) that there is considerable heterogeneity in the relationship between age and GMFM DE, with an R^2-adjusted of below 0.10. Using the 75.9 value for all patients results in the predicted distribution at baseline being markedly different from the other estimates as shown in the plot.

Company response (updated): We had initially considered a simulation of GMFM DE stratified by starting GMFCS health state, whereby the predicted GMFCS distribution over time, conditional on starting GMFCS health state, was combined into a single distribution of GMFCS for the cohort. Given the substantial amounts of heterogeneity and poor model fit, we would have preferred that patients enter the model at their *observed* mean GMFM DE stratified by *observed* GMFCS category. However, GMFM DE was not captured in the burden of illness (BoI) study (1), therefore it would not be possible to incorporate the data from these patients, which contributed 25% of the base case model cohort.

Start of updated section

In addition to re-running the regressions using a fresh dataset (see Appendix A and Appendix B to these responses), we have updated the model to generate:

(1) A GMFM DE score over time, stratified by GMFCS.

The starting GMFM DE score by GMFCS health state was calculated as the mean GMFM DE score by GMFCS from the pooled PEACE/phase 1/2 baseline data ([redacted] for GMFCS I-IV, respectively)

(2) Transition probabilities by GMFCS at baseline

These are generated by applying the ordered logit model to the stratified GMFM DE scores. In contrast with the submitted model (where we assumed a coefficient for GMFCS IV to V for the ordered logit model), we now assume that transition probabilities for GMFCS IV to V are the same as for III to IV.

The transition probabilities stratified by GMFCS are then combined based on the weighted average of GMFCS distribution at baseline (see new sheet in the model called **Progression estimates**).

Using this approach results in a higher proportion of patients distributed in the GMFCS IV and V health states over the lifetime of the model (see Table 1). It also generates better cost effectiveness estimates (see Table 2), which additionally incorporate the Hernandez-Alava utility values, a phased HAC treatment effect (see question B18) and an SMR multiplier of 800 (see question B6), and removal of special schooling (see question B25).

Table 1: Time in GMFCS health states for IDM arm

	GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
Submitted model					
Time in state (years)	1.7	2.9	0.6	0.6	0.0
Proportion of time in state	29.0%	49.9%	9.6%	11.0%	0.5%
Updated model					
Time in state (years)	0.9	1.7	0.9	0.6	0.1
Proportion of time in state	21.4%	40.0%	22.2%	14.5%	1.9%

Key: GMFCS: Gross Motor Function Classification System.

In response to question A2 below we additionally consider an approach which circumvents the need for a prediction of GMFCS occupancy using the logistic regression, which renders use of the predicted mean GMFM DE score redundant.

Table 2. Updated results using logistic regression of GMFM DE stratified by GMFCS

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
Analysis stratified by GMFCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using Hernandez-Alava utility values. Includes lower HAC rate in double-blind period as per question B18 and SMR multiplier of 800 as per question B6.

End of updated section

A2. Priority: The current approach for calculating state occupancy from the ordered logistic model results in the transition probabilities being dependent on both state occupancy and the age of the patient. For example, the transition probability of moving from GMFCS-III to GMFCS-IV is essentially [redacted] in the early cycles as no patients are predicted to start the model in GMFCS-III; as patients age, and more are estimated to be in GMFCS-III, the transition probabilities increase. Clarify whether this was the intention, and if so, what clinical support you had for this approach. We also note that the transition probabilities for exiting GMFCS-IV is identical to leaving GMFCS-III. Clarify whether there was clinical support for this approach. Commonly, cohort models without tunnel states (as this model is) would have a fairly constant transition probability from one health state to another and we anticipate that this is what the Appraisal Committee would expect to see here having noted the limitations in the company's methodology (which are also noted on page 175 of CS doc B). Clarify why the approach taken in the company's model is preferred to either of the following options, which the EAG believes are better:

- Eliciting the average time spent in each health state under current care from clinical experts and using this within the model to estimate constant transition probabilities (as happened in NICE HST29)

- Estimating threshold levels of GMFM_DE at which patients move to a different GMFCS and estimating the time that would be spent in each state assuming a decrease of 1.44 in GMFM_DE per year (as currently assumed). These times could be used to estimate constant transition probabilities.

Company response: We have clearly acknowledged the weaknesses of our approach outlined by the EAG in our submission. As discussed in the submission, a number of alternative approaches were attempted including using registry data. It was not possible to assign patients to GMFCS or GMFM DE scores using these data, therefore we looked to the clinical data itself to predict progression.

Start of updated section

As discussed in question A1, we have updated the analysis to generate transition probabilities stratified by GMFCS at baseline, which leads to a larger proportion of transitions to the GMFCS IV and V health states. We disagree with the statement that

transition probabilities should stay constant over time. Logically, as GMFM DE score reduces, the probability that the patient will be in a more severe GMFCS health state increases, though we acknowledge the issues of these time-changing probabilities once a patient changes GMFCS health state.

End of updated section

We provide responses regarding the two methods proposed by the EAG below:

Clinician elicitation

Immedica took the decision not to conduct a formal clinician elicitation exercise, considering that with so few patients (compounded by a change in clinician at adulthood) and large heterogeneity, clinicians would be unlikely to provide much additional information on natural history beyond that provided by the literature, ARG1-D registry data, trial and/or BoI study. This was borne out during the conceptual modelling validation calls, in which clinicians were asked the following questions regarding progression (2):

- "Is the progression of patients from one GMFCS level to the next constant, or do patients get 'stuck' at a particular level for long periods or even permanently?"

- "What is the shortest/longest time period for a patient to progress from GMFCS 1 to GMFCS 5?"

The responses in Table 3 indicate wide variability and inconsistency with the observed data e.g. Clinician 1, who manages adult patents, indicated that the slowest progression time was 5-6 years despite patients in the pegzilarginase trials and/or BoI study living into their 30s and even the occasional patient in their late forties. Clinician 2 (paediatric care) was unable to provide a range while clinician 3 provided a large range between less than a decade up to two to three decades (2). We therefore believe that, given the ultra-rarity of the condition (a subgroup of an already rare group of urea cycle disorders), a formal elicitation exercise would not be more informative than the information provided by UK clinicians.

Table 3: Summary of clinical responses: Progression time for ARG1-D patients

Clinical expert	Age group managed (#patients)	Is the progression of patients from one GMFCS level to the next constant, or do patients get 'stuck' at a particular level for long periods or even permanently?	What is the shortest/longest time for a patient to progress from GMFCS I to GMFCS V?
Clinician 1	Adult patients Current number of ARG1-D patients: 9	The duration spent in each GMFCS health state for ARG1-D is analogous to that of MLD. MLD patients spend roughly the same amount of time in each health state until they reach GMFCS-MLD-6, where they become stuck. In ARG1-D, patients become stuck in the GMFCS Level V health state. ARG1-D patients can progress slowly, but they can stay in a particular GMFCS health state for 2-3 years before moving onto the next GMFCS level.	Shortest time for a patient to progress from GMFCS II to IV could be 2-3 years. A speed of 3-4 years between each stage is possible in GMFCS III to V. The longest time for a patient to progress was 5-6 years
Clinician 2	Paediatric patients Experience: Six patients have been treated at GOSH over the last 25 years. Current number of ARG1-D patients: 2	It can be difficult to determine a patients progress through the different GMFCS levels over time as each patient is heterogenous in their symptomology and clinical management. Progression can be dependent on whether the patient adheres to the diet, the efficacy of the restricted diet in terms of managing their symptoms, frequency of HA crises etc.	Shortest time cited as 'a few years', without quantification. The longest time referred to was 'decades. The clinician mentioned an example of a patient who is 17 and is still able to walk without any mobility aids.
Clinician 3	Paediatric patients	Patients with ARG1-D tend to spend longer in the earlier GMFCS levels compared to MLD. This can depend on the severity of the condition.	The shortest time: 6-7 years. The longest time: 20-25 years.

	Experience: 10-12 patients. No patients in his current centre		

Key: ARG1-D: arginase 1 deficiency; MLD: Metachromatic leukodystrophy; HA: hyperammonaemia.
Source: Data on File – Clinical Expert Validation (2).

Prediction of time in state using GMFCS cutoffs

We agree with the EAG that this is a reasonable approach to implement in the model. We have therefore used the following approach to generate transition probabilities:

1) Specify cut-off values in GMFM DE score that determine when a patient moves from one GMFCS state to the next most severe state.

Start of updated section

- Medians, maximums and minimums of GMFM D and E score by GMFCS are available from the cerebral palsy (CP) literature (3, 4), but a comparison of these vs. the mean GMFM D and E scores by GMFCS in the clinical data showed the mean GMFM DE to be lower in ARG1-D, particularly in GMFCS I. This is to be expected given the progressive nature of ARG1-D, in which GMFM DE decreases over time, whereas in CP it will be largely static. GMFM DE cut offs which determine when a patient moves to the next GMFCS health state were therefore generated from the observed data (all observations, pooled PEACE and phase 1/2). We have used the mid-point between the lower confidence interval (CI) and upper CI of the GMFM DE score of adjacent GMFCS health states as the cut-off (see Table 4).

- When the CP literature is used, we use the minimum and maximum values reported in Table I from Lidbeck et al., 2021 (3), these statistics being the only estimates reported, with some data manipulations (see footnote to Table 4). We selected Lidbeck as the literature source as it was the only CP publication we identified that reports GMFM D and E values for GMFCS IV.

2) Estimate the time required to move from one GMFM DE cut-off value to the next based on the regression of GMFM DE vs. age (which predicts a reduction in GMFM DE score per year of age of 1.45 for IDM patients). The time required to move from one GMFM DE cut-off value to the next determines the mean time in GMFCS state. For GMFCS I, we assume that the time in state is the time to progress from a GMFM DE score of 107 (the mean GMFM DE score of patients in GMFCS I in the pooled PEACE and phase 1/2 data) to the cut off value for GMFCS I.

4) Generate constant transition probabilities using the inverse of the mean time in state, converting from annual to cycle-specific transition probabilities before implementation in the model.

The values used for this approach are summarised in Table 4. Updated cost effectiveness results are detailed in Table 5, with all results generated using Hernandez-Alava utility values, a phased HAC treatment effect and an SMR multiplier of 800. The progression based on mean time in state is slower than that using the logistic regression, leading to lower QALY gains from pegzilargiinase. The CP cut offs lead to better cost effectiveness results than using the ARG1-D data as the cut off for moving from GMFCS I to II is higher, leading to a shorter average time in GMFCS I and a higher transition probability for GMFCS I patients. This has a substantial impact on the model as [redacted] occupies GMFCS I at baseline.

Table 4: Calculation of transition probabilities based on time in state

	GMFCS I	GMFCS II	GMFCS III	GMFCS IV
Lidbeck et al. (2021) cerebral palsy (3)				
Min,Max GMFM DE score*	96,103	37,103	18,77	2,22
Lower cut off GMFM DE value for transition to next GMFCS	100 (average of 96 and 103)	57 (average of 37 and 77)	20 (average of 18 and 22)	2
Time from previous cut off to next cut-off in years	5.2 (time from GMFCS I mean GMFM DE score of 107)	29.4	25.4	12.7
Annual transition probability (inverse of row above)	19.3%	3.4%	3.9%	7.9%
PEACE and phase I/II all observations				
CI of GMFM DE score	[redacted]	[redacted]	[redacted]	[redacted]
Lower cut off GMFM DE value for transition to next GMFCS	[redacted] (average of [redacted] and [redacted])	[redacted] (average of [redacted] and [redacted])	[redacted] (average of [redacted] and [redacted])	[redacted]

Time from previous cut off to next cut-off in years (inverse of row above)	[redacted] (time from GMFCS I mean GMFM DE score of [redacted])	[redacted]	[redacted]	[redacted]
Annual transition probability	[redacted]	[redacted]	[redacted]	[redacted]

Key: GMFCS: Gross Motor Function Classification System.
Notes: *Scores in Lidbeck Table I are reported as % of maximum score. These were converted to absolute GMFM D and E scores based on the maximum D and E score of 39 and 72, respectively. Minimum and maximum GMFM DE values from Lidbeck were calculated as the sum of the minimum and maximum GMFM D and E values, respectively..

Table 5. Scenario analyses using different methods of prediction of progression

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Logistic regression of GMFM DE stratified by GMFCS (as per question A1)	[redacted]	17.479	[redacted]	£839,044	[redacted]	[redacted]	£285,286
Time in state using ARG1-D GMFM DE cut-offs derived from the pooled PEACE and phase 1/2 data	[redacted]	17.286	[redacted]	£884,777	[redacted]	[redacted]	£308,375
Time in state using Lidbeck et al. cerebral palsy GMFM DE cut-offs (3)	[redacted]	17.317	[redacted]	£873,586	[redacted]	[redacted]	£302,540

Key: ARG1-D: arginase 1 deficiency; GMFCS: Gross Motor Function Classification System; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using Hernandez-Alava utility values. Includes lower HAC rate in double-blind period as per question B18 and SMR multiplier of 800 as per question B6.

End of updated section

A3. Clarify whether the GMFM D&E score is simply an addition of the GMFM D and GMFM E. Clarify whether any analyses were conducted using the GMFM D and E scores individually when predicting GMFCS.

Company response: The GMFM D&E score (referred to simply as DE in this response document) is the sum of the two scores.

No attempt was made to conduct regression analyses for the two individual scores, as the combined measure was considered to be a more comprehensive patient level measure of patient motor function.

Start of updated section

Furthermore, GMFM D was found to correlate strongly with GMFM E in the trial data (see Figure 1 and Table 6).

Figure 1: correlation between GMFM D and E score

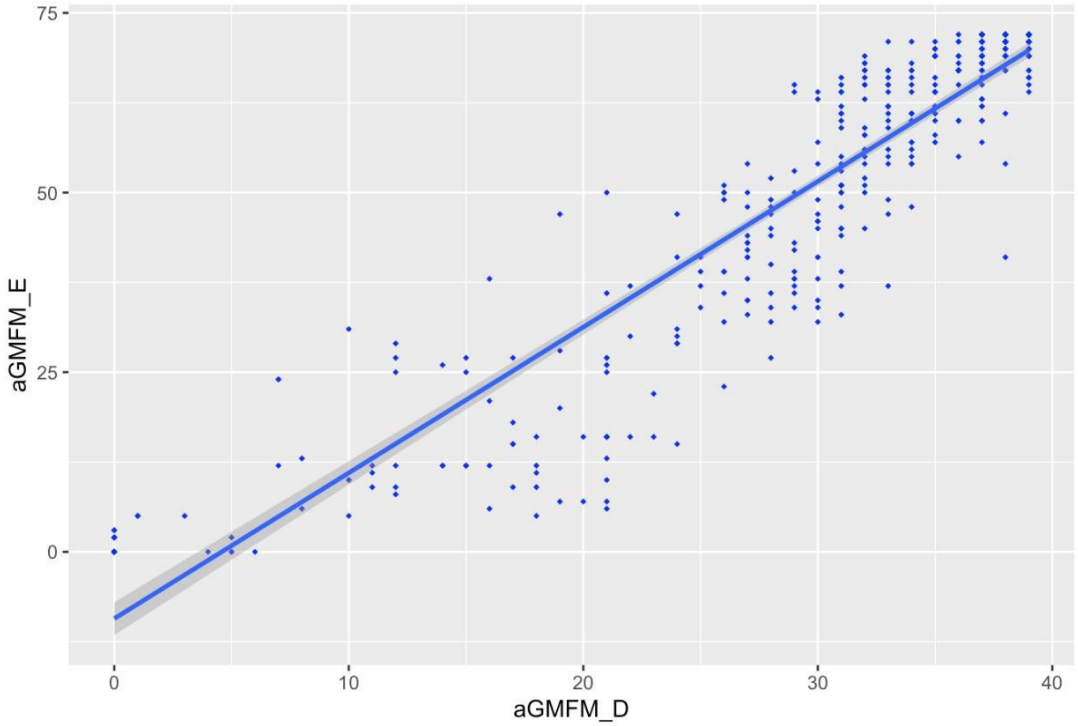


Table 6: Regression analysis of GMFM E vs D

	aGMFM_E		
Predictors	Estimates	CI	p
(Intercept)	-9.2929	-11.5761 – -7.0098	**<0.001**

aGMFM D	2.0283	1.9562 – 2.1005	**<0.001**
Observations	442		
R^2 / R^2 adjusted	0.874 / 0.874		

End of updated section

This aligns with the observation that both GMFM D and E correlate strongly with GMFCS in the analyses undertaken by Oeffinger *et al.* (2004) in CP (though only GMFM E score was a significant predictor in their logistic regression) (4).

The only other analysis undertaken was generation of simple summary statistics of GMFM E by GMFCS to allow comparison of the ARG1-D patient values with the means and ranges of GMFM E score by GMFCS reported in Oeffinger et al. Table II. This was conducted to determine whether the relationship between GMFM E score and GMFCS in CP was generalisable to ARG1-D. The mean GMFM E by GMFCS was much lower in ARG1-D vs. CP, which is not unexpected given the progressive nature of the disease, as GMFM score will be moving downwards over time whereas in CP it will remain largely static.

A4. In CS doc B, page 140 to 141, a linear regression was fitted using baseline data.

1) A linear model assumes that the GMFM D&E score changes at a constant rate with age. Please justify this assumption.

2) Also, in CS doc B, Figure 26, 42 out of 45 patients are between age 2 and age 15. Please justify why such a relationship can be expected to be the same for patients over 15 years old.

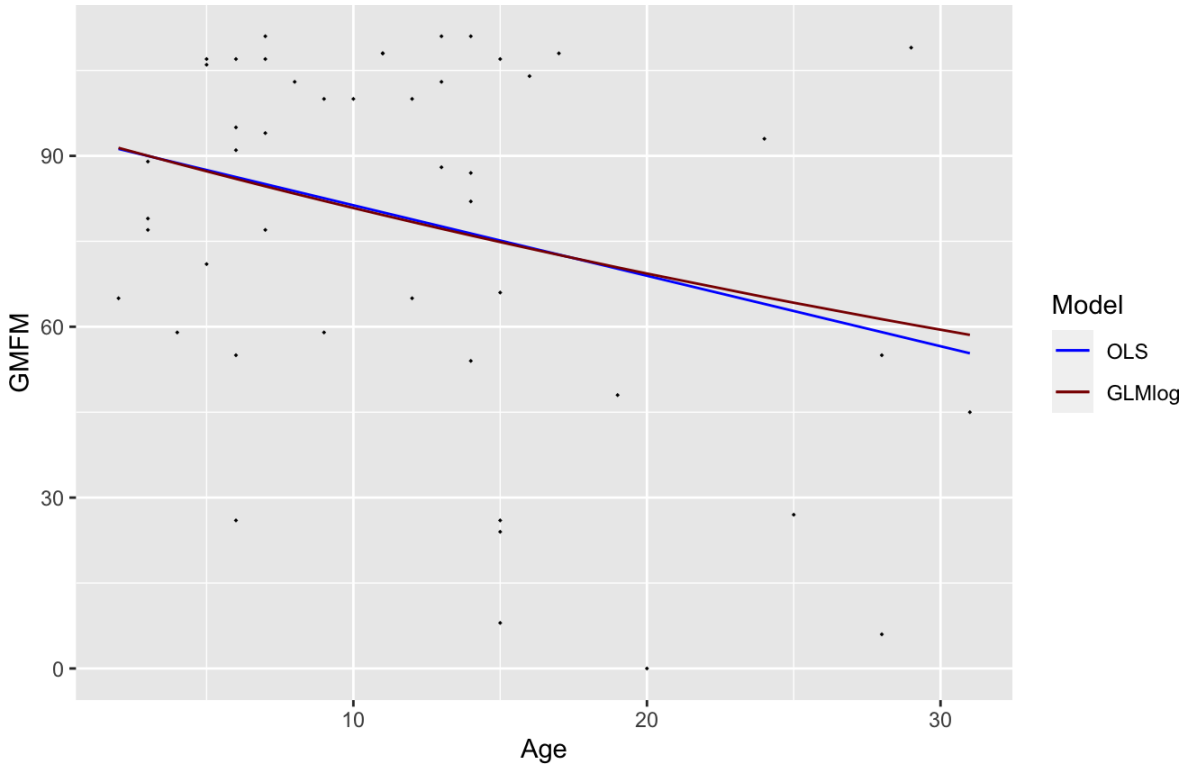
3) The baseline data include the GMFM D&E scores from 45 different patients at one time point, without information on how individual score changes over time. Please justify how such a cross sectional data would be informative on predicting GMFM D&E scores over time, considering that the R^2 is low.

Company response:

Start of updated section

1) A Generalised Linear Model (GLM) regression analysis was also attempted vs. age with a log link (that is, assuming an exponential rather than linear relationship), but the differences between the OLS and GLM models was not considered material (R^2 0.112 vs. 0.086 for the OLS and GLM, respectively), and there was little difference in visual fit (see Figure 2), therefore the linear regression of GMFM DE vs. age was retained for the model for simplicity.

Figure 2: Comparison of OLS linear and GLM log link model fits (double blind and phase I/II)



Key: OLS, ordinary least squares; GLM, generalised linear model.

End of updated section

2) During the conceptual model development clinicians were asked the following question: “Are there any subgroups we should consider based on e.g. age at onset, speed of disease progression, symptomology etc.?” None of the clinicians indicated that speed of progression might differ according to age.

3) As explained in our submission and in the response to A2, Immedica investigated other methods, including registry data, to generate progression estimates. The placebo follow-up time was too short to derive a patient-level change over time. As the

clinician estimates of speed of progression varied so wildly, there is no way of validating whether the cross-sectional approach is valid or not. Currently, Immedica considers it to be the best approach available for modelling,

A5. CS doc B, page 142, states that "*an important assumption underpinning ordered logistic regression is the presence of proportional odds*". Please justify the appropriateness of this assumption using statistical tests.

Company response:

Start of updated section

A Brant test confirmed that the assumption of proportional odds was not violated (p = 0.783). Note that this test can only be run on the non-random effects version of the model (which does not account for correlation of observations between the same patient).

End of updated section

A6. CS doc B, page 141 to page 143, states that "cumulative logistic regression was carried out using a random effects model for repeated measures, with the continuous variable GMFM D&E total score as the predictor as shown in Table 28". Please provide the equations for this model. Please clarify whether D&E scores at baseline or D&E scores over time are included as predictors and justify why treatment groups are excluded as predictors. Please also provide evidence of goodness-of-fit.

Company response:

Start of updated section

GMFM DE scores over time were included as predictors. Treatment arm generated highly insignificant p values (p>0.8, whether including or excluding phase 1/2 data). We are not aware of any available goodness of fit test for the *xtologit* command in STATA, however, the pseudo-R^2 value of the non-random effects version of the model (that is, a version not accounting for repeated measures) was 0.58.

End of updated section

The equation for deriving a probability for the model is summarised below:

Equation 1:

$EXP(\beta_{GMFCS\ x} - GMFM\ DE\ score*\beta_{GMFM})/(1+EXP(\beta_{GMFCS\ x} - GMFM\ DE\ score*\beta_{GMFM})$

The linear predictor portion of Equation 1 predicts the log(odds) that a patient falls within that GMFCS category vs. the preceding categories, with $\beta_{GMFCS\ x}$ representing the intercept for each GMFCS category and β_{GMFM} representing the slope, as follows:

$\beta_{GMFCS\ x} - GMFM\ D\&E\ score*\beta_{GMFM}$

The formula EXP(linear predictor)/(1-EXP(linear predictor) transforms the linear predictor from log(odds) scale to a probability.

Clinical questions

A7. Priority: CS doc B, Figure 28 suggests that there are longitudinal data on both GMFCS and GMFM_DE for patients receiving pegzilarginase treatment. Tabulate the transitions between GMFCS for patients on pegzilarginase treatment (with and without prior placebo treatment) for each 12-week period. Also provide a stacked plot of GMFCS by time period similar to the plot below (which has used data in the Excel model taken from patients in PEACE and Phase II) to show movement in GMFCS over time.

Company response: Start of updated section

For transparency we have provided the longitudinal PEACE data in a separate Excel file entitled **GMFCStrans 13.05.24** which includes both GMFCS and GMFM DE scores. Regarding the request to tabulate 12-week transitions, we do not believe these transitions to be useful as there are material amounts of missing data at each observation point, which means that the observations at the beginning and end of each 12-week period do not come from the same patients. When dealing with small sample sizes such as the PEACE data even small amounts of missing data can lead to highly skewed transition probabilities. The level of missing data is evident from a plot of the number of patients in each GMFCS state by period, as shown in Figure 3 below (noting that this chart assumes that week 24 is baseline for placebo patients).

To deal with the missingness, one approach is to assume the last observation carried forward (LOCF). However, this approach is also problematic, as temporary changes in GMFCS (both increases and decreases) were observed for some patients, meaning that when applying LOCF a temporary change in GMFCS may be converted into a permanent one. These issues aside, an additional plot based on the last observation carried forward (LOCF) approach (see Figure 4) shows that patients over time generally see a steady improvement in their GMFCS score, noting that this chart assumes that week 24 is baseline for placebo patients. Inspection of the GMFM DE scores in the patient data also reveals continued improvement past week 96 for a number of patients, justifying a forward extrapolation of improvement in GMFCS.

Twelve-week transition probabilities (using LOCF and assuming that week 24 is baseline for placebo patients) can be found in sheet **GMFCStrans LOCF w pbo** of the supplied Excel file.

Figure 3: Patients in each GMFCS state by study period (observed numbers)

Key: GMFCS: Gross Motor Function Classification System.
Note: Study week 24 set as baseline for placebo patients. EOS150 represents either the week 150 visit OR the patient's last study visit.

Figure 4: Proportions in each GMFCS state by study period (LOCF)

Key: GMFCS: Gross Motor Function Classification System; LOCF: last observation carried forward.
Note: Study week 24 set as baseline for placebo patients. EOS150 represents either the week 150 visit OR the patient's last study visit.

End of updated section

A8. Priority: Please clarify why patients who switched to pegzilarginase after the double-blind period do not appear to show the same degree of response to pegzilarginase over multiple outcomes at week 24 of the LTE as those who were in the pegzilarginase arm of the trial did over the same period of time on treatment (24 weeks). For example, in CS doc B, Figure 15, those starting on pegzilarginase treatment there were increases in 2MWT of 12.8 in the first 24 weeks and of 26.3 in the second 24 weeks (noting that the number of respondents changed over time); for those starting on placebo the gain after 24 weeks of pegzilarginase treatment was 0.1 (with the caveat as for pegzilarginase arm). For later time points, please clarify whether the apparent response is due to patients who had poor/no response at earlier timepoints not being included in the analysis.

Company response: To compare the results of the pegzilarginase/pegzilarginase and placebo/pegzilarginase treatment groups throughout the double-blind and long- term extension (LTE) portions of the study, the company has provided side-by-side comparisons of the mean change from baseline for the 2-Minute Walk Test (2MWT; Figure 5), Gross Motor Function Measure, Part E (GMFM-E; Figure 6) and Gross Motor Function Measure, Part D (GMFM-D; Figure 7) below.

Figure 5: Change from baseline in distance walked for 2MWT (metres) (PEACE; FAS)

Key: 2MWT: 2-Minute Walk Test; EOS: end of study; FAS: Full Analysis Set; LTE: long-term extension; W: week.
Note: For the pegzilarginase, placebo, and pegzilarginase/pegzilarginase groups, baseline was defined as the baseline value obtained at the screening/baseline period prior to the first dose of blinded study treatment. For the placebo-pegzilarginase group, baseline was defined as the last value obtained during the double-blind Week 24 timepoint. Change from Baseline is the value at the timepoint – the baseline value.
Source: Table 21 & Table 39; PEACE CSR (5).

Figure 6: Change from baseline in GMFM-E score (points) (PEACE; FAS)

Key: EOS: end of study; FAS: Full Analysis Set; GMFM-E: Gross Motor Function Measure-88, Part E; LTE: long-term extension; W: week.

Note: For the pegzilarginase, placebo, and pegzilarginase/pegzilarginase groups, baseline was defined as the baseline value obtained at the screening/baseline period prior to the first dose of blinded study treatment. For the placebo-pegzilarginase group, baseline was defined as the last value obtained during the double-blind Week 24 timepoint. Change from Baseline is the value at the timepoint – the baseline value.
Source: Table 22 & Table 40; PEACE CSR (5).

Figure 7: Change from baseline in GMFM-D score (points) (PEACE; FAS)

Key: EOS: end of study; FAS: Full Analysis Set; GMFM-D: Gross Motor Function Measure-88, Part D; LTE: long-term extension; W: week.
Note: For the pegzilarginase, placebo, and pegzilarginase/pegzilarginase groups, baseline was defined as the baseline value obtained at the screening/baseline period prior to the first dose of blinded study treatment. For the placebo/pegzilarginase group, baseline was defined as the last value obtained during the double-blind Week 24 timepoint. Change from Baseline is the value at the timepoint – the baseline value.
Source: Table 35 & Table 41; PEACE CSR (5).

During the LTE portion of the study, functional mobility outcomes (2MWT, GMFM-E and GMFM-D) varied for both treatment groups at each of the study timepoints highlighted in the figures above. The baseline performance of patients across each of the functional mobility assessments had a large influence on the observed clinical responses to pegzilarginase treatment; patients with near-normal baseline scores were unable to meet the thresholds for clinical response because their baseline scores limited the magnitude of possible effect size. In addition, due to missed assessment visits as a result of the COVID-19 pandemic, and variable durations of study participation during the LTE portion of the study as a result of early study completion (range: [redacted] to [redacted] weeks) (5), the outcomes data at each study timepoint contained a sample of different patients who had data available. Data wasn't censored, hence the sample size at each study timepoint reflects all patients with available data. The inclusion or exclusion of patients with near-normal baseline scores may therefore have a profound effect on the observed response to pegzilarginase across each treatment group. Hence, the results presented in Figure 5, Figure 6 and Figure 7 should be interpreted with caution.

It should be noted that for the placebo/pegzilarginase group, pegzilarginase treatment was initiated six months later in these patients, allowing for further deterioration from baseline during the double-blind period (5). Given the limited sample size in the placebo/pegzilarginase arm, the observed effect of pegzilarginase at LTE Week 24 is likely to have been compounded by the exclusion of patients who did not observe a worsening in functional mobility outcomes from baseline.

Overall, patients in the placebo/pegzilarginase arm demonstrated sustained improvement in neuromotor function with longer duration of therapy.

A9. Clarify whether the outcomes of the one patient who discontinued pegzilarginase treatment in PEACE due to '*personal reasons*' were similar to, or worse than patients who continued treatment.

Company response: One patient randomised to receive pegzilarginase in the double-blind period of PEACE ([redacted]) discontinued treatment at Week 6 due to personal reasons unrelated to pegzilarginase (5, 6).

At study baseline, this patient was [redacted] years old, classified as Gross Motor Function Classification System (GMFCS) Level I and had near-normal GMFM-D and GMFM-E scores of [redacted] (maximum score: 39 points) and [redacted] (maximum score: 72 points) points, respectively (5, 7).

Prior to study withdrawal, this patient did not normalise plasma arginine (pArg) (baseline pArg: [redacted] µM; Week 1 pArg: [redacted] µM, Week 6 pArg: [redacted] µM) (5, 7). PArg reduction in this patient during dosing may have been limited by the development of anti-drug antibodies (ADAs). As highlighted in Table 37, page 133, of the Company Evidence Submission, 12 of 48 patients (25%) across all the clinical studies of pegzilarginase developed ADAs against pegylated therapeutic proteins and/or protein moiety of pegzilarginase, which were typically transient and resolved with continued treatment (5, 6). Therefore, it is plausible to assume that with continued treatment, the patient who discontinued at Week 6 could have experienced a clinical meaningful change and normalised pArg upon completion of the double-blind portion of the study. At Week 24 of the double-blind period, pArg below the guideline-recommended level (<200 µM) was achieved by 90.5% (19 of 21 patients) on pegzilarginase, and normalisation (40-115 µM) by 90.5% (19 of 21 patients) (all $p < 0.0001$ vs placebo) (5, 6).

In addition, given withdrawal from the study at Week 6, the patient did not have a neuromotor function and/or neurocognitive assessment across any of the study timepoints post-baseline. Hence, it is not possible to determine the outcomes of the patient relative to the remainder of the PEACE trial cohort.

A10. Please clarify how long patients in Study 101A were receiving a dose equivalent to the licensed dose for, prior to joining Study 102A. Would it be appropriate to combine the time on treatment in Study 101A with the time on treatment in Study 102A, to work out the time point of outcomes with respect to the commencement of treatment?

Company response: As mentioned in the pegzilarginase Summary of Product Characteristics (SmPC), '*The recommended initial dose of Loargys is 0.1 mg/kg per week. This dose may be increased or decreased in 0.05 mg/kg increments to achieve therapeutic goals' (8)*. Given the weight-based dosing of pegzilarginase, it is difficult to define the licensed dose as this varies between patients. During Part 2 of Study

101A, [redacted] of patients ([redacted] of 14 patients) underwent dose adjustments prior to or at the time of the last administration to achieve further improvements in pArg control (9). Therefore, one could assume that at least [redacted] of the cohort were not an optimal licensed dose during the previous part of the study. For each individual patient at the start of Study 102A, the dose of pegzilarginase was selected based on the dose and regimen last received at the end of Study 101A.

All 14 patients who completed Study 101A Part 2 were enrolled and treated in Study 102A. However, the median duration of time between the last dose of pegzilarginase in Study 101A and the first dose in Study 102A was [redacted] weeks (range: [redacted] weeks) (Table 7) (10). During this time period, patients were not receiving active treatment with pegzilarginase, and given the progressive nature of the disease, results of clinical outcomes may have worsened. Therefore, combining time on treatment in Study 101A with Study 102A would not provide a true reflection of the efficacy of pegzilarginase over time for patients with ARG1-D.

Table 7: Duration of time between Study 101A Part 2 and Study 102A (FAS)

	Duration (Weeks) (n=14)
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Patient	
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]

Key: FAS: Full Analysis Set; SD: standard deviation.
Notes: Dosing in Study 102A was to commence approximately 4 weeks (but no sooner than 3 weeks) after the last dose of pegzilarginase in Study 101A.
Source: Table 9; Study 102A CSR (10).

A11. Please clarify the reason(s) why, given the trial guidelines, 38.1% of patients in the pegzilarginase group had >15% protein in their diet compared to 18.2% in the

placebo arm (CS doc B, page 123). Could this difference indicate that blinding may have been subverted by some patients or clinicians. Please clarify if the 15% change was permitted during the 24-week randomisation period plus the 8-week blinded LTE period, or only after this period, or across all periods, and which time point the data relate to. Clarify whether there are any long-term data on the proportion of patients that have increased their protein intake whilst on pegzilarginase treatment. Clarify what these protein improvements mean in terms of food to provide context to the committee (for example, does the increase allow an additional egg per day or a handful of nuts).

Company response: The 24-week placebo-controlled, randomised portion of PEACE was double-blinded. During this time, all site personnel involved with the study, including patients, families, caregivers, investigators and expert assessors of relevant endpoints, and all sponsor and contract personnel, were blinded to the patient's randomised treatment assignment to minimise potential biases in assessment of safety and clinical outcomes, as per study protocol (5, 6).

Throughout the entire duration of the blinded-period, which included the 24-week randomisation period and the first eight weeks of the LTE, sites were instructed to minimise changes to within 15% of baseline for patient's dietary protein intake to keep the diet as stable as possible throughout the study. Despite this, an increase in total consumed protein >15% from baseline was observed in both treatment groups across the double-blind period (Table 8) (5). At Week 12, the total consumed protein was similar across the pegzilarginase and placebo treatment groups (Table 8) (5), hence there was no difference in the proportion of patients exceeding their total prescribed protein during the first half of the double-blind period. However, as the EAG have correctly highlighted (albeit with values referencing total consumed calories as opposed to total protein consumption), 34.4% of patients (11 of 32 patients) treated with either pegzilarginase (9 of 21 patients, 42.9%) or placebo (2 of 11 patients, 18.2%) increased their total protein consumption by >15% at Week 24 of the double-blind period, despite trial guidelines (5, 6).

Table 8: Summary of total protein consumption during the double-blind period (PEACE; FAS)

Total Consumed Protein/Day (g)	Pegzilarginase (n=21)	Placebo (n=11)	Total (n=32)
Week 12			
Increase of >15%, n (%)	[redacted]	[redacted]	[redacted]
Within ± 15%, n (%)	[redacted]	[redacted]	[redacted]
Decrease of <15%, n (%)	[redacted]	[redacted]	[redacted]
Week 24			
Increase of >15%, n (%)	9 (42.9)	2 (18.2)	11 (34.4)
Within ± 15%, n (%)	[redacted]	[redacted]	[redacted]
Decrease of <15%, n (%)	[redacted]	[redacted]	[redacted]

Key: FAS: Full Analysis Set; g: grams.
Notes: Percentages are based on the total number of subjects in each respective treatment groups.
Source: Sanchez Russo *et* al. (2024) (6); Table 32; PEACE CSR (5).

Considering the study protocol, the hypothesis from the EAG that blinding may have been subverted by some patients or clinicians seems unfeasible. Instead, the company hypothesises that the reduction in pArg levels and subsequent control of disease as a result of pegzilarginase treatment may be responsible for the reduction in natural protein aversion. Like other urea cycle disorders (UCDs) (11, 12), patients with ARG1-D also experience natural protein aversion (13, 14).

Upon completion of the blinded-period of the study, diet prescription changes were permitted. According to treatment guidelines, modifications to the prescribed protein consumption could be adjusted as clinically indicated to maintain pArg within the normal range (40 - 115 µM) (5, 15). Data on the proportion of patients that increased their protein intake in the double-blind period whilst on pegzilarginase treatment is provided below in Table 9. Overall, fluctuations in the amount of total protein (natural protein and essential amino acids [EAAs]) were observed amongst patients treated with pegzilarginase, but a clear indication on liberalisation of diet was seen during the LTE period, with consumed total protein observed to increase over time (Table 9) (5, 16). Importantly, dietary fluctuations did not impact the ability of patients to maintain pArg within the normal range.

Table 9: Summary of total protein prescription and consumption during the LTE period (PEACE; FAS)

Total Protein /Day (g)	Pegzilarginase/ Pegzilarginase (n=21)		Placebo/ Pegzilarginase (n=11)		Total (n=32)	
	Prescribed n (%)	*Consumed n (%)*	*Prescribed n (%)*	*Consumed n (%)*	*Prescribed n (%)*	*Consumed n (%)*
LTE09						
<-15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-15% - 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0% - 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not calculated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTE21						
<-15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-15% - 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0% - 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not calculated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTE45						
<-15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-15% - 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0% - 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not calculated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTE93						
<-15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-15% - 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0% - 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not calculated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOS/LTE150						
<-15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-15% - 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

0% - 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not calculated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: EOS: end of study; FAS: full analysis set; LTE: long-term extension.
Notes: Percentages are based on the total number of patients in the respective treatment groups.
Source: Table 14.2.16.1; PEACE CSR (5, 16).

At study baseline, patients in the pegzilarginase arm consumed a mean (SD [redacted] ([redacted]) of protein per day (5, 16). When referring to the baseline value in the pegzilarginase treatment group, a 15% increase from baseline in protein consumption would represent a mean increase of [redacted], which is equivalent to [redacted]. It is acknowledged, however, that a 15% change in protein consumption would vary per patient in terms of food, as it is ultimately dependent on the individual patient's baseline protein consumption. For example, when considering the range of total consumed protein at baseline in the pegzilarginase group (range: [redacted]), a 15% increase from baseline could represent a mean change of [redacted] versus [redacted] (5, 16).

A12. Please clarify what restricted medications and interventions (e.g. surgery) were administered in each intervention arm.

Company response: In PEACE, according to the study exclusion criteria, the use of botulinum toxin to treat spasticity-related complications was prohibited until all patients had completed the blinded portion of the study (LTE09). Despite this, no patients required treatment with botulinum toxin during the LTE portion of the study (5).

Similarly, surgical procedures (e.g., tendon release surgery) to correct disease-related abnormalities were not prohibited throughout the study, but the recommendation was that they were not administered during the double-blind period. Across both the blinded and LTE portions of the study, no patients in either treatment arm required a surgical procedure (5).

A13. Please clarify the reasons for the 12 screening failures (CS doc B, Table 10). Clarify how might this impact the generalisability of the study results.

Company response: Of the 44 ARG1-D patients who consented to participate in PEACE, 12 (27.3%) were screen failures. As highlighted in the footnotes of Figure 36, Appendix D.1.2, screen failures failed due to meeting the following exclusion criteria:

hyperammonaemic history (n=1), other medical condition judged by investigator to interfere with study assessments (n=1); or not meeting the following inclusions criteria: provision of informed consent (n=4), arginine elevation ≥250 µM (n=2), able to complete the study assessments and had a baseline deficit in at least one component (n=4) (5, 6).

The 44 ARG1-D patients who consented to participate in PEACE represented ~10% of all estimated total ARG1-D cases amongst countries with clinical study sites (5, 6, 17). The observed number of patients with a hyperammonaemic history (1 patient, 2.3%) or a medical condition that could interfere with study assessments (1 patient, 2.3%) was low, hence it is anticipated that minimal patients with the aforementioned clinical characteristics would be observed in clinical practice, given that a large proportion of the ARG1-D population amongst the countries with clinical study sites was screened.

For entry into PEACE, the average of all measured values of pArg during the screening period prior to the randomisation visit was required to be ≥250 uM (5, 6). Hence, enrolled patients with a relatively modest level of hyperargininaemia <250 uM (2 of 32 patients, 4.5%) were excluded from the study. As per the SmPC, these patients are included in the marketing authorisation for pegzilarginase and are eligible for treatment (8).

In Study 102A, there was no inclusion/exclusion criteria based on pArg level; this was an open label-extension study for patients who had previously completed participation in Study 101A, albeit the median time between Study 101A completion and Study 102A initiation was [redacted] weeks (see A10) (10). At Study 102A baseline, [redacted] of 14 patients) had a baseline pArg level of <250 uM (range: [redacted] uM). All patients were female and aged between [redacted] years of age. [redacted] patients were classified as GMFCS Level I, [redacted] classified as GMFCS Level II and [redacted] classified as GMFCS Level III (10).

Results from functional mobility assessments over time are presented overleaf in Table 10. Overall, the functional mobility outcomes for patients with pArg <250 uM treated with pegzilarginase in Study 102A were consistent with the findings in PEACE.

Therefore, the exclusion of patients with pArg <250 uM is unlikely to affect the generalisability of PEACE results.

Table 10: Individual patient change from baseline in functional mobility assessments (Study 102A; pArg <250 µM)

	BL	Change from Study 102A Baseline							
	BL	Week 12	Week 24	Week 48	Week 72	Week 96	Week 120	Week 144	Follow-Up
6MWT, metres									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFM-D, points									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFM-E, points									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key:6MWT: 6-Minute Walk Test; BL: baseline; GMFM-D: Gross Motor Function Measure-66, Part D; GMFM-E: Gross Motor Function Measure-66, Part E; pArg: plasma arginine.
Source: Tables 26 – 28; Study 102A CSR (10).

The requirement for a measurable deficit at baseline in at least one of the functional mobility assessments (2MWT, GMFM-E and/or GMFM-D) was required in order to demonstrate clinically relevant treatment effects in PEACE. As highlighted in A8 and demonstrated in Study 102A, the magnitude of possible effect size is more limited in patients with functional mobility outcomes close to or at the ceiling of normality, and hence little improvement in outcomes is observed. Despite this, the maintenance of normal functional mobility would be viewed as a positive outcome given the progressive nature of the disease. With current individualised disease management (IDM) approaches, the patient would otherwise be predicted to experience disease progression and a decline in functional mobility, based on historical observations (13, 18-20).

Finally, the baseline characteristics of patients who did not received informed consent to participate in the study are unknown. However, given the small number of patients (4 patients, 9.1%), it is unlikely that the absence of these patients would affect the generalisability of the study results.

A14. CS doc B, Table 10 – footnote c states "*One patient completed dosing but did not attend the final follow-up visit and was reported as discontinued (reason: family bereavement).*" Please clarify if this is the same patient who discontinued at 6 weeks, or another patient. If this is another patient, clarify why the total who completed LTE is 20, not 19, in accordance with footnote c (reported as discontinued).

Company response: The patient who completed dosing but did not attend the final follow-up visit ([redacted]) was not the same patient who discontinued the study at Week 6 due to reasons unrelated to pegzilarginase ([redacted]) (5).

As the EAG correctly highlights, footnote c for Table 11 in the PEACE CSR reports '*One subject completed dosing but did not attend the final follow-up visit and was reported as discontinued (reason: family bereavement)*'. This patient ([redacted]) received the last dose of study drug at LTE Week 80 (after 104 weeks of pegzilarginase treatment), with the last study assessment occurring at LTE Week 62. Despite being reported as discontinued, the patient was still considered to have completed the LTE period of the study (as highlighted in the footnotes of Figure 2, PEACE clinical study reports [CSR]), and hence was included as part of the cohort

who completed the LTE period of PEACE in Table 10, Section B.2.3.1.7 and Figure 36, Appendix D in the Company Evidence Submission (5-7).

A15. Two patients did not continue from 101A to 102A. Please clarify, across all three trials, how many patients discontinued treatment and the reasons why.

Company response: Across the three clinical studies of pegzilarginase, five patients (5 of 48 patients, 10.4%) discontinued treatment: two from Study 101A, one from Study 102A, and two from PEACE. Reasons for treatment discontinuation across each study are listed below:

- **Study 101A**: Two patients withdrew from the study due to personal reasons. One patient decided to withdraw to focus on high school, whilst another patient withdrew due to the sudden unexpected death of a family member (9).
- **Study 102A**: One patient had withdrawn consent and discontinued at Week 26. The mother of the patient reported being dissatisfied with the medical care they were receiving from the hospital and withdrew consent; she did not report being dissatisfied with the study treatment (10).
- **PEACE**: One patient in the pegzilarginase group discontinued treatment at Week 6 of the double-blind period due to personal reasons unrelated to pegzilarginase. Another patient completed dosing but did not attend the final follow-up visit due to a family bereavement and was reported as discontinued (as reported in response to A14, although this patient was reported as "discontinued", they completed dosing up to LTE Week 80, with final assessment on LTE Week 62. They were therefore deemed to have completed the study despite missing the final visit) (5, 6).

A16. Please clarify why the historical pArg levels reported in Table 15 of the CSR ([redacted] for PEACE differ from those reported in the CS doc B, Table 11 (365.4 (93.7); 471.7 (79.9); 402.0 (101.8) and the Sanchez Russa 2024 Journal article Table 1. Please clarify which values are correct. Please also clarify why historical pArg is more relevant than baseline pArg.

Company response: Sanchez Russo *et al.* (2024) and Table 11, page 56 in the Company Evidence Submission report baseline pArg values. The company

acknowledges that the latter incorrectly labels the values as historical pArg values, which is an incorrect reference; the label should instead refer to baseline pArg. The baseline value for pArg was defined as the mean of all logged values obtained during the screening/baseline period and prior to the first dose of blinded study treatment (5). By contrast, Table 15 of the CSR reports historical values of pArg, as available, for the year previous to study enrolment, rather than baseline pArg values. Overall, the company believes that baseline pArg is more relevant than historical pArg values.

A17. Please clarify if the baseline data for pArg placebo group should be 471.7 (79.9) as reported in Table 19 of the PEACE CSR, or 464.7 (1.21) as reported in CS Appendix M, Table 92. Also, the MMRM p-value and WRS p-value (and some of the outcome data) for GMFM-D differ in Table 95 of the CS Appendix M (0.0208; 0.0939) compared to the PEACE CSR Table 27 (0.3037; 0.2509).

- Please clarify which data is the most up to date and/or correct
- Since the PEACE CSR has a later data cut than the published paper (Sanchez Russa 2024), should the PEACE CSR be considered the most up to date analysis for all outcomes?
- When interpreting the p-values for the GMFM-D, please clarify which analysis, MMRM or WRS, is more appropriate, and why.

Company response: As correctly highlighted by the EAG, Table 19 of the PEACE CSR and Table 92 in Appendix M of the Company Evidence Submission provide different baseline values for pArg in the placebo group . Table 19 of the PEACE CSR reports on the observed pArg values, which were used to calculate descriptive statistics (5). By contrast, Appendix M, Table 92, reports on log-transformed values of pArg, the data of which was used for the primary analysis of the primary endpoint. In both tables, the baseline value was defined as the arithmetic mean of all pArg values obtained during the screening period and prior to the first dose of blinded study treatment. Within the context of the submission, the observed baseline data for pArg placebo in Table 19 of the CSR (5), which is also reported in Table 11 in the Company Evidence Submission, is the most appropriate for the interpretation of clinical effectiveness.

Furthermore, in the final analysis for the double-blind period, presented in PEACE CSR Table 27, a data error was noted for one patient. This patient had the largest change from baseline in the GMFM-D. The patient was not tested at baseline yet had a score of zero entered, which resulted in incorrect baseline and confounded change from baseline scores. A corrected analysis, removing this patient, was subsequently performed, which demonstrated a statistically difference between treatment groups in favour of pegzilarginase (p=[redacted]) (5). Results from the corrected analysis are presented in Appendix M, Table 95 of the Company Evidence Submission and PEACE CSR Table 35. The company acknowledges an error in the footnote of Appendix M, Table 95; the source should reference Table 35 of the PEACE CSR rather than Table 27. The result from the corrected analysis is the most appropriate data for the interpretation of GMFM-D results from the double-blind portion of the study.

As highlighted in Section B.2.2 of the Company Evidence Submission, Sanchez Russo *et al*. (2024) report on final data from the double-blind period and interim data for the LTE (up to LTE Week 24), with a data cut-off date of March 24th 2022 (6). The PEACE CSR reports on final data from the double-blind period and final data for the LTE, with the last patient visit on February 1st 2023 (5). The results published in Sanchez Russo *et al*. (2024) are presented in the relevant sections of the PEACE CSR. Considering this, the PEACE CSR be considered the most up to date analysis for all outcomes.

Although the Mixed Model Repeated Measures (MMRM) and Wilcoxon Rank Sum (WRS) analyses are both appropriate for the interpretation of p-values for GMFM-D, the MMRM should be considered first, since the WRS is provided as a sensitivity analysis. The WRS p-value is only considered more appropriate when the MMRM analysis has not been adjusted for indications of heteroscedasticity.

A18. CS doc B, page 63 states *"In Study 102A, 76.9% of patients (10 of 13 patients) received SC administration by home healthcare (23, 96)."* On P64 it states "*Patients received weekly IV pegzilarginase for the first 24 weeks of Study 102A, with the SC dosing route investigated as an option post 24-weeks if considered safe by the investigator (see Figure 13, Section B.2.3.2.2). In total, all eligible patients (13 of 14 patients) opted to have SC pegzilarginase (see Section B.2.10.2) (23, 96)".* On CS doc B, page 116, it states *"All patients transitioning to SC treatment (n=13)…"*

- The first of these statements appears to be at odds with the other two statements. Please clarify.
- Please clarify what the equivalent number was for the PEACE study.
- Please clarify for both studies why any patients were not treated at home.

Company response: Patients in Study 102A were required to utilise intravenous (IV) administration of pegzilarginase for Weeks 1 through 24. The first 12 doses were administered in the clinical research unit (CRU). After 12 initial IV doses, patients were dosed outside of the CRU by home health care professionals, if considered safe and appropriate to do so in the opinion of the investigator. After 24 weeks of IV treatment, patients had the option of switching to the same dose via SC administration from Week 25 onwards. All patients switched to subcutaneous (SC) administration, except for one patient, who withdrew consent for personal reasons and discontinued the study after 26 IV doses (13 of 14 patients, 92.6%). For patients who switched to the SC dosing route, the first four SC doses were provided at the investigational site. Subsequent SC injections were allowed to be administered outside the investigational site by appropriately trained home healthcare personnel. In total, 10 of 13 patients (76.9%) received SC administration by home healthcare (10). The remainder received SC administration at the hospital; these patients lived within close proximity and chose to continue receiving pegzilarginase treatment by a healthcare professional in this setting.

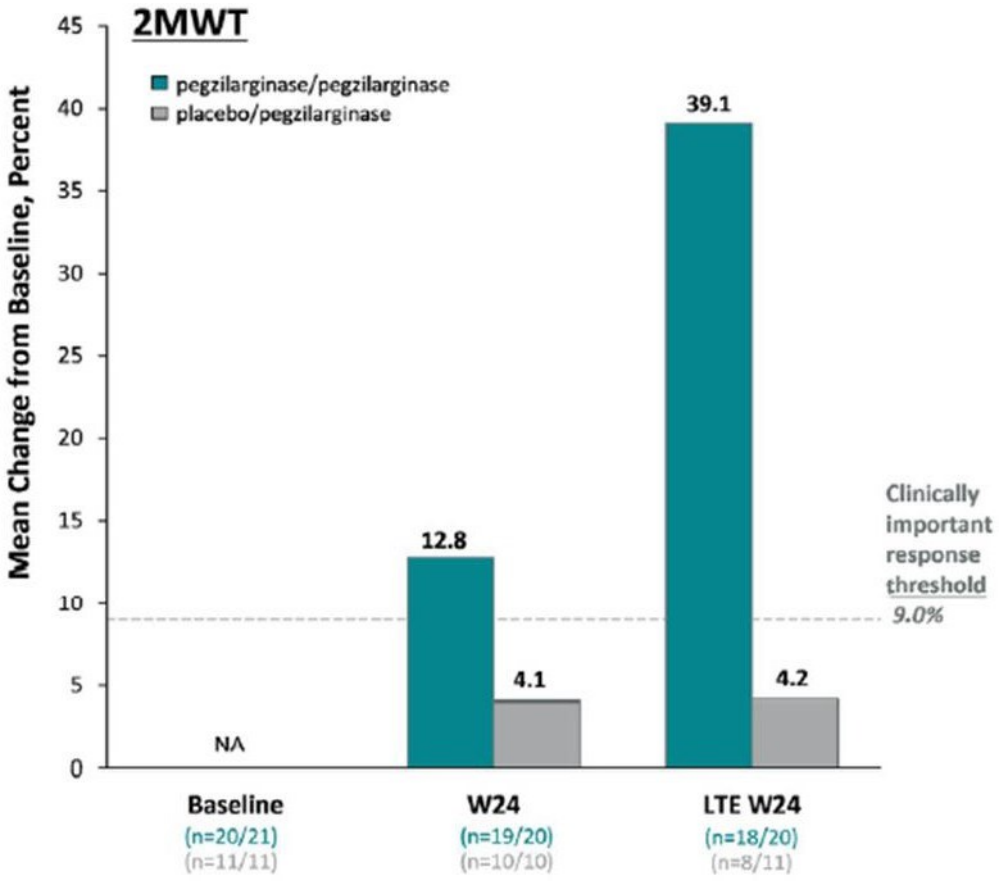
In PEACE, patients had the option to receive pegzilarginase by SC administration after the first eight weeks of the blinded LTE period. As observed in Study 102A, the first four SC doses were provided at the investigational site, with subsequent SC doses administered outside of the investigational site by appropriately trained home healthcare personnel if considered safe and appropriate in the opinion of the investigator. All 31 patients who completed the double-blind period switched from IV to SC administration (5). A similar proportion of patients in PEACE received SC administration of pegzilarginase by home healthcare ([redacted] of 31 patients, [redacted]) compared to Study 102A. The remaining [redacted] patients ([redacted]) received SC administration at the study site only (5, 7); as highlighted above, these patients lived within close proximity of the study site and chose to continue receiving pegzilarginase via SC administration in this setting.

A19. 2MWT data (CS doc B, page 78) - "*changes from baseline exceeded the minimal clinically important difference (MCID) threshold and demonstrated clinically meaningful improvement*". Please clarify what the mean change from baseline between groups was.

Company response: The 2MWT evaluates distance travelled on a flat surface in 2 minutes (with bracing or assistive devices). The clinical important response thresholds for the 2MWT was defined using criteria established for cerebral palsy. The minimal clinically important difference (MCID) was based on a 9% change from baseline in distance travelled for all patients for the 2MWT (21).

At baseline, the mean (SD) distance walked over 2 minutes for patients who received treatment with pegzilarginase was 109.0 (55.76) metres, compared to 99.9 (49.0) metres for patients who received placebo. At Week 24, the mean (SD) distance walked over two minutes in the pegzilarginase group was 115.9 metres (51.81), representing a 7.3-metre increase (+12.8%) from baseline, compared to the mean distance walked in the placebo group of 102.3 (51.10) metres, representing a 2.7-metre (+4.1%) difference from baseline (Figure 8) (5, 6). Although the change from baseline to Week 24 for the LS mean difference in the 2MWT between the pegzilarginase and placebo groups (5.5 metres) did not meet statistical significance (p=[redacted]), there was numerical improvement in the pegzilarginase group compared to the placebo group which was clinically meaningful (5, 6). A summary of 2MWT and change from baseline at Week 12 and Week 24 during the double-blind period is presented in Appendix M, Table 93.

Figure 8: Effect of pegzilarginase on 2MWT at Week 24 (PEACE; FAS) – Company Evidence Submission, Figure 15



Key: 2MWT: 2-Minute Walk Test; FAS: Full Analysis Set; LTE: long-term extension; W: week.
Notes: Group sizes reflect all patients with data at each time point; there was no imputation for missing values. LTE data cut-off date: March 24th 2022.
Source: Figure 4, Sanchez Russo *et al*. (2024) (6).

A20. CS doc B, Figure 15 – we cannot locate the value 12.8 in Table 93 of the CS Appendix M, or in Table 21 of the PEACE CSR. Nor can we locate the value 4.1. We also cannot locate the value 39.1, or 4.2 in Table 97 of the CS Appendix M or Table 39 of the PEACE CSR. However, CS doc B, Figures 16 and 18 contain data locatable in the CS Appendix M, Tables 94 and 95. Please clarify where the values in Figure 15 come from and why data for Figures 16 & 18 are as in the CS appendix M, but are not for Figure 15. If appropriate, please redraw Figure 15 with the correct values.

Company response: Figure 15 in the Company Evidence Submission (as depicted in Figure 8 above) is sourced from Figure 4 in the publication of final analyses from the double-blind period, and interim analysis through LTE Week 24 of the LTE, by Sanchez Russo *et al*. (2024) (6). Figure 8 visualises the change from baseline in

distance travelled for the 2MWT in the pegzilarginase group compared to the placebo group, and whether the changes from baseline in either treatment group at study timepoints exceeded the threshold for a clinically important response.

As discussed in A19, the MCID for the 2MWT was defined as a 9% change from baseline in distance travelled (21). To demonstrate the latter, data on the mean change from baseline for the pegzilarginase group was required to be converted to a percentage from an absolute value to assess whether either treatment group had exceeded the threshold for a clinically meaningful response. This calculation was done for the purposes of the publication only and was not provided in the PEACE CSR for the pegzilarginase group. Data on the mean change from baseline (metres) for the pegzilarginase is provided in the PEACE CSR and is provided in the Company Evidence Submission in Table 93 Appendix M.

Furthermore, Figures 16 and 18 in the Company Evidence Submission visualise the mean change from baseline (points) for GMFM-E and GMFM-D, respectively, across the pegzilarginase and placebo groups. The data provided in these figures is provided in the PEACE CSR, and is locatable in Appendix M, Tables 94 and 95. No data processing was required to demonstrate whether either treatment group had exceeded the threshold for a clinically important response at each timepoint; the MCIDs for GMFM-D (≥2.4 for GMFCS I, ≥3.3 for GMFCS II, and ≥1.5 for GMFCS III) and GMFM-E (≥4.0 for GMFCS I, ≥2.8 for GMFCS II, and ≥1.8 for GMFCS III) use the same units as the scores collected in each assessment (units: points) (21).

It should also be noted that the mean change from baseline for LTE Week 24 presented in Figures 15, 16 and 18 of the Company Evidence Submission uses an earlier data cut-off (March 24th 2022) than the final CSR (last patient's last visit: February 1st 2023) (5, 6). As such, these values are not locatable in the PEACE CSR.

A21. Please clarify why long-term data from PEACE and 102A were not pooled to provide greater certainty in long term outcomes, and more data upon which to conduct subgroup analyses.

Company response: As highlighted in Section B3 of the Company Evidence Submission, pooled clinical data from PEACE and Study 102A were used for the majority of regression analyses informing the model. However, as noted by the EAG,

pooled analyses of the clinical outcomes from PEACE and Study 102A were not presented in Section B2.

The company was requested to explore the possibility of a pooled analysis of the available studies by the EMA, as part of the D120 clarification call (February 1st 2023), to provide further insight into the treatment effects of pegzilarginase. The primary analysis of the pooled data used a MMRM method for the primary efficacy endpoint (pArg concentration), two key secondary endpoints (2MWT and GMFM-E), and GMFM-D. No pooled analyses for individual subgroups (age, sex, region, and GMFCS Level) were undertaken. The MMRM model for each endpoint included baseline values, treatment group, study (Study 102A and PEACE), visit and interaction between visit and treatment groups as covariates in the model. The study factor was included to adjust the study differences between Study 102A and PEACE (22).

The results of the pooled analyses are described below:

- **PArg:** At baseline, the geometric mean (SD) pArg levels were lower in the pegzilarginase group (329.2 µM [30% CV]) than in the placebo group (464.7 µM [19% CV]). Similar to PEACE, the analysis with the pooled data showed treatment with pegzilarginase resulted in significant reductions ($p<0.00001$) in pArg compared to placebo starting at Week 6 and were maintained through Week 24 of treatment. At Week 24, pegzilarginase demonstrated a 77.9% reduction (versus 76.7% in PEACE) in mean pArg compared to placebo ($p<0.0001$) (5, 6, 22).

- **Timed Walk Test (TWT):** In Study 102A and PEACE, the 6MWT and 2MWT were assessed, respectively. To analyse the data in the same scale, percentage of change from baseline was used, instead of the observed walking distance in metres. At Week 24, the mean (SD) percentages of change from baseline in TWT were 9.2% (34.6%) and 4.1% (25.7%) for the pegzilarginase and placebo treatment groups, respectively. The LS mean difference between the treatment groups was 6.0% (95% CI: -19.6%, 31.6%; p=0.6409), which was similar to the result observed in PEACE (p=0.5961) (5, 6, 22).

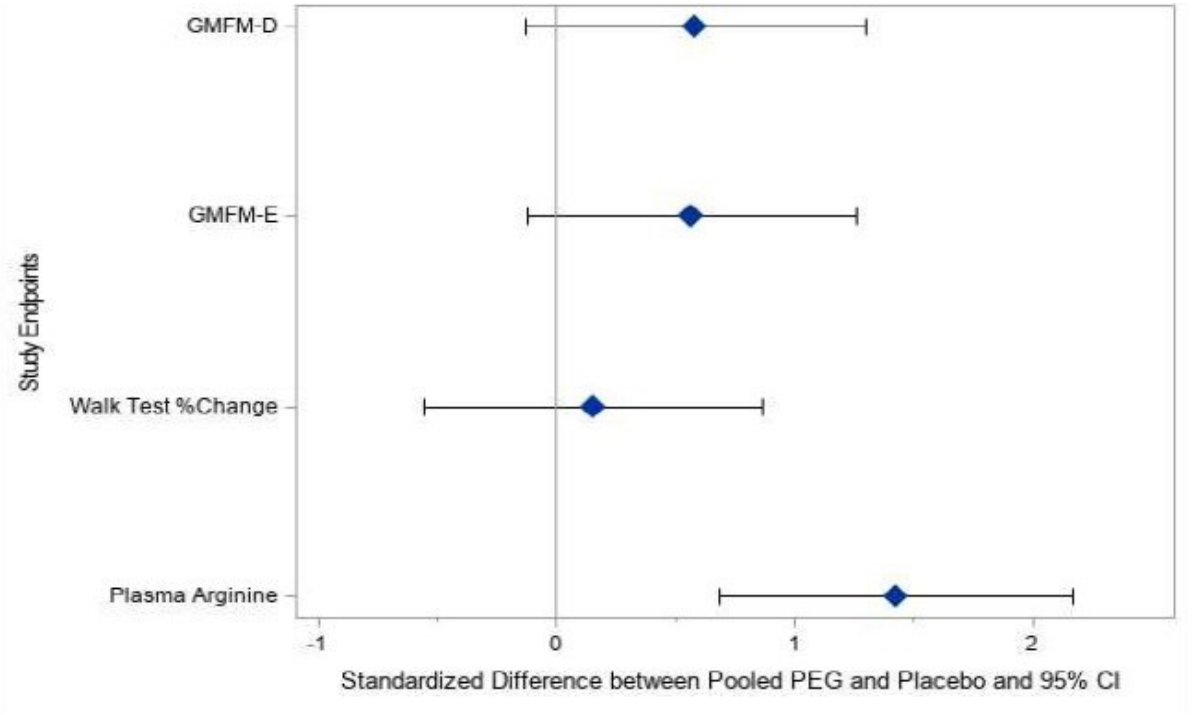
- **GMFM-E**: The mean (SD) baseline GMFM-E values for the pooled pegzilarginase and placebo treatment groups were similar, 47.8 (22.4) and 46.5

(24.6), respectively. At Week 24: the LS estimates of the mean change from baseline in GMFM-E for the two treatment groups were 3.5 (95% CI: 1.2, 5.8) and -1.1 (95% CI: -5.3, 3.2), respectively. The corresponding LS mean difference was 4.6 with a p-value of 0.0703 (improved compared to PEACE result [p=0.1077]) (5, 6, 22).

- **GMFM-D**: The mean (SD) baseline GMFM-D values for the pooled pegzilarginase and placebo treatment groups were similar, 28.0 (10.4) and 26.8 (14.8), respectively. At Week 24: the LS estimates of the mean change from baseline in GMFM-E for the two treatment groups were 2.2 (95% CI: 1.2, 3.2) and 0.0 (95% CI: -2.0, 1.9), respectively. The corresponding LS mean difference was 2.2 with a p-value of 0.0504 (worsened compared to PEACE result [p=0.0208]) (5, 6, 22).

The forest plot below provides a visual summary of the combined analyses of primary and selected secondary endpoints for Study 102A and PEACE, and clearly demonstrates the superiority of pegzilarginase treatment in pArg reduction and functional mobility outcomes (Figure 9) (22).

Figure 9: Meta-analysis Forest plot (Study 102A & PEACE)



Key: CI: confidence interval; GMFM-D: Gross Motor Function Measure, Part D; GMFM-E: Gross Motor Function Measure, Part E; PEG: pegzilarginase.
Note: All endpoint measurements were converted so that higher values (to the right) represent favouring pegzilarginase.

Source: Data on File – D120 Pooled Analyses (22).

In conclusion, the pooled data from Study 102A and PEACE demonstrate the treatment effect of pegzilarginase on clinical outcomes in ARG1-D with improved statistical measurements.

A22. Considering CS doc B, Figures 19 and 24, patients with GMFCS data IV were excluded. Please provide the numerical patient level outcome data for these patients, as given in CS doc B, Figure 24.

Company response: Patients classified as GMFCS IV (5 of 32 patients; 15.6%) were excluded from the original composite clinical outcomes responder analysis presented in Section B.2.6.3, page 106 of the Company Evidence Submission as there was no published MCID for response for the GMFM-D and GMFM-E assessments (5, 6). The threshold for a clinically important response in the 2MWT, defined as a 9% change from baseline in distance travelled (21), was however still applicable to this patient cohort. Numerical patient level outcomes data across the mobility assessments is provided below in Figure 10.

Figure 10: Heatmap of responders in PEACE (patients with GMFCS Level IV)

Key: 2MWT: 2-Minute Walk Test; GMFCS: Gross Motor Function Classification System; GMFM-D: Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88, Part E; LTE: long-term extension.
Notes: There are no response thresholds available for GMFCS Level IV for GMFM-D and GMFM-E. Placebo/pegzilarginase group at Week 24 is not on active treatment. One patient ( ) was non-ambulatory at baseline and wheelchair dependence.
* Actual timepoint not at defined timepoint but within specified range.
Source: Listing 16.2.6.1.1, Listing 16.2.6.1.2, Listing 16.2.6.1.3; PEACE CSR (5, 7).

A23. Please clarify whether interaction tests were performed for the subgroup analyses, and if so, what the results of these tests were. If they were not performed, please clarify why.

Company response: Interaction tests were not performed for subgroup analyses according to the Statistical Analysis Plan. From a statistical perspective, the populations in the subgroup analyses would be too small (low power) for valid interaction test analyses to be performed.

A24. Please provide more information about VABS-II, including which domains are included in the tool.

Company response: The Vinelands Adaptive Behaviour Scale, Second Edition (VABS-II) is a scale designed to measure adaptive behaviour of individuals from birth to age 90 years (23). The VABS-II contains 11 general subdomains grouped into four domains as follows:

1. Communication domain evaluates the receptive, expressive, and written communication skills of the child
2. Daily living skills domain measures personal behaviour, as well as domestic and community interaction skills
3. Socialisation domain covers play and leisure time, interpersonal relationships, and various coping skills
4. Motor skills domain measures both gross motor and fine motor skills.

The 4 domain composite scores then combine to form the adaptive behaviour composite for those individuals aged birth to 6 years 11 months. Three domain composite scores (communication, daily living skills, and socialisation) combine to form the adaptive behaviour composite for those ages 7 through 90 years. The VABS-II scoring system describes how adequate adaptive behaviour by subdomain as 13 to 17 and 86 to 114 for the composite score (23).

The Company Evidence Submission reports on the VABS-II adaptive composite scores across the double-blind period (Section B.2.6.1.1.c.iii, page 84) and LTE (Section B.2.6.1.2.f, page 92) portions of PEACE, and Study 102A (Section B.2.6.2.8,

page 103). Results for each of the four individual domains of the VABS-II scale can be found in the PEACE and Study 102A CSRs (5, 10).

A25. Please clarify why there is no data beyond LTE96 for pArg for the pegzilarginase-pegzilarginase arm (CS Appendix M, Table 96). Please clarify what these data were at 120 weeks and 150/End of Study if available, since there are data for other outcomes at these timepoints.

Company response: As highlighted in Section B.2.6.1.2.a in the Company Evidence Submission, the number of patients in across the pegzilarginase/pegzilarginase group receiving treatment beyond LTE Week 96 (≤5 at each assessment timepoint) was low, with data available up to LTE Week 138.

At LTE Week 120, [redacted] patients in the pegzilarginase/pegzilarginase group were still receiving treatment. The mean (SD) change from baseline in pArg for the pegzilarginase/pegzilarginase group at LTE Week 120 was [redacted] µM (n=[redacted]) (5, 16). Outcomes data on pArg was not available at LTE Week 150/end of study (EOS) as no patients in the pegzilarginase/pegzilarginase group were receiving treatment at this timepoint (5, 16).

The low frequency of patients with data at and beyond LTE Week 96 can be attributed to the early completion of the study. The LTE portion of the study was planned to be performed for up to 150 weeks and was completed on February 1st 2023. At this time, patients who entered the LTE had variable study participation, raging from [redacted] weeks (5). The proportion of patients across each treatment duration category is provided below in Table 11.

Table 11: Figure 4: Duration of treatment in the LTE period (PEACE; FAS)

Treatment duration categories, n (%)	Pegzilarginase/ Pegzilarginase (n=20)	Placebo/ Pegzilarginase (n=11)	Total (n=31)
≥24 to <48 Weeks	[redacted]	[redacted]	[redacted]
≥48 to <72 Weeks	[redacted]	[redacted]	[redacted]
≥72 to <96 Weeks	[redacted]	[redacted]	[redacted]
≥96 to <120 Weeks	[redacted]	[redacted]	[redacted]
≥120 to <144 Weeks	[redacted]	[redacted]	[redacted]
≥144 to <168 Weeks	[redacted]	[redacted]	[redacted]

Key: FAS: Full Analysis Set.
Source: Table 61; PEACE CSR (5).

A26. CS doc B, page 86 – please provide the BSID-III data.

Company response: The BSID-III is a performance-based, clinician-reported outcome assessment for use in children aged 2-3.5 years. Scales include Cognitive Language (Receptive Communication and Expressive Communication subscales), and Motor (Gross and Fine Motor subscales). Each (sub)scale yields a total raw score, which is then standardised according to the patient's chronological age (scaled score).

As highlighted in Section B.2.6.1.1.d.ii, page 87 of the company evidence submission, only one patient completed the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). The results for this patient are presented overleaf in Table 12. This patient was randomised to pegzilarginase during the double-blind period of the study, and had measurements recorded at screening visit 3 and Week 24 (completion of double-blind period). No measurements were recorded in the LTE. Overall, there was no meaningful observed change in the neurocognition and memory of this patient at Week 24, aligning with results observed in other assessments measuring neurocognitive function in the study (Wechsler intelligence batteries; see Section B.2.6.1.1.d.ii, page 86 of the Company Evidence Submission) (5, 7).

Table 12: Bayley Scales of Infant and Toddler Development III (BSID-III) score (PEACE; FAS)

			Score			Age Equivalent		
Visit	Domain	Subdomains	Raw	Scaled	Composite	Years	Months	Days
Screening Visit 3	Cognitive	Cognitive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Language	Receptive Communication	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
		Expressive Communication	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
		Language Sum		[redacted]		-	-	-
		Language Overall	-	-	[redacted]	-	-	-
	Motor	Fine Motor	-	-	-	-	-	-
		Gross Motor	-	-	-	-	-	-
		Motor Sum	-	-	-	-	-	-
		Motor Overall	-	-	-	-	-	-
Week 24	Cognitive	Cognitive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Language	Receptive Communication	-	-	-	NA	NA	NA
		Expressive Communication	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
		Language Sum	-	-	-	-	-	-
		Language Overall	-	-	-	NA	NA	NA
	Motor	Fine Motor	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
		Gross Motor	[redacted]	[redacted]	-	3	2	0
		Motor Sum	-	[redacted]	-	-	-	-
		Motor Overall	-	-	[redacted]	NA	NA	NA

Key: NA: not applicable.
Notes: Only one patient was eligible for and completed the BSID-III.
Source: Listing 16.2.6.11; PEACE CSR (5, 7).

A27. CS doc B, page 93 – "[redacted] patients with data at LTE Week 150 (end of study) had a mean (SD) change from baseline of [redacted] (84)." – please clarify if these were pegzilarginase or placebo-pegzilarginase patients, and if there were any other data for this outcome at this timepoint.

Company response: At LTE Week 150/EOS, [redacted] patients in the pegzilarginase/pegzilarginase group had a mean (SD) change from baseline of [redacted]. [redacted] with data in the placebo/pegzilarginase group had a stable score from baseline. No additional data is available for this outcome at this timepoint (5).

A28. CS doc B, page 75 – "*At Week 24, pegzilarginase demonstrated a 76.7% reduction in mean pArg compared to placebo (95% CI: -67.1%, -83.5%; p<0.0001).*" – please clarify how this number was calculated as we cannot find this in the data tables provided. Please clarify if this is based on the geometric or the arithmetic mean change from baseline.

Company response: As highlighted in Sanchez Russo *et al*. (2024), pegzilarginase statistically significantly reduced geometric mean (SD) baseline pArg from 354.0 (0.27) µM to 86.4 (0.50) µM at Week 24 of the double-blind period; a 76.7% reduction compared to placebo (95% CI: -67.1%, -83.5%; p<0.0001) (5, 6). This reduction of 76.7% was calculated using the geometric mean ratio at Week 24 ([redacted]), which is provided in Table 20 of the PEACE CSR and Table 92, Appendix M of the Company Evidence Submission (value rounded to two decimal places; [redacted]) (5).

A29. Please clarify how many patients in each arm of PEACE achieved the MCID for VABS-II and the neurocognitive outcomes at all relevant timepoints.

Company response: A detailed description of the VABS-II assessment tool is described in response to A24. In PEACE, a responder was defined as a patient with ≥7.5-point improvement in adaptive behaviour composite score (24). At Week 24, the number of patients who achieved a response was low for both the pegzilarginase and placebo groups. The proportion of patients who achieved a response from the pegzilarginase group in VABS-II adaptive behaviour were [redacted] ([redacted] of 21 patients, [redacted]) in the pegzilarginase group and [redacted] ([redacted] of 11 patients) in the placebo group. In the LTE, the proportion of responders for VABS-II remained stable through LTE Week 150/EOS across both treatment groups (5, 16).

Table 13: Proportion of responders for VABS-II during double-blind and LTE periods (PEACE; FAS)

	Pegzilarginase/ Pegzilarginase	Placebo/ Pegzilarginase
Week 24		
n	21	11
Responders, n (%)	[redacted]	[redacted]
LTE Week 24		
n	20	11
Responders, n (%)	[redacted]	[redacted]
LTE Week 48		
n	20	11
Responders, n (%)	[redacted]	[redacted]
LTE Week 72		
n	20	11
Responders, n (%)	[redacted]	[redacted]
LTE Week 96		
n	20	11
Responders, n (%)	[redacted]	[redacted]
LTE Week 150/EOS		
n	20	11
Responders, n (%)	[redacted]	[redacted]

Key: EOS: end of study; FAS: Full Analysis Set; LTE: long-term extension; VABS-II: Vinelands Adaptive Behaviour Scales, Second Edition.
Notes: Response for VABS-II adaptive behaviour score defined as an improvement by ≥7.5 points from baseline. Otherwise, including if the change was missing, the patient was classified as a non-responder.
Source: Table 14.2.6.4.1; PEACE CSR (5, 16).

With regards to neurocognitive outcomes, a change of ≥7.5 points in full-scale IQ (FSIQ) score from baseline is considered to be clinically significant (24). By applying this threshold to patients with assessable FSIQ data, [redacted] of patients ([redacted] patients [pegzilarginase/pegzilarginase: [redacted] patients; placebo/pegzilarginase: 2 patients]) at the last assessment visit were assessed as improved (i.e., exceeded the ≥7.5-point change from baseline). A further [redacted] of patients ([redacted] of [redacted] patients [pegzilarginase/pegzilarginase: p[redacted]tients; placebo/pegzilarginase: patient[redacted]]) improved FSIQ score but not to the level of clinical significance, or improved to clinical significance but did not maintain this change at the final assessment and were stable overall. [redacted] of [redacted] patients ([redacted], [pegzilarginase/pegzilarginase: [redacted] patients;

placebo/pegzilarginase: [redacted] patients]) had scores that were stable over the duration of the study period, while [redacted] patients ([redacted] patients, [redacted] [pegzilarginase/pegzilarginase: [redacted] patients; placebo/pegzilarginase: [redacted]) experienced a decline from baseline in FSIQ over the duration of the study (5).

A30. Table 3 of the CS doc B – there are asterisks (* and **) in the table that are not defined. Please clarify what they mean.

Company response: The asterisks have been included in the table in error. An update to Table 3 of the Company Evidence Submission is provided below (Table 14).

Table 14: Disease and symptoms reported in the European BoI study (Table 3 - Company Evidence Submission)

Variable	Proportion (%) of patients if not other stated	n
Mobility and cognitive ability		
Limited mobility only	10	2
Cognitive deficiency only	10	2
Both	52	11
None	24	5
Do not know	5	1
Mean (SD) age at first sign of limited mobility	9.2 (12.6)	13
Mean (SD) age at first sign of cognitive deficiency	5.0 (3.5)	13
Spasticity		
Lower limbs	57	12
Upper limbs	0	0
Both lower and upper limbs	5	1
No	38	8
Experienced seizures		
Yes	29	6
No	62	13
Do not know	10	2
Taking anti-epileptic medication to control seizures (n=20)		
Yes	20	4
No	75	15
Do not know	5	1
Missing	--	1
Other symptoms[a]		
Yes	33	7
No	62	13
Do not know	5	1
Other long-term illness or disability[b]		
Yes	19	4
No	81	17

Key: BoI: burden of illness; SD: standard deviation.
Notes: Number of patients = 21.
[a]For example, vomiting, confusion, and dizziness.
[b]For example, hypertension, type 2 diabetes, low body weight/eating disorder.

Source: Table 4, A European Survey of Resource Use and Health-Related Quality of Life in Patients with Arginase 1 Deficiency and their Caregivers (46).

A31. The PRISMA flow diagram in Appendix D states that 171 articles were selected for the review, but the review does not list all 171 articles, nor are 171 likely to be of prime importance to the appraisal. Please clarify why 171 are included, but not listed.

Company response: As described in Appendix D, two published systematic literature reviews (SLRs) were used as the foundation to build from for the SLR update (25, 26). These SLRs were conducted by the originator company and are listed below:

- Bin Sawad A, Jackimiec J, Bechter M, Trucillo A, Lindsley K, Bhagat A, Uyei J, Diaz GA. Epidemiology, methods of diagnosis, and clinical management of patients with arginase 1 deficiency (ARG1-D): A systematic review. Mol Genet Metab. 2022 Sep-Oct;137(1-2):153-163. doi: 10.1016/j.ymgme.2022.08.005. Epub 2022 Aug 25. PMID: 36049366.

- Bin Sawad A, Pothukuchy A, Badeaux M, Hodson V, Bubb G, Lindsley K, Uyei J, Diaz GA. Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. JIMD Rep. 2022 Mar 25;63(4):330-340. doi: 10.1002/jmd2.12283. PMID: 35822089; PMCID: PMC9259395.

The PRISMA flow diagram in Appendix D presents the flow of literature for the SLR update only. The SLR update identified 16 eligible articles identified through the database search, and a further 5 records identified from the Bin Sawad *et al*. (2022) epidemiology SLR through citation chasing. The list of 21 included studies is provided in Table 68, Appendix D of the Company Evidence Submission.

The additional 150 articles identified through citation chasing represents all of the additional studies that were included in the two Bin Sawad SLRs. These were reported under the citation chasing header because it was unclear according to the PRISMAs which studies from the SLRs aligned with the SLR inclusion/exclusion criteria. For the sake of brevity, these studies were not included in the list of included studies identified in the SLR update, as their results were summarised in the Bin Sawad publications.

A32. CS doc B, page 43 states that Study 101A was on safety, pharmacokinetics, and pharmacodynamics of IV pegzilarginase, and text on CS doc B, page 45 states

"*was not designed to measure the efficacy of pegzilarginase*," but then in CS doc B, Table 12 it states Study 101A is "*An open-label, multicentre study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in patients with ARG1-D*". Please clarify which statement is correct.

Company response: Study 101A is a Phase 1/2 open-label study in patients with ARG1-D to investigate the safety, pharmacokinetics, and pharmacodynamics of IV pegzilarginase. The study was designed to evaluate the safety and tolerability of IV administration of pegzilarginase in patients with ARG1-D (9, 27). As highlighted on page 45 of the Company Evidence Submission, the study was not designed to measure the efficacy of pegzilarginase; the evaluation of efficacy was an exploratory objective of the study.

Section B: Clarification on cost-effectiveness data

Modelling questions

B1. Priority: Please provide revised base case analyses and sensitivity analyses should the economic model be revised based on the clarification process.

Company response: Start of updated section

Immedica has revised the base case as follows:

- Incorporation of new regressions from our updated patient dataset (ordered logit, GMFM DE vs age, pegzilarginase dose by trial period)
- Method of predicting progression for IDM based on time in state, using cut offs for each GMFCS from the trial data (as per question A2)
- SMR multiplier manually changed to 800 (question B6)
- Utility values using Hernandez-Alava (question B17)
- HAC rate on pegzilarginase stratified by first 6 months vs post-6 months (question B18)
- Special schooling removed from NHS costs and incorporated into societal (question B26)

Changes that do not affect the base case include:

- Implementation of progression estimates from the ordered logit model based on GMFM DE stratified by GMFCS (see question A1).
- Correction of the error in B11
- Reallocation of MLD health state costs to ARG1-D health states aligned with clinician feedback
- Optional continuity correction for baseline distribution (excluding GMFCS V)
- Dirichlet added for baseline GMFCS distribution (note that this leads to a materially higher PSA ICER)
- Pooled BoI carer disutility values for GMFCS IV & V
- CEAC code changed to incorporate optional QALY weight

A list of changes made in the model can be found in the **Change log** sheet of the updated model (just before the **References** tab).

Updated base case and scenario analysis results are presented in Table 15, Table 16 and Table 17, with sensitivity analysis results presented in Table 43, Table 44, Figure 11 and Figure 12 in the Appendices accompanying this document.

Table 15: Updated base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pegzilarginase + IDM	[redacted]	21.405	[redacted]				
IDM	[redacted]	4.119	[redacted]	£10,726,318	17.286	12.123	£884,777

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 16: Updated base-case results with QALY modifier applied

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Undiscounted incremental QALYs	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Pegzilarginase + IDM	[redacted]	[redacted]	[redacted]	28.692	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 17: Updated Net Health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Weighted incremental QALYs	NHB at £100,000	NHB at £100,000 (with QALY weighting)
Pegzilarginase + IDM	[redacted]	[redacted]					
IDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

End of updated section

B2. Priority: Clarify whether any analyses using continuity corrections were performed to alleviate the possibility that the probability of some plausible events would be zero. Instances where using continuity corrections may be beneficial include the distribution of ammonia levels in patients having HACs whilst on pegzilarginase treatment where a distribution has been defined based on [redacted] events.

Company response: A sensitivity analysis using continuity corrections by adding 0.5 to the number of patients at each ammonia level is presented in Table 18. These corrections led to a marginally higher ICER (£873,681 vs £871,279 for base case), and impacted the weighted ICER by only 3.91%, increasing the ICER from £298,565 (base case) to £310,251.

However, while this approach is appropriate for large sample sizes, we do not believe this to be appropriate when dealing with a sample of [redacted] events (5). For example, adding 0.5 to all categories for the pegzilarginase arm increases the proportion of events in the two upper ammonia categories from 0% to 8% (16% combined). This is a higher proportion in the upper categories than observed in the placebo group, which is not realistic. We also believe it to be plausible for patients on pegzilarginase to not have hyperammonaemia events that reach these levels, given the correlation between pArg and ammonia levels already described in the dossier. Therefore, we reiterate that we do not believe this scenario to be reasonable.

Continuity corrections could have been applied to the patient transitions, but we believe the approach taken, using the average transition probability of two adjacent health states, to be more clinically plausible.

B3. Priority: Provide results from a scenario analysis where the SMR has been calculated based on the company's base case population as defined by cells H33:H40 in the 'Settings' sheet but maintaining the assumption that all patients would be dead by 35 years in the IDM arm

Company response: The exploratory analysis where the SMR was calculated based on the company's base case population (GMFCS distribution and age) while keeping the age of death assumption decreased the ICER by 1.30% and increased the weighted ICER by 2.25%. The change was caused by a reduction in the QALYs captured for IDM arm that caused higher incremental QALYs compared with the base case. Further details are presented in Table 19.

Table 18. Submitted base-case results vs sensitivity analysis (Continuity corrections - distribution of ammonia levels)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
Continuity corrections – distribution of ammonia levels in patients having HACs	[redacted]	15.993	[redacted]	£873,681	[redacted]	[redacted]	£310,251

Key: HACs: Hyperammonaemia crises; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using van Hout utility values.

Table 19. Submitted base-case results vs sensitivity analysis (SMR calculations considering base case population)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
SMR without changing baseline characteristics	[redacted]	16.961	[redacted]	£859,938	[redacted]	[redacted]	£292,483

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using van Hout utility values.

B4. Priority: Provide more explanation on why the caregiver disutility from the Burden of Illness study is assumed to lack face validity (CS doc B, Section 3.4.3.3. As a bespoke study has been performed to collect these data, they should be more appropriate than using values from a different disease. Comment on whether the carer disutilities for MLD may be underestimated instead, as, for example it seems unlikely that there would be minimal impact on a carer with a child in GMFCS-I. Provide caregiver disutilities from other relevant diseases to allow the Appraisal Committee to see all relevant evidence. Additionally, comment on the likelihood that other data from the Burden of Illness study may also be incorrect if the caregiver utility data is to be discarded.

Company response: As we now have access to the individual patient data, we have been able to generate individual carer disutilities by subtracting the UK population norm (calculated using the Ara and Brazier algorithm (28)) from the carer's utility value (mapped using Hernandez-Alava (29), as per question B17). These disutilities align more closely in magnitude to the MLD carer utilities than those reported in the submission. However, likely due to small sample size, they do not follow the expected trend of worsening with more severe mobility or cognitive health states (see Table 20 and Table 21). Further issues [redacted] (1). As they now have face validity in terms of their general magnitude but not in terms of their ordinal value, we believe that the MLD values remain the most appropriate to be used in the model.

Table 20: Carer disutility values derived from BoI study patient-level data (including one double-counted carer)

	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS IV (n=2)	GMFCS V (n=1)
GMFCS Mean	-0.019	-0.149	-0.133	0.098
No/mild cognitive impairment (n)	-0.028 (7)	-0.034 (1)	-0.161 (1)	
Moderate/severe cognitive impairment (n)	0.050 (1)	-0.177 (4)	-0.105 (1)	0.098 (1)

Key: BoI: burden of illness; Gross Motor Function Measure Classification System.
Note: No patients in GMFCS III. [redacted]. Utilities derived using Hernandez-Alava algorithm.

Table 21: Carer disutility values derived from BoI study patient-level data (excluding one double-counted carer)

	GMFCS I (N=7)	GMFCS II (N=5)	GMFCS IV (N=1)	GMFCS V (N=1)
GMFCS Mean	0.002	-0.149	-0.105	0.098
No/mild cognitive impairment (n)	-0.006 (6)	-0.034 (1)		
Moderate/severe cognitive impairment (n)	0.050 (1)	-0.177 (4)	-0.105 (1)	0.098 (1)

Key: BoI: burden of illness; Gross Motor Function Measure Classification System.
Note: No patients in GMFCS III. Utilities derived using Hernandez-Alava algorithm.

Carer disutilities for MLD were obtained from Pang *et al.* (2020). This study assessed the burden of MLD based on a survey of 21 caregivers across different domains such as personal and family relationships, personal time, daily activities, physical and mental health, social life, leisure activities, work productivity and finances. Interviews of caregivers from Germany (n=7), the United States (n=8) and the UK (n=6) were performed as a semi-structured telephone interview (30).

Caregiver disutilities from other relevant diseases are presented in Table 22 to allow the Appraisal Committee to see all relevant evidence. HST2, HST3, HST12, HST15 and HST18, for Mucopolysaccharidosis type IVa, Duchenne muscular dystrophy, Neuronal Ceroid Lipofuscinosis – type II, Spinal Muscular Atrophy and Metachromatic Leukodystrophy, respectively are reported in this table. The size of carer HRQoL effect reported in those technology appraisals ranged from 0 to 0.189, and carer disutilities were generally modelled by patients' severity of the disease.

We believe that the BoI study patient utility values are relevant for the model, while acknowledging the issues relating to double-counting cognitive disutility discussed in B5.

Table 22. Carer health related QoL in NICE technology appraisals

TA	Indication population	Method for including carer HRQoL	Size of carer HRQoL effect	Carer details
HST2 (31)	Mucopolysaccharidosis type IVa (MPS IVa)	Carer disutility modelled by patient's disease severity	Disutility ranged from 0.00 to 0.14	1 carer
HST3 (32)	Duchenne muscular Dystrophy (DMD)	Carer disutility modelled by patient's ambulatory status	Disutility of 0.11	Company original submission: 1 carer. Company revised model: 3 carers. ERG analysis: 2 carers
HST12 (33)	Neuronal Ceroid Lipofuscinosis – type II (CLN2)	Carer disutility assumed to increase as disease's severity does	Disutility ranged from 0.02 to 0.189	1 carer
HST15 (34)	Spinal Muscular Atrophy (SMA)	Carer disutility varies by the health state of the patient	Disutility ranged from 0.03 to 0.08	1 carer
HST18 (35)	Metachromatic Leukodystrophy (MLD)		Disutility ranged from 0.00 to 0.189	Company original submission: GMFCS 0-4: 0 GMFCS 5-6: 1 Company scenario: GMFCS 0-1: 0; GMFCS 2-3: 0.5; GMFCS 4-6: 2 ERG analysis: GMFCS 0: 0; GMFCS 1: 0.5; GMFCS 2-3: 1; GMFCS 4-6: 2

Key: GMFCS: Gross Motor Function Classification System; HRQoL: health-related quality of life.

B5. Priority: The company's statement that if there were no further decrements associated with cognitive deficit then the model could not distinguish between people in the same GMFCS with mild and severe impairment is valid. However, as some patients will have had impairment a more appropriate method would be to estimate the utility in each GMFCS for people with no or mild impairment and then apply disutilities for more severe impairments. Attempt to perform these analyses.

Company response: We have further stratified the utility values from the BoI study according to whether patents had no/mild cognitive impairment vs. moderate/severe cognitive impairment. As described in the dossier section B.3.3.2, no cut offs were defined for total cognitive score (only subdomain scores) for mild, moderate or severe

cognitive impairment in the BoI study. However, there were 13 questions in total, in which “no/some problems” scored <2, “moderate” scored 2 and “severe/cannot do at all” scored ≥3. We have assumed that a total score of 0-20 denotes normal/mild impairment and 21-52 moderate-severe impairment.

Whether using the van Hout or Hernandez-Alava algorithm (see Table 23) (29, 36), these stratified values lack face validity, doubtless due to small sample size. For example, the utility of GMFCS II patients with no or mild impairment is higher than that of GMFCS I patients with no or mild impairment. Similarly, the utility of GMFCS II patients with moderate to severe impairment is higher than that of GMFCS I patients with moderate to severe impairment. The pooled values for GMFCS IV-V are more realistic, with negative utility values for no or mild cognitive impairment patients and highly negative utility for moderate to severe cognitive impairment. But these again come from very small patient samples.

Although the overall health state values lack face validity, the disutility values calculated from them may be realistic. That is, the disutility of cognitive impairment may be less impactful in patients with more severe motor impairment (as was considered in MLD). We therefore conduct a scenario analysis whereby the separate moderate and severe cognitive disutilities from MLD are replaced by the pooled moderate to severe disutilities calculated in Table 23. For GMFCS III, we take the average of GMFCS II and the pooled GMFCS IV-V value from Table 23. This scenario analysis has been conducted using the Hernandez-Alava GMFCS health state utilities reported in B17.

Table 23. Utility values stratified by level of cognitive impairment (Hernandez-Alava algorithm)

Cognitive impairment	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS (average or GMFCS II and GMFCS IV-V)	GMFCS IV-V (n=3)
0-20=no to mild cognitive impairment*	0.835 SD=0.176 Min=0.516 Max=0.987 (n=7)	0.925 SD=NA (n=1)	0.414	-0.098 SD=NA (n=1)
21-52=moderate to severe/extreme	0.231 SD=NA (n=1)	0.523 SD=0.215 Min=0.236	0.234	-0.091 SD=0.049 Min=-0.126

cognitive impairment		Max=0.728 (n=4)		Max=-0.056 (n=2)
Disutility of moderate to severe cognitive impairment	-0.605	-0.401	-0.234	-0.006

Key: GMFCS: Gross Motor Function Classification System; NA: not applicable; n: number of patients; SD: standard deviation.
Notes: Three patients reported no cognitive impairment (all in GMFCS Level I). There were no patients in GMFCS III.

Replacing the MLD moderate and severe cognitive disutilities lead to a slightly decreased ICER (-1.52%): £884,488 vs £871,279 reported for base case scenario (updated base case scenario with Hernandez-Alava utilities: ICER=£887,643), and a 3.63% increment in the weighted ICER that changed from £298,565 to £309,398. The change was mainly explained by the decrease in the QALYs of IDM, which experienced a reduction in 11.11% compared to the pegzilarginase + IDM impact observed (-2.90%). Results are reported below in

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]
Submitted base case using Hernandez-Alava algorithm	[redacted]	16.440	[redacted]	£887,643	[redacted]
MLD disutilities replaced by the combined moderate/severe disutilities	[redacted]	16.440	[redacted]	£884,488	[redacted]

.

Table 24. Submitted base-case results vs sensitivity analysis (MLD replaced by the combined moderate/severe disutilities).

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
Submitted base case using Hernandez-Alava algorithm	[redacted]	16.440	[redacted]	£887,643	[redacted]	[redacted]	£310,647
MLD disutilities replaced by the combined moderate/severe disutilities	[redacted]	16.440	[redacted]	£884,488	[redacted]	[redacted]	£309,398

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using van Hout algorithm.

B6. Priority. Economic Model: Clarify whether the calibration to obtain the SMR Weight is working as intended in the OS_calibration macro. It is believed that the goal for 'output_dead' is 'ARG1D_input_dead' although this does not appear to be in the model, ('input_dead' is however) with 'ARG1D-SMR-weight' being changed to achieve the goal. Goal Seek arrives at a value of 554.94, with a difference between the value and the goal of 0.08% (shown by putting a break point in the macro when the overrides are set to their original values). Manually changing 'ARG1D-SMR-weight' to a higher value, for example 800, before the overrides a reset would result in the target being met more closely.

Company response: This does indeed appear to be the case. The 'goal seek' method was implemented for efficiency when carrying out scenario analyses of different ages at death. However, we note that there is a <£10k difference in the ICER when applying the 554.94 vs. 800 (£298,565 vs £289,036, respectively) We agree that goal seek should be used to obtain an initial estimate and the final weight should be implemented manually for accuracy.

B7. Priority Explore the impact on the ICER of changing the age at which all people would be expected to die under IDM to 50 years rather than 35 years. Conduct this for both the company's base case and the requested analysis where the SMR has been estimated using the company's baseline characteristics.

Company response: Two scenario analyses were performed in this section; both considered a change in the ARG1-D patients age of death which was set to 50 years instead of the 35 years reported in the submitted base case. The first one uses the original SMR approach, which modifies the model baseline characteristics prior to calibration, while the second one explored the SMR estimation using the company's baseline characteristics.

The two scenarios presented in Table 11 resulted in higher ICERs as patient survival age was prolonged and more QALYs and costs were accumulated over time. The more significant increases in total costs were observed for the IDM (£342,692 and £332,484 respectively vs £184,702 reported for base case), compared to the effect those observed changes had for Pegzilarginase + IDM model patients (£10,874,508 and £10,873,048 vs £10,854,418 presented for base case).

The exploratory analyses increased the ICER by 10.01% and 9.42%, respectively. Those increments were caused by the magnitude of the impact in costs that were not compensated by the QALYs gained in those additional 15 years added to the age dead umbral. The two scenarios increased the weighted ICER by 16.88 and 15.82%, respectively changing from £298,565 (base case) to £348,976 in SMR original approach and £345,798 using the SMR requested approach.

Table 25. Submitted base-case results vs sensitivity analysis (ARG1-D age of dead: 50 years).

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
ARG1-D age of dead equal to 50 years	[redacted]	12.318	[redacted]	£958,513	[redacted]	[redacted]	£348,976
ARG1-D age of dead equal to 50 years and SMR estimated using the company's baseline characteristics.	[redacted]	12.576	[redacted]	£953,337	[redacted]	[redacted]	£345,798

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SMR: Standardised mortality ratios.
Notes: Results using submitted van Hout utility values.

B8. Economic model: Clarify whether using a variable name for starting age ('n_age_bl') in calculating the time horizon ('Settings' sheet cell D22) but not in row 35 of settings could cause errors when performing sensitivity analyses where age is changed.

Company response: We do not believe that this would result in an error, as 'n_age_bl' is the 'live' value from the Parameters sheet (after any varying in sensitivity analysis) whereas the lifetime time horizon is always 100 minus the live age, unless replaced by an alternative time horizon, in which case the time horizon is fixed at the user's specified value.

B9. Economic model: Clarify whether there is a conflict on the formulas for calculating cumulative logit by GMFCS between the CS doc B (page 144) and the Excel model (sheet 'Transitions', columns AG:AK). Clarify the formulas for cumulative logit by GMFCS.

Page 144 in the CS	**Excel model**
$\frac{e^{-17.2355-0.1951*GMFM\ D\&E\ score}}{1+e^{-17.2355-0.1951*GMFM\ D\&E\ score}}$	$\frac{e^{-17.2355-(-0.1951)*GMFM\ D\&E\ score}}{1+e^{-17.2355-(-0.1951)*GMFM\ D\&E\ score}}$

Company response: We can confirm that the CS is incorrect whereas the Excel model is correct**.**

B10. Economic model: In the Excel model (sheet 'Transitions', columns AG:AK), the log-odds of GMFCS-III and lower (-2.7166) is assumed to be the same as GMFCS-IV and lower (-2.7166); thus, the cumulative probability for GMFCS 4 and lower is the same as GMFCS 3 and lower, resulting in zero probability of being in GMFCS 4. Please clarify the justification for this assumption.

Company response:

Start of updated section

As discussed in question A1, we have updated the logistic regression model as well as how it is applied, now stratifying GMFM DE by GMFCS health state at baseline

before combining as a weighted average probability. In this updated approach, the probability of transitioning from GMFCS IV to GMFCS V is now assumed to be the same as that of transitioning from GMFCS III to GMFCS IV, thus removing the need to make an assumption regarding the ordered logit model coefficient. We have received no feedback from clinicians to suggest that speed of progression from either health state is likely to differ.

End of updated section

B11. Economic model: Clarify whether cells BU10:BU109 in the sheet 'Life Table HRQoL Weight' should be changed so that these contain formulae as in cell BU9.

Company response: The EAG is correct, we have corrected this in the updated model.

B12. Economic model: Clarify that all cells that are confidential in a revised model are marked as such.

Company response: This will be provided with the updated model.

B13. When mapping the GMFC-MLD states to GMFCS clarify why MLD3 is not merged with another state to inform the mapping. We would anticipate that this would be combined with MLD2 or MLD4 to use all data as similar approaches have been undertaken elsewhere in the model.

Company response: The specific rules that have been used throughout the model regarding combining health states were based on responses from clinicians who were asked which MLD health states should be collapsed into GMFCS health states (see Table 26). Only one clinician provided a response to this question and their suggestion was to combine states GMFC-MLD-0 and 1 to align with GMFCS 1, while GMFC-MLD-5 and 6 were merged into GMFCS 5. We therefore followed this rule when collapsing states in the model.

Table 26: Summary of clinical responses: MLD health states and applications for ARG1-D

Clinical expert	Patient experience population	Individual response
Clinician 1	Adult patients	"GMFC-MLD 5 and 6 could be combined into GMFCS 5 while

		GMFC-MLD-0 and GMFC-MLD-1 could be combined to align with GMFCS 1”
Clinician 2	Paediatric patients	“The two scales are not directly comparable and integrating health states would be challenging”
Clinician 3	Paediatric patients	CP was cited as a better proxy for utilities compared to MLD

Key: ARG1-D: arginase 1 deficiency; CP: cerebral palsy; MLD: metachromatic leukodystrophy.

Table 27. Allocation of GMFC-MLD states to GMFCS: Utilities.

MLD Health State	ARG1-D Health State	Notes
GMFC-0 GMFC-1	GMFCS-I	GMFC-MLD-0 and 1 were combined to align with GMFCS 1
GMFC-2	GMFCS-II	Aligned with GMFCS-2
GMFC-3	GMFCS-III	Aligned with GMFCS-3
GMFC-4	GMFCS-IV	Aligned with GMFCS-4
GMFC-5 GMFC-6	GMFCS-V	GMFC-MLD 5 and 6 were combined into GMFCS 5

Key: GMFCS: Gross Motor Function Classification System; GMFC-MLD: Gross Motor Function Classification in MLD; MLD: metachromatic leukodystrophy.

With respect to the mortality values, Increased MLD-related mortality in GMFC-MLD 1-5 was considered based on NICE ERG report on CLN2 (HST12). In that case, the following rule applied for the Selected SMRs after reassignment to GMFCS I-V (see Table 28).

Table 28. Allocation of GMFC-MLD states to GMFCS: Mortality.

MLD Health State	ARG1-D Health State	Notes
GMFC-0 GMFC-1	GMFCS-I	GMFC-MLD-0 and 1 were combined to align with GMFCS 1
GMFC-2	GMFCS-II	Aligned with GMFCS-2
GMFC-3	GMFCS-III	Aligned with GMFCS-3
GMFC-4	GMFCS-IV	Aligned with GMFCS-4
GMFC-5	GMFCS-V	Aligned with GMFCS 5
GMFC-6	Not used	

Key: GMFCS: Gross Motor Function Classification System; GMFC-MLD: Gross Motor Function Classification in MLD; MLD: metachromatic leukodystrophy.

Regarding health state costs in the updated model to be submitted at clarification, Immedica will change the approach used in the previous version of the model to be consistent with the clinical responses presented in Table 29, noting that MLD was only implemented as a scenario analysis. We acknowledge that there is an inconsistency with respect to allocation of utility and mortality, which we will correct in the updated model. However, we would like to point out that the model is currently using the ARG1-

D BoI study as a cost and HRU source for the base case, and that the model has not shown evidence of being sensitive to health state costs.

Table 29. Allocation of GMFC-MLD states to GMFCS: health state costs

MLD Health State	ARG1-D Health State	Notes
GMFC-0	GMFCS-I	
GMFC-1	-	GMFC-1 was not used in the allocation to ARG1-D
GMFC-2	GMFCS-II GMFCS-III	GMFC-MLD-2 and 3 were combined to align with GMFCS 2
GMFC-3	GMFCS-III	Aligned with GMFCS-3
GMFC-4	GMFCS-IV	Aligned with GMFCS-4
GMFC-5 GMFC-6	GMFCS-V	GMFC-MLD 5 and 6 were combined into GMFCS 5

Key: GMFCS: Gross Motor Function Classification System; GMFC-MLD: Gross Motor Function Classification in MLD; HRU: healthcare resource use; MLD: metachromatic leukodystrophy.

B14. Clarify why the utility of GMFC-MLD 0 was not assumed to be applicable to GMFCS-I despite assuming that other GMFC-MLD states were generalisable to GMFCS. Provide analyses using GMFC-MLD 0. Provide exploratory analyses where the cognitive distribution per GMFCS is independent of treatment so the Appraisal Committee can gauge the impacts of the assumptions made in CS doc B, Table 38.

Company response: The company considered that gross motor function abilities associated with the MLD GMFCS scale were not applicable to GMFCS I since GMFC-MLD 0 considers patients that are able to walk without support with quality of performance normal for age. This situation was not assumed to be applicable to GMFCS I as in this health state patients have already shown problems in balance, coordination, or speed and the inclusion criteria for in the PEACE study required that patients have at least one motor deficit at baseline (see Table 17 of the protocol). The presence of the GMFC-MLD 0 state in the Libmeldy® appraisal may reflect differences between the indications and/or trials for Libmeldy® (a gene therapy) vs. pegzilarginase: children who have the late infantile or early juvenile types of MLD must have no clinical signs or symptoms of disease to be eligible for Libmeldy®, thus the model had to be able to capture patients with no mobility issues.

The PEACE trial, conversely, required that patients have at least one motor deficit to be recruited. However, a number of patients were rejected at screening due to not having motor deficit (see A13) and there were patients in the BoI study in GMFCS I without motor deficit. Furthermore, there were patients without motor symptoms in the

BoI study who were coded as GMFCS I. This ‘normal’ health state can therefore be considered as an omission from the model, not only because some patients without symptoms may be eligible for pegzilarginase but also because patients with mild motor deficit treated with pegzilarginase might revert to normal mobility levels, which the model is not currently able to capture. Without a formal GMFCS 0 state, it is important that the utility and survival of the GMFCS I health state reflects the fact that a proportion of patients have normal mobility.

The two requested scenario analyses are presented in Table 30 and described below:

1. The scenario in which the GMFCS-I utility is equal to GMFC-MLD 0 utility generates higher QALYs for both pegzilarginase + IDM and IDM, reflected as a lower ICER (£810,212 vs £871,279 reported for base case). This scenario decreased the weighted ICER by 9.54%, changing from £298,565 (base case) to £270,071.

2. The exploratory analysis where the cognitive disutilities are the same in each arm (both as per IDM) increased the ICER and the weighted ICER by 4.57% and 9.02%, respectively. The increment was caused by the reduction in the QALYs generated for pegzilarginase + IDM and IDM, compared to base case.

Table 30. Submitted base-case results vs sensitivity analysis (GMFCS-I utility is equal to GMFC-MLD 0 utility).

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
GMFCS-I utility equal to GMFC-MLD 0 utility	[redacted]	16.440	[redacted]	£810,212	[redacted]	[redacted]	£270,071
Cognitive distribution per GMFCS is independent of treatment	[redacted]	16.440	[redacted]	£911,053	[redacted]	[redacted]	£325,492

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using van Hout utility values.

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B15. Clarify that according to the model, in the company's base case a price reduction of approximately [redacted] of the list price is required to produce a weighted ICER of £100,000/QALY gained.

Company response: The EAG's interpretation is correct.

B16. Clarify why it was deemed appropriate to use the hourly costs of a nurse to provide IV treatment (CS doc B, Table 56) rather than NHS Reference Costs such as SB13Z, SB14Z and SB15Z.

Company response: The company considered that IV administration in hospital could be better represented by 1 hour of a band 5-6 nurse's time as 30-minute infusion are generally required for the administration of pegzilarginase, then adding extra time for preparation and observation.

In contrast, NHS Reference costs such as SB13Z, SB14Z and SB15Z refer to the more complex administration of chemotherapy treatments (which often require pre-medication and/or more careful handling due to their toxic nature, requiring more resource use), such as Complex Parenteral Chemotherapy, Complex Parenteral Chemotherapy including Prolonged Infusion Treatment, and Subsequent Elements of a Chemotherapy Cycle, respectively.

B17. Clarify the problem in updating the results to use the Hernandez Alava method for mapping to the EQ5D-3L from the EQ5D-5L rather than the Van Hout approach. Assuming that it is possible, provide results using the Hernandez Alava method of mapping to EQ5D-3L.

Company response: We have now generated utility values using the Hernandez-Alava algorithm (see Table 31 and Table 32). We report results here replacing the van Hout values with the Hernandez-Alava values (using the average of GMFCS II and IV for GMFCS III, and assuming that the utility of GMFCS I is equal to the average of the general population utility and the BoI GMFCS I value, as per our submitted model).

Replacing the GMFCS health state utilities with the Hernandez-Alava algorithm reduced the QALYs in each group: 2.48% and 6.42% for pegzilarginase + IDM and IDM, respectively.

The change in the utilities translated into a reduction of 1.84% for incremental QALYs. Therefore, an ICER increase of 1.88% was observed (£887,643 vs £871,279 reported for base case), while the weighted ICER increased by 4.05%, changing from £298,565 (base case) to £310,647. Results are presented in Table 33.

Table 31: Patient utility weights by GMFCS level, by mapping algorithm

Mapping algorithm	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS III (average of II and IV)	GMFCS IV (n=2)	GMFCS V (n=1)
Van Hout algorithm, mean (SD)	0.783 (0.228)	0.598 (0.276)	0.344	0.09 (0.086)	0.028 (NA)
Hernandez-Alava algorithm mean (SD)	0.759 (0.269)	0.604 (0.258)	0.263	-0.077 (0.029)	-0.126 (NA)

Key: GMFCS: Gross Motor Function Classification System; NA; not applicable; n: number of patients; SD: standard deviation,

Table 32: Caregiver utility weights by GMFCS level, by mapping algorithm

Mapping algorithm	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS III (average of II and IV)	GMFCS IV (n=2)	GMFCS V (n=1)
Van Hout algorithm, mean (SD)	0.821 (0.162)	0.732 (0.218)	0.749	0.765 (0.04)	1.000* (NA)
Hernandez-Alava algorithm mean (SD)	0.864 (0.122)	0.733 (0.225)	0.735	0.737 (0.001)	0.985 (NA)

Key: GMFCS: Gross Motor Function Classification System; NA; not applicable; n: number of patients; SD: standard deviation.
***Note**: [redacted]

Table 33. Submitted base-case results vs sensitivity analysis (Hernandez-Alava method)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case. (using Hernandez-Alava method for mapping utilities)	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
Hernandez-Alava method for mapping to the EQ5D-3L from the EQ5D-5L	[redacted]	16.440	[redacted]	£887,643	[redacted]	[redacted]	£310,647

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B18. It is noted that the rate ratio of HACs for pegzilarginase is derived using only data from the long-term extension phase as it takes time for the full treatment effect of pegzilarginase to be obtained. Clarify why the model does not apply a higher rate of HACs in the pegzilarginase arm for the first 6 months when the full treatment effect has not been reached and provide a sensitivity analysis using an appropriately increased rate ratio in the first two cycles.

Company response:

Start of updated section

The treatment effect on HAC rate in the updated base case is now stratified between the first 6 months and follow-on months in the model, based on the results of a Poisson regression model (see Table 34). As expected, this change has had little impact on the results; applying the HAC rate from the LTE period to the first 6 months decreases the QALY-weighted ICER in the updated base case from £308,375 to £307,112.

Table 34: Poisson model for HAC rate ratio

Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.0021	0.0006 – 0.0048	<0.001
Peg DB period	0.3977	0.0783 – 1.8043	0.227
Peg LTE period	0.0764	0.0106 – 0.3912	0.003
Observations	51		
R^2 Nagelkerke	0.321		

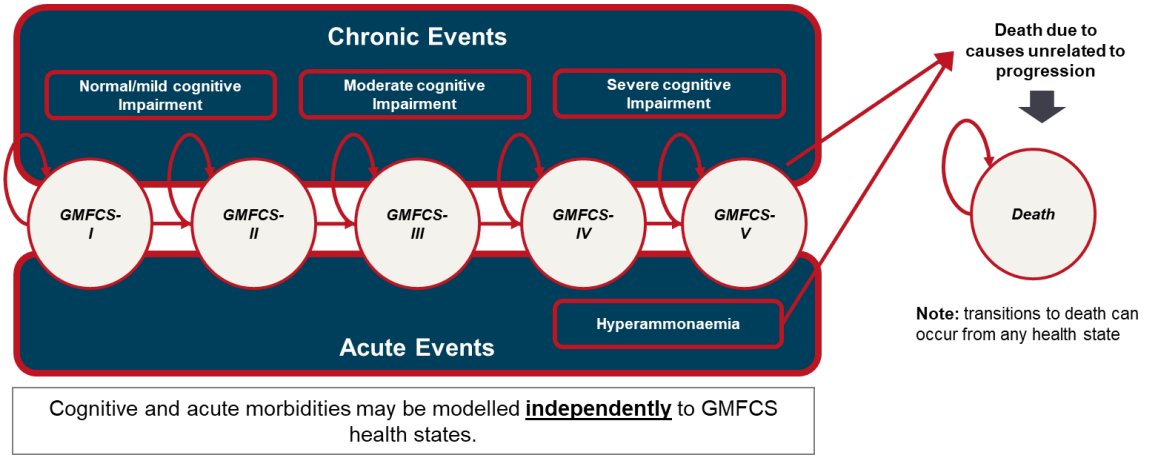
Key: Peg: pegzilarginase; DB: double blind period; LTE: long-term extension period.

End of updated section

B19. Please redraw the model structure in CS doc B, Figure 25 to clearly indicate which health states and conditions are considered in the model. For example, seizures and nausea should be removed from the diagram.

Company response: Figure 25 was updated and is now available below:

Figure 25: Model structure diagram



Key: GMFCS: Gross Motor Function Classification System.

B20. Clarify why cognitive limitations would not have an impact on any of the five EQ-5D domains particularly self-care, usual activities, and anxiety / depression.

Company response: This statement more accurately relates to patients completing the EQ-5D themselves (2 of 16 patients in this analysis) as patients with more severe cognitive deficits become less capable to self-report and tend to report higher HRQoL values than proxy completers (37). However, a concern regarding proxy values is that factors such as the relationship of the proxy, and specific characteristics of the proxy themselves can impact proxy assessments of HRQoL, as well as more pragmatic aspects such as the perspective the proxy is told to adopt when completing the measure and mode of administration (i.e., telephone, postal or interview) (37). This issue will clearly be more impactful with smaller sample sizes.

B21. Please provide a table summarising the utilities of all combinations of GMFCS, cognitive impairment, and treatment used in the company's base case.

Company response: Table 35 summarises these values. The net value comprises the sum of the health state, cognitive disutility and utility gain from diet, where relevant. Note that the utility values are restricted to a minimum value of -2.5.

Start of updated section (table updated with Hernandez-Alava utility values)

Table 35: Summary of all utility values applied in the model

	GMFCS I	GMFCS II	GMFCS III	GMFCS IV	GMFCS V
IDM					
Health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Moderate cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain from diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net utility (mild/no cognitive impairment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net utility (moderate cognitive impairment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net utility (severe cognitive impairment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegzilarginase + IDM					
Health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain from diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net utility (mild/no cognitive impairment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net utility (moderate cognitive impairment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net utility (severe cognitive impairment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

End of updated section

B22. Re CS doc B, Table 49: Provide results using a pooled GMFCS IV and V group which would not discard a data point rather than setting the GMFCS V value to that of GMFCS IV. This would also have a knock-on effect for the GMFCS III group if this was calculated based on the GMFCS-IV value.

Company response: We provide a pooled analysis of the Hernandez-Alava values presented in Table 36 below.

Table 36: Caregiver utility weights by GMFCS level, by mapping algorithm, pooled GMFCS IV-V

Mapping algorithm	GMFCS I (n=8)	GMFCS II (n=5)	GMFCS III Average of GMFCS II and pooled IV/V	GMFCS IV-V (n=3)
Van Hout algorithm, mean (SD)	0.821 (0.162)	0.732 (0.218)	0.788	0.843 (0.211)

Van Hout carer disutility (vs general population value of 0.882)	-0.061	-0.15	-0.094	-0.039
Hernandez-Alava algorithm mean (SD)	0.864 (0.122)	0.733 (0.225)	0.776	0.820 (0.143)
Hernandez-Alava carer disutility (vs general population value of 0.882)	-0.018	-0.149	-0.106	-0.062

Key: GMFCS: Gross Motor Function Classification System; NA; not applicable; n: number of patients; SD: standard deviation,

Immedica has performed a sensitivity analysis using a pooled GMFCS IV and V group to avoid discarding a data point rather than setting the GMFCS V value to that of GMFCS IV. The results are presented in Table 37 using the Hernandez-Alava algorithm for all utility values. As the BoI carer utilities were not used in the original base case, to permit comparison, we present:

- The base case using MLD carer utility values (as per the updated results in B17).
- The scenario aligned with our original scenario analysis (whereby the GMFCS V perfect health value was discarded and GMFCS V was assumed to equal GMFCS IV). That is, the values presented in Table 38 (but exchanging the van Hout values for Hernandez-Alava).
- The scenario whereby the GMFCS V value is not discarded and the pooled GMFCS IV to V value is used.

The results demonstrate an increase in the ICER and weighted ICER caused by the reduction in the QALYs gained by each group over time. The change in the caregiver disutilities using the BoI source led to an increase in the ICER equal to 3.31% and 3.06% for the GMFCS = GMFCS IV and the pooled GMFCS IV-V scenarios, respectively. Therefore, the weighted ICER increased by 7.96% and 7.16%, respectively (£335,368 and £332,899 vs £310,647 reported for the updated base case). Results are presented in Table 37.

Table 37. Base-case results vs sensitivity analysis (Pooled value for GMFCS 4-5 group).

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case (MLD carer utility)	[redacted]	16.440	[redacted]	£887,643	[redacted]	[redacted]	£310,647
Scenario using BoI carer utility (GMFCS V= GMFCS IV)	[redacted]	16.440	[redacted]	£917,022	[redacted]	[redacted]	£335,368
Scenario using BoI carer utility (pooled GMFCS IV-V)	[redacted]	16.440	[redacted]	£914,823	[redacted]	[redacted]	£332,899

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. BoI, burden of illness.
Note: Using the Hernendez-Alava algorithm for all utility values.

B23. Clarify whether the Population norm value in CS doc B, Table 49 is incorrect or whether the estimated disutilities are incorrect. Currently the addition of utility and (-) disutility provides a value for GMFCS-I to GMFCS - IV that does not equal 0.882.

Company response: This was a transcription error, Table 38 below presents the actual values from the model.

Table 38: ARG1-D caregiver disutility values from the BoI study

Health State	Utility	Disutility	Source
GMFCS-I	0.821	-0.06	Difference between population norm and carer utility. (1)
GMFCS-II	0.732	-0.15	Difference between population norm and carer utility. (1)
GMFCS-III	0.599	-0.28	The average of GMFCS II and GMFCS IV
GMFCS-IV	0.465	-0.42	Difference between population norm and carer utility. (1)
GMFCS-V	1.000	-0.42	Disutility assumed equal to GMFCS IV
Population norm	0.882		Ara and Brazier, aged 44, 66% female (27)

Key: ARG1-D: arginase 1 deficiency; BoI: burden of illness; GMFCS: Gross Motor Function Measure Classification System.

B24. Clarify why the utility in GMFCS-I estimated from the burden of illness study [redacted] is assumed to be an underestimate when [redacted]

Company response: The methodology of the two CP studies differs substantially from that in the BoI (see Table 39). The Ryan *et al.* (2020) study used the EQ-5D-Y instrument and patients completed the instrument themselves (with some assistance from the researcher where required) (38). As discussed in B20, proxy completers tend to report worse EQ-5D scores than patients themselves where there is more severe cognitive impairment, thus a lower mean score in the BoI study reflects the proxy completer's perspective of the impact of cognitive impairment in GMFCS I patients (5 of 8 having mild-severe impairment). The mean EQ-5D (Hernandez-Alava) utility for those in GMFCS I with no cognitive impairment in the BoI study (n=3) was 0.83, which is only slightly lower than the value used for GMFCS I without cognitive impairment in the economic model.

In the Jarl *et al.* (2019) study the EQ-5D3L instrument was completed, but this study enrolled adults aged 18-73, thus the mean utility value also reflects the disutility associated with an older population (39).

Referring back to question B17, without a formal GMFCS 0 state, it is important that the utility of the GMFCS I health state reflects the fact that a proportion of patients have normal mobility, either because they have been treated before the appearance of symptoms, or because they revert to normal mobility.

Table 39. Characteristics of responders from the cerebral palsy studies.

Cerebral palsy QoL study	Person completing	QoL measure
Ryan *et al.* (2020)	Paediatric and adolescent patients (aged 10-19)	EQ-5D-Y
Jarl *et al.* (2019)	Adult patients (aged 18-73)	EQ-5D-3L

Key: EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; EQ-5D-Y: EuroQol-5 Dimensions-Youth; QoL: quality of life.

B25. Clarify whether it is plausible that the costs of professional caregiving costs (CS doc B, Table 57) are [redacted] for GMFCS-V given that [redacted]

Company response: Both the professional caregiving and health care costs from the BoI for GMFCS V were zero (though note that the [redacted]), therefore we looked to MLD to populate these. The closest category to 'professional caregiving' costs we could identify in the MLD HRU was 'respite care', but this was also zero in MLD GMFC states 5 and 6. We therefore assumed that professional caregiving costs were probably included within the MLD 'hospitalisation' category. Furthermore, the three cost categories taken from MLD (medical tests, hospitalisation and medical visits and procedures) sum to a total of £71,456 per year (vs. £13,657 in GMFCS IV from the BoI), thus we believe that this would adequately capture any costs relating to the respite care category.

B26. Section 4.2.10 of the NICE manual states that technologies which may have substantial benefits to other government bodies should be identified during the scoping stage. If these are agreed with the Department of Health and Social Care and other relevant government bodies these would be included in the final scope. As the costs of special schooling are not in the final scope, clarify why these are

included in the company's base case (CS doc B, Table 57). Provide analyses with costs of special schooling excluded.

Company response: We had thought that special schooling costs were covered by personal social services, hence their inclusion. However, the model is insensitive to these costs. Reducing the costs by excluding special schooling had a more significant impact for IDM than for pegzilarginase + IDM, as it decreased the total costs for the IDM by 15.15%, compared to the 0.25% reduction for pegzilarginase + IDM costs. Thus, special schooling costs exclusion leads to a slightly increased ICER (£871,342 vs £871,279 reported for base case) and a weighted ICER increased by 0.007%, changing from £298,565 (base case) to £298,587.

The results of the scenario analysis are presented in Table 40.

Table 40. Submitted base-case results vs sensitivity analysis (special schooling costs excluded).

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
Costs of special schooling excluded	[redacted]	16.440	[redacted]	£871,342	[redacted]	[redacted]	£298,587

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results using van Hout utility values.

B27. Clarify whether the marginal cost of delivering pegzilarginase as part of homecare delivery is assumed to be zero as the company has agreed to pay this cost. If not, estimate the costs of home care delivery and include in the model.

Company response: Immedica will cover the marginal costs of homecare delivery.

B28. Clarify whether the 23-item PedsQL can be mapped onto the EQ-5D-3L. If it can be done, perform sensitivity analyses using these values conditional on GMFCS.

Company response: This was discussed in section B.3.4.2 of our submission, which we restate below:

The only algorithm we were able to identify which maps the PedsQL onto the EQ-5D was one by Khan *et al.* (2014) (40). This algorithm had poor predictive ability for poorer health states (utility <0.6) and was stated to be robust for populations comparable to that used to generate the algorithm; that is, children aged 11-15 years in attendance at secondary school. Given the substantial difference between the Khan population and ARG1-D patients, both in terms of age but also morbidity, no attempts were made to map using this algorithm.

An attempt was made to map the baseline PedsQL onto the CHU9D and stratify by GMFCS, as reported in section B.3.4.2 of our submission, but no relationship between HRQoL and GMFCS was observed.

B29. Given that the magnitude of the benefit of cognitive improvement was a point of debate in HST18, perform a sensitivity analysis where the disutilities associated with cognitive impairment presented in CS doc B, Table 48 are halved.

Company response: The requested sensitivity analysis has shown that once the disutilities associated with cognitive impairment were halved (as presented in Table 41), QALYs obtained by each group become higher, improving the incremental QALYs results. Therefore, an ICER reduction of 0.71% was observed (£871,279 vs £871,279 reported for base case), while the weighted ICER decreased by 2.04%, changing from £298,565 (base case) to £292,488.

Results for scenario requested in B29 are presented in Table 42.

Table 41. Cognitive substate disutilities for sensitivity analysis - B29.

Health State	Moderate Impairment	Severe Impairment
GMFCS-I	-0.12	-0.27
GMFCS-II	-0.14	-0.29
GMFCS-III	-0.14	-0.25
GMFCS-IV	-0.08	-0.17
GMFCS-V	-0.08	-0.14

Key: GMFCS: Gross Motor Function Classification System.

Start of updated section

We have not provided responses to the additional three clarification questions sent to us later. Health state costs do not appear at all in the tornado diagram, with the impact of individual cost components in GMFCS IV and V on the ICER being <£100. However, we can confirm that MLD costs were not inflated.

End of updated section

Table 42. Submitted base-case results vs sensitivity analysis (disutilities associated with cognitive impairment).

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	QALY weight	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)
Submitted base case	[redacted]	16.440	[redacted]	£871,279	[redacted]	[redacted]	£298,565
Disutilities associated with cognitive impairment	[redacted]	16.440	[redacted]	£865,104	[redacted]	[redacted]	£292,488

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Results using van Hout utility values

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Section C: Textual clarification and additional points

Literature review searches

C1. In CS appendix D, Section 1.1 Identification and selection of relevant studies, figure 35: the PRISMA flow of literature (page 7) shows that 155 out of the 171 records were identified and included in the review through citation chasing compared to 16 from the database searches. Clarify the reason(s) for the database searches not retrieving the 155 records. Please provide the list of 16 studies included from the database search that were used in the citation chasing.

Company response: As described in response to A31, the Bin Sawad SLRs were used as the foundation for the SLR update (25, 26). As it was unclear according to the PRISMAs in the publication which identified studies were aligned with the SLR inclusion/exclusion criteria, all citations from these two studies were identified via citation chasing and incorporated into the PRISMA for the SLR update. The Bin Sawad SLRs were then updated by running the original search strategy again to find more recent publications since they ran the original searches.

The update search began at the beginning of the year in which the Bin Sawad searches were run (January 2020) but did not go further back because it was assumed that the search strategy for the Bin Sawad SLRs had identified all relevant older publications. This explains why the updated database searches did not identify the 155 records identified in the Bin Sawad SLRs.

As highlighted above, the two Bin Sawad SLRs were utilised for citation chasing. No additional articles were used in the citation chasing.

Potential typographical errors

C2. Confirm whether the data seen by the EMA was up to week 120 (CS doc B, page 44) or week 190 (CS doc B, page 45).

Company response: As highlighted in Section B.2.2 of the Company Evidence Submission, the most-recent patient-level analyses of pegzilarginase effect on pArg and clinical response in the LTE of PEACE, and Study 102A, was recently shared with the EMA as part of mandatory post-authorisation measures for the marketing authorisation under exceptional circumstances. The heatmap was developed on

March 18th 2024 (41), and utilises the final data analysis of the double-blind and LTE periods from the PEACE CSR (final data cut-off date: February 1st 2023) and Study 102A CSR (final data cut-off date: December 15th 2022) (5, 10). This analysis is presented in Figure 24, Section B.2.6.3 of the Company Evidence Submission. For PEACE, the responder heatmap for the evaluable patients for the LTE period was up to LTE Week 120 (Week 144), while for Study 102A, the responder heatmap for evaluable patients was up to Week 190. Hence, the responder analyses seen by the EMA was up to LTE Week 120 for PEACE and Week 190 for Study 102A.

C3. Confirm whether the numbers on CS doc B, pages 84 and 85 are correct. An increase of [redacted] compared with a decrease of [redacted] appears to be a difference that isn't 4.9.

Company response: The company assumes that the EAG is referring to the following narrative from Section B.2.6.1.1.c.iii: *'At Week 24 of the double-blind period, the mean (SD) change from baseline was an increase of* [redacted] *points in the pegzilarginase group, compared to a decrease of* [redacted] *points in the placebo group (LS mean difference:* [redacted]*, 95% CI:* [redacted]*). The change from baseline to Week 24 indicates numerical improvement in VABS-II score in the pegzilarginase group'*.

The results described above align with those reported in Table 30, pg. 119 of the PEACE CSR (5). The LS mean difference (pegzilarginase-placebo) is based on an MMRM with visit, randomised study treatment, interaction between visit and randomised study treatment as effects, and baseline values are included as a covariate.

C4. Clarify whether the time horizon in the model should be marked as commercial-in-confidence (CIC) as the baseline age (which has been marked as CIC can be calculated) from this number.

Company response: Yes, the company agrees with the EAG that the time horizon in the model should be marked as CIC.

C5. In CS doc B, Table 48, should the 3rd to 5th rows omit 'and 1' from the source.

Company response: GMFCS-I already includes information from GMFC-MLD 0 and 1. 3rd to 5th rows now omit the text 'and 1' from the source, which was included in error and is not considered for calculations.

Table 48: Cognitive substate disutilities from MLD

Health State	Moderate Impairment	Severe Impairment	Source
GMFCS-I	-0.24	-0.53	Average of GMFC-MLD 0 and 1 (125)
GMFCS-II	-0.28	-0.57	GMFC-MLD 2 (125)
GMFCS-III	-0.28	-0.49	GMFC-MLD 3 (125)
GMFCS-IV	-0.16	-0.33	GMFC-MLD 4 (125)
GMFCS-V	-0.17	-0.28*	Average of GMFC-MLD 5 and 6 (125)

Note: Values were redacted in HST18, therefore we apply the utility values reported in the ICER group evaluation of Libmeldy®.
*Original value -0.33; 0.28 after application of minimum utility restriction.

Section D: References

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2. Immedica Pharma AB. Data on File - Clinical Expert Validation. 2023.

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4. Oeffinger DJ, Tylkowski CM, Rayens MK, Davis RF, Gorton GE, 3rd, D'Astous J, et al. Gross Motor Function Classification System and outcome tools for assessing ambulatory cerebral palsy: a multicenter study. Dev Med Child Neurol. 2004;46(5):311-9.

5. Immedica Pharma AB. Data on File - CAEB1102-300A (PEACE) Clinical Study Report. 2024.

6. Sanchez Russo R, Gasperini S, Bubb G, Neuman L, Sloan LS, Diaz GA, et al. Efficacy and safety of pegzilarginase in arginase 1 deficiency (PEACE): a phase 3, randomized, double-blind, placebo-controlled, multi-centre trial. eClinicalMedicine. 2024;68.

7. Immedica Pharma AB. Data on File - PEACE Consolidated Listings. 2024.

8. Medicines and Healthcare products Regulatory Agency. Loargys | Summary of Product Characteristics 2023 [Available from: https://mhraproducts4853.blob.core.windows.net/docs/72ef9201a40c63d480c8c06ec3ce85dd931f57e2.

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Appendix A: Updated sensitivity analysis results

Table 43: Updated probabilistic results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Weighted Incremental QALYs	Weighted ICER incremental (£/QALY)	ICER incremental (£/QALY)
Pegzilarginase + IDM	[redacted]	[redacted]					
IDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£918,250	£338,263

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs,

Table 44: Updated scenario analysis results

Scenario	Base case setting	Scenario setting	Incremental costs	Incremental QALYs	QALY weight	Weighted incremental QALYs	ICER	Weighted ICER
Base case			[redacted]	[redacted]	[redacted]	[redacted]	**£884,777**	**£308,375**
Baseline GMFCS distribution and age	PEACE + Phase I/2 + BoI pooled (and age 13)	Phase I/2 (and age 15.1)	[redacted]	[redacted]	[redacted]	[redacted]	£831,079	£280,700
Duration of improvement in GMFCS	36 months	24 months	[redacted]	[redacted]	[redacted]	[redacted]	£944,478	£350,949
		48 months	[redacted]	[redacted]	[redacted]	[redacted]	£844,392	£281,464
Source of GMFCS cut-off values	Pooled PEACE and phase I/2	Lidbeck et al., 2021	[redacted]	[redacted]	[redacted]	[redacted]	£873,566	£302,540
Method of predicting progression	Tiem in state using GMFCS cut offs	Ordinal logistic model stratified by starting GMFCS	[redacted]	[redacted]	[redacted]	[redacted]	£839,044	£285,286

Long-term GMFCS progression rate	No progression	90% reduction in GMFCS progression	[redacted]	[redacted]	[redacted]	[redacted]	£952,476	£374,525
		80% reduction in GMFCS progression	[redacted]	[redacted]	[redacted]	[redacted]	£1,023,060	£451,984
Weight ratio of ARG1-D patient vs general population	[redacted] for paediatric, [redacted] for adult	Same as general population	[redacted]	[redacted]	[redacted]	[redacted]	£1,050,569	£366,160
GMFCS health state utility values	ARG-1D patient survey	X-ALD	[redacted]	[redacted]	[redacted]	[redacted]	£783,519	£261,173
		MLD	[redacted]	[redacted]	[redacted]	[redacted]	£775,070	£258,357
Cognitive decline disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	£861,643	£290,502
Carer disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	£863,194	£292,603
Utility gain from improved diet	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	£899,249	£318,414
Drug costs	Dose banding	Wastage	[redacted]	[redacted]	[redacted]	[redacted]	£939,913	£327,592
Perspective	NHS and PSS	Societal	[redacted]	[redacted]	[redacted]	[redacted]	£899,113	£313,372
Age at which all IDM patients are dead	All IDM patients are dead by age 35	All IDM patients are dead by age 50	[redacted]	[redacted]	[redacted]	[redacted]	£983,754	£365,448

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs,

Figure 11: Updated CEAC (QALY weighted in qualifying simulations)

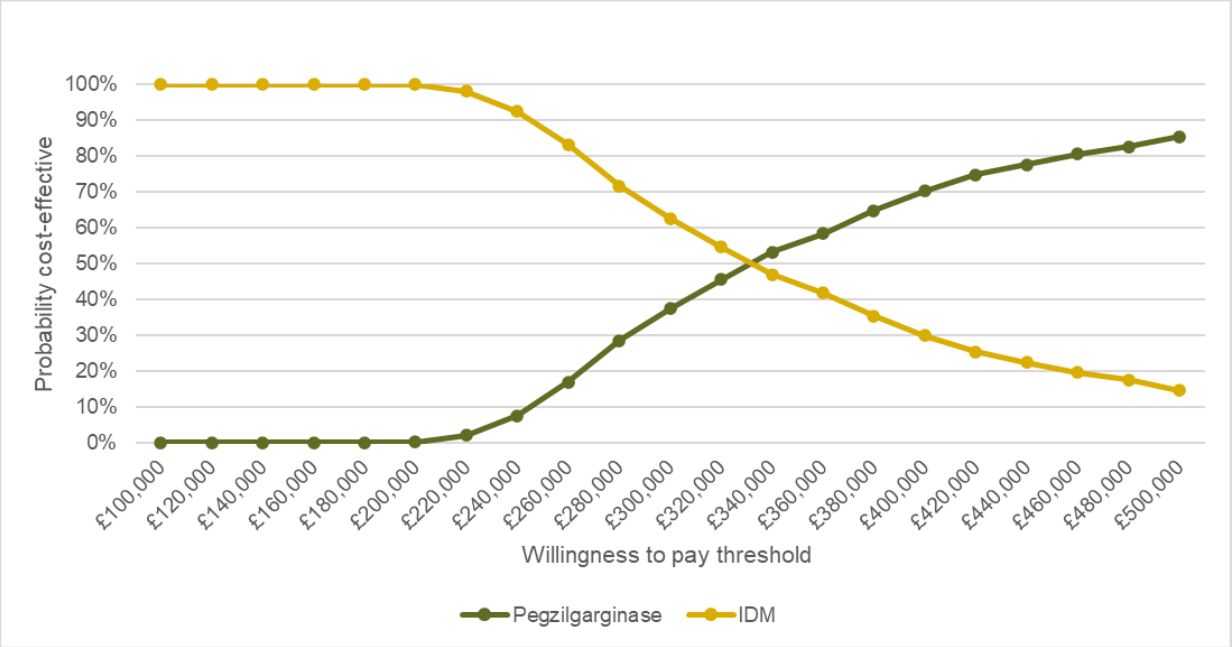
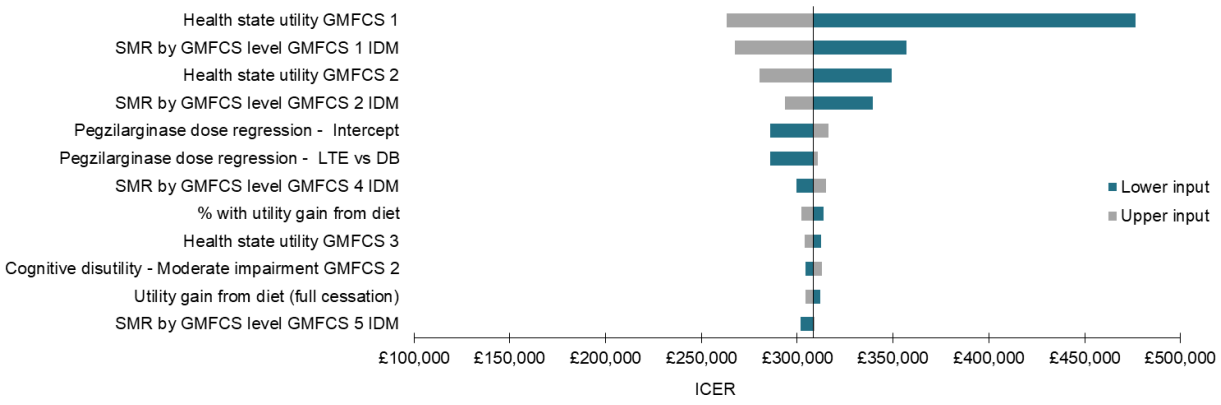


Figure 12: Updated one-way sensitivity analysis



Appendix B: Updated regression models

Table 45: Linear regression of GMFM DE score vs age

Predictors	Estimates	95% Confidence interval	p
(Intercept)	94.7843	77.3135 – 112.2551	<0.001
b age	-1.4452	-2.6646 – -0.2257	0.021
Observations	47		
R2 / R2 adjusted	0.112 / 0.093		

Key: CI: confidence interval.

Table 46: Random effects ordered logit of GMFCS vs GMFM DE

Predictors	Coefficient	Standard error	P>z	95% Confidence interval	
GMFM DE	-0.1864771	0.0539585	0.001	-0.2922337	-0.0807204
/cut1	-16.48208	4.772774		-25.83655	-7.127614
/cut2	-7.547909	3.204317		-13.82825	-1.267564
/cut3	-2.305604	2.420046		-7.048808	2.437599
/sigma2_u	8.853564	5.160105		2.824971	27.7474

Key: GMFCS: Gross Motor Function Classification System.

Table 47: Mixed model of pegzilarginase dose per time period

Predictors	Coefficient	Standard error	P>z	95% Confidence interval	
LTE	0.0256367	0.0041807	0.000	0.0174427	0.0338306
_cons (DB period)	0.1380118	0.0104592	0.000	0.1175121	0.1585114
sigma_u	0.04350208				
sigma_e	0.03320922				
rho	0.63180365				

Key: LTE: long-term extension; DB: double-blind.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation
Pegzilarginase for treating arginase-1 deficiency [ID4029]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Metabolic Support UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Metabolic Support UK are the leading organisation for Inherited Metabolic Disorders (IMDs), supporting thousands of people worldwide through providing individual support, building communities, and continually advocating for and empowering those living with IMDs. Using qualitative and quantitative data generated via various methodologies, our small, dedicated team works to proactively identify priority needs and develop evidence-based outputs and programmes to ensure the maximum impact for individual patients, collective patient communities and the wider IMD community. Metabolic Support UK receives its funding from corporation, community fundraising and grants, trusts and giving.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Metabolic Support UK received 5000 GBP in funding from Immedica towards the organisation of our annual conference in 2023. Metabolic Support UK received 350 GBP in reimbursement from the comparator company, Eurocept, for participating in a CPD training on hyperammonaemia for healthcare professionals in January 2024. Metabolic Support UK received 4300 GBP from the comparator company, Eurocept, towards our patient education programme “Access to Medicines” on hyperammonaemia.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information contained within this submission has been gathered in collaboration with the Arginase 1 Foundation (ARG1D foundation). A draft of the submission was reviewed by several families affected by ARG1d. The submission relies on information gathered through on-going discussions with families affected by ARG1d, including resources shared by the ARG1D foundation (1-3), a dedicated survey (4), our ARG1d disorder page (5) and our Think Ammonia! campaign (6). (1) ARG1D Foundation. 2023. Personal Stories about Living with ARG1d from Eleven Families. Data on file. (2) ARG1D Foundation. 2021. Meet our Families. Accessible via: https://arg1d.org/meet-our-families/ (3) ARG1D Foundation. 2021. FDA Patient-led Listening Session Report. Accessible via: https://arg1d.org/wp-content/uploads/2021/10/Family-Listening-Session-FDA-Arg1-D.pdf (4) Metabolic Support UK & ARG1D Foundation. 2024. Arginase 1 Deficiency Questionnaire. Data on file. (5) Metabolic Support UK. 2024. Arginase Deficiency. Accessible via: https://metabolicsupportuk.org/condition/arginase-deficiency/ (6) Metabolic Support UK. 2024. Think Ammonia! Accessible via: https://metabolicsupportuk.org/news-and-events/policy-hub/our-campaigns/think-ammonia-campaign/ Additionally, the following freely accessible published literature is referenced in our submission: (7) Scaglia & Lee. 2006. Clinical, Biochemical, and Molecular Spectrum of Hyperargininemia Due to Arginase I Deficiency. Am J Med Genet C Semin Med Genet; 0(2): 113–120. (8) Bin Sawad, Pothukuchy et al. 2022. Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. JIMD Rep; 63(4): 330–340.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Arginase 1 deficiency (ARG1d) is an ultrarare, autosomal recessive inherited metabolic disorder (IMDs). It is a progressive disorder associated with considerable physical and cognitive impairments, as well as mental health impacts, resulting in premature death. People living with ARG1d generally put a high demand on the healthcare system, requiring regular medical appointments with various specialist, as well as hospitalisations, including life-threatening emergency admissions, the number of which increases by age. The condition has a profound impact on the parents and carers of those living with ARG1d, including their mental health, day-to-day life, social life and ability to be in paid-employment. <u>ARG1d</u> ARG1d is a disorder which impacts the body's ability to break down protein (5). Many foods contain protein. To remove waste protein, the body produces the toxic chemical ammonia. Through the urea cycle, ammonia is subsequently turned into urea, which is secreted by the body through urine. In people living with a urea cycle disorder (UCD), one of the reactions in the cycle is impacted by a deficiency of one of the enzymes involved. Arginase 1 (ARG1) is the last enzyme of the urea cycle, breaking down the amino acid arginine, produced earlier in the urea cycle, into urea. In ARG1d, the body lacks the enzyme ARG1, which leads to toxic arginine levels which cause the signs and symptoms of the disorder (5). <u>Birth and diagnosis</u> All families have shared that their child was born healthy and that there were initially little to no concerns: *"[She] was born happy, healthy and lively […] She checked all the boxes and was sent on her way to start a young family life […] with her mom and dad" (1)* *"[She] ate and slept well and met her developmental milestones on time [during her first year]" (2)* *"His newborn screening came back positive for PKU (phenylketonuria) but repeated testing came back negative and results showed [he] didn't have PKU, giving us the belief he was a healthy baby boy." (1)* Clarification note: PKU is also an IMD. After receiving a false-positive, the family assumed they had a healthy son; they received an ARG1d diagnosis after his third birthday.

	Families report a wide timeframe during which ARG1d symptoms first present, ranging from the newborn stage all the way to early adulthood. In line with published literature (7,8), numerous families indicated that symptoms started during late infancy or pre-school age, i.e. around 2 to 4 years of age: *"He had symptoms most of his life" (4)* *"Right around 6 months old [he] started having seizures." (1)* *"The first year of [her] life she was able to meet all her milestones. It wasn't until she was 1.5 years old when she began to have symptoms such as nosebleeds and bruising." (1)* *"Between the ages of 2 and 3, [he] wasn't meeting milestones. He was a picky eater and wouldn't eat meat. He was very hyperactive, a toe walker, and his legs were tight. [He] started showing signs of developmental delay." (1)* *"After a few months we started to notice a decline in her motor abilities which resulted in an inaccurate diagnosis of "low tone". For the first couple of years, she was slow to meet her milestones but did eventually reach them. Around the age of 3, she started to decline much more noticeably and seemed to be losing all the progress, she had worked so hard to reach. It was now obvious that there was something terribly wrong. [She] had no growth or weight gain during her 4th year of life. She was labelled "Failure to Thrive"." (1)* *"I was diagnosed with ARG1-D at the age of 4.5 years old." (1)* *"At the age of 10, [she] began to experience fatigue and would stumble frequently causing her to fall." (1)* *"[She] was 18 years old and had just graduated from high school when she began to show similar symptoms as her older sister." (1)* As can be deduced from the excerpts above, initial symptom presentation varies. However, in line with the literature (7,8), missed milestones and mobility problems were common initial symptoms. From there, the disorder gradually progresses, with all survey respondents describing the general health of the person living with ARG1d as "poor" (measured by a six-level Likert scale ranging from "excellent" to "very poor") when not receiving pegzilarginase. Specifically, families describe how the lives of their child changed as the disorder progressed: *"He had many abilities throughout his life. Crawling, walking, propelling his chair, use of his hands, feeding himself, eating orally and the list goes on of his abilities. Slowly over time these things stopped one by one." (1)* *"She could once dance, run, jump, play tag, and chase her puppy but now we are seeing her fall constantly, struggle to walk, and not want to eat anything. She was having 30 - 40 seizures a day and when the seizures were controlled with medication, she would have horrible night terrors." (1)*

	"Before the onset of the symptoms, [he] enjoyed life fully, was very active and an outdoor person, made friends and socialised. [He] can no longer do any of the above and lost confidence and feels confined and not able to participate with others." (4) Mental health Many of these responses hint towards the underreported impact of ARG1d on the mental health of the individual living with the condition. This was also picked up by our survey, in which all respondents were asked to complete the EQ-5D-Y-3L. All respondents reported that their child was either "very worried, sad or unhappy" or "a bit worried, sad or unhappy". Additionally, families have shared: *"I worry my daughter could become depressed if she is unable to live an independent life." (1)* *"[She] is socially on point. This means that she is able to now recognize her differences and struggles with being so different from her classmates. […] Honestly, this is the hardest part, knowing that my kid is aware of her differences and is sad and alone." (1)* *"He is so isolated that he doesn't like to meet people and doesn't want to go anywhere. He is always at home in front of his computer and very much isolated." (1)* *"Due to [her] inability to walk and run like other children her age has caused [her] to experience depression and withdraw from society." (1)* Physical and cognitive symptoms Next to the impact ARG1d has on the mental health of people living with the condition, it is also associated with numerous physical and cognitive symptoms. Our survey respondents all mention experiences with the following symptoms in relation to the ARG1d diagnosis: missed developmental milestones / intellectual delays, stiff/rigid muscles (spasticity), seizures, vomiting, fatigue, falls and muscle weakness (4). Additionally, hyperammonaemia, behavioural issues, blood clotting difficulties, protein aversion and osteoporosis or fractures were also highlighted as symptoms (4). A separate report from the ARG1d Foundation, based on the experiences of five families living with ARG1d, also mentions each of these symptoms, with the exception of protein aversion. This report also highlights that some people living with ARG1d experience glaucoma, weakened immunity and liver dysfunction (3). Nonetheless, it is important to note that the severity of the disorder and its symptoms does vary between individuals (1,3,4,8). Finally, the disorder is known to lead to premature death due to the complications of the condition and hyperammonaemia (6,8). Missed developmental milestones / intellectual delays

	As detailed previously, missed developmental milestones are often one of the first symptoms observed by family members of a child who will later be diagnosed with ARG1d (4). The missing of developmental milestones and intellectual delays become more pronounced over time: *"[She] had to drop out of school" (1)* and *"School is a challenge as [she] is about 4 grade levels behind in math. She only just caught up to grade level with reading and is still multiple grade levels behind in spelling. Her handwriting is often illegible, even after 6 years of physical therapy focusing on this." (1)* Additionally, as also detailed previously, developmental regression also occur (4), with a child or teenager consistently hitting developmental milestones, only to regress and lose physical and intellectual capabilities over time: *"Throughout the years witnessing how my child has been progressively losing his walking mobility has been the worst experience of my life" (1)*. In line with this, parents report that their adult child has the *"mental age of a child"*, needing *"fulltime care"* (4). This was also reflected in the EQ-5D-Y-3L responses, with all respondents stating their child either has "some problems completing age-appropriate activities" or "a lot of problems completing age-appropriate activities" (4). <u>Stiff / rigid muscles (spasticity)</u> Similar to missed milestone, spasticity is often one of the first symptoms observed by family members of a child who will later be diagnosed with ARG1d (4). This was also found in the report from the ARG1d Foundation (3). The spasticity remains and similar to other symptoms of the disorder, progresses over time: *"[She] suffers from spasticity in all of her limbs but predominantly in her legs. This diagnosis is probably her most debilitating physical symptom. The spasticity requires her to wear AFOs (braces that wrap around her foot, ankle, and knee) to walk with proper alignment. Even with these, she often trips over her feet and stumbles on uneven ground. Just a crack in the pavement can cause her to fall." (1)* *"[She] started to show spasticity in both legs after 2 months after being diagnosed. A few weeks later, she began toe walking and started to lose mobility. She could no longer walk without assistance." (1)* *"His spasticity had become tighter and he is struggling with daily living skills and walking." (1)* This progression is also reflected in the EQ-5D-Y-3L responses, with the parents reporting on behalf of the youngest responder indicating that the child has "no problems walking or crawling", while those reporting on behalf of the oldest respondents indicate "a lot of problems walking or crawling" (4). <u>Seizures</u>

	Seizures are also common amongst those diagnosed with ARG1d (4). At least two families indicated that seizures were the first symptom of ARG1d *"right around 6 months old [he] started having seizures" (1)* and *"[he] had his first gazing seizure when he was six months old" (3).* For other families, seizures are an additional symptom that present over time, sometimes in conjunction with night terrors: *"Right before [his] 3rd birthday, he had an onset of seizures" (1)* *"[She] also suffers from night terrors and seizures" (1)* *"She was having 30 - 40 seizures a day and when the seizures were controlled with medication, she would have horrible night terrors" (1)* <u>Vomiting & protein aversion</u> Vomiting is often regarded as an undescriptive early symptom of ARG1d as it is common among babies in general. Several families indicated frequent and profuse vomiting during infancy (1,3,4) which may persist through childhood and into adulthood: *"If we walked out the front door, we always had the pan and towels to catch his vomit. He vomited 6 to 12 times a day, throwing up what little he could eat and all of his formula. […] he was unable to walk, run, or laugh without vomiting, his world was limited to riding in a stroller or a little red wagon, and no cartoons which he would laugh at"* (3). Some families also noted that their child had a protein aversion (4). <u>Fatigue</u> Fatigue is common among children and people living with ARG1d (4) and was highlighted as an issue for all participants who contributed to the report from the ARG1d Foundation (3). Additionally, families shared: *"[She] was constantly tired and wouldn't want to leave her room. She was no longer social with others and would experience anxiety." (1)* *"She can't walk for long distances as it takes a lot of exertion to lift her legs. A trip to the grocery store can physically wipe her out. She can't take part in a lot of kid focused activities because they usually require more physicality than what [she] is able to manage. She gets fatigued very quickly and has to sit out and watch the other kids play." (1)* <u>Falls and muscle weakness / osteoporosis and fractures</u>

	As a result of a number of the other symptoms of ARG1d, especially spasticity and fatigue, falls and muscle weakness are commonplace for people living with ARG1d. In some cases, people also reported the emotional impact of falls *"multiple unexplained falls a day caused injuries and were embarrassing" (1)*; while others shared that muscle weakness has led to individuals losing the ability to walk (1,3,4) or requiring mobility devices or wheelchairs to remain mobile (3,4). Symptoms persist with age and in older patients have led to further complications such as contractures, hip dysplasia, osteoporosis and fractures (3,4). Hyperammonaemia Hyperammonaemia, a metabolic crisis during which the toxic substance ammonia builds up in the body, can be extremely dangerous. It can lead to irreversible brain damage, as well as death, if not treated on time (6). Hyperammonaemia is common among all UCDs and often a presenting symptom. In ARG1d, "all of the families said they most feared this symptom" (3) because of the irreversible impact, "resulting in frequent serious admissions to A&E" (4). Hyperammonaemia most commonly occurs in people living with ARG1d after they have contracted an infection. *"The doctors were concerned about hyperammonaemia due to the high ammonia. What was he going to be like, had this caused brain damage? […] He will never get back all the abilities he lost but we are in a good spot right now." (1)* *"A cold isn't just a cold with these kids. It could potentially spin into a life and death situation, and we are constantly worried about this." (3)* *"We were told Arginase 1 Deficiency could be controlled with a low protein restricted diet and that Hyperammonaemia was uncommon. That was not the case for us. [He] was hospitalized many times for high ammonia and it can be life threatening." (1)* Behavioural issues Several families have raised behavioural issues, ranging from short attention spans, hyperactivity and poor impulse control to outbursts, fear and anger (1,3): *"There is a constant ever changing state of health. Depending on his levels and his neurological state, we have sleepless nights, whining or yelling and behavioural issues that can lead to aggressive behaviours. He needs 24 hour care from myself and paid nurses." (1)* Blood clotting difficulties

	In three families, the person living with ARG1d also has blood clothing difficulties. For one family, nosebleeds were the presenting symptom (1,3). The other two families have a formal diagnosis, with one being diagnosed with superior vena cava syndrome (3) and the other with factor 7 deficiency (4). **Healthcare visits** Overall, respondents to our survey indicated that the complex care needs of the individual living with ARG1d required the involvement of many different professionals (4), including a metabolic consultant, consultant neurologist, clinical nurse specialist, specialist dietician, physiotherapist, general practitioner and social worker. Other specialists, such as a gastroenterologist, hepatologist, occupational therapist and community healthcare teams are also often involved in care. Most of these are seen on at least a monthly basis and require families to travel to receive care; some provisions are local (e.g. GP, physio), while provisions provided by specialist hospitals generally require longer travel (2-3hours), including some provisions being spread over several hospitals (4). Visits are often planned, however, unplanned hospitalisation are also common (1), with one family reporting 10 hospitalisations between the age of three and nine and a further 55 between the ages of 10 and 25 (1), and other families sharing: *"She was hospitalized several times throughout the years, and would experience memory loss" (1)* *"Unplanned visits can vary year on year, from not frequent, to, very common and frequent in our experience sometimes, up to 3 - 4 a year." (4)* **Pegzilarginase and ARG1d** We are in touch with a few families (globally) who have experience with pegzilarginase through its clinical trial program. The impact of pegzilarginase on the presentation of the symptoms associated with living with ARG1d have been substantial, impacting all elements of life for both the individuals living with ARG1d, as well as their parents or carers: *"The treatment changed [her] life. The results were better than anyone expected. [Her] condition improved dramatically. 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. She was able to fully stop her seizure medications, her protein was upped to around 30 grams and her formula was reduced by about one third. This drug changed lives. [She] made giant strides at school and her teachers were shocked that anyone could gain so much in such a short time." (1)*

	"Joining the study was the best decision I ever made to help my child. For the first time in thirteen years, my child's arginase levels were within normal range. This was a tremendous blessing to our family. I was delighted that the drug was making a positive impact in my child's life. As a parent' it was the best feeling ever to realize that my child was experiencing what we had waited for all of our lives. An opportunity for him to enjoy life as a typical teenage boy and stopping this disease from progressing. 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." (1) *"Having seen the significant improvements as a direct result of the PEACE trial clinical trial drug, the benefits on both our son and the emotional impact on the family are key elements. This treatment enables improvements in the brain development of the patient as well as major improvements in cognitive behaviour and physical & psychological elements. This treatment will benefit the well-being of both the patient and their carers & family. Furthermore, the treatment will enable the patient to live a more normal life with less reliance on external support." (4)* Other families similarly outline the transformative impact that pegzilarginase has had on their families (1). **Carer impact** Through our ARG1d survey, we asked parents and carers about the impact ARG1d has on their lives. Parents and carers shared the extensive impact caring for someone living with ARG1d has had on their life: *"We have had to drastically reduce our social life, are unable to take holidays as a family based on the use of annual leave for appointments and based on the constant worry tend to stay at home. Going out is severely restricted, with constant changing to plans." (4)* On the note of holidays, one family explained the complexity based on everything that is needed: *"Holidays are difficult due to (i) need to have easy-access to hospitals with metabolic teams, (ii) need to carry medications and supplements (iii) not having the critical IV medication made available to take on holidays, to manage acute and life threatening elevated ammonia." (4)* Further to this, parents and carers also shared the need to give up or reduce work: *"I have had to step back from an Executive/Director level career, utilise annual leave days for appointments and furthermore work longer hours to juggle priorities." (4)* *"I am not able to work due to caring work" (4)* The caring work was further detailed through descriptions of what their day-to-day looks like and how a substantial part is dedicated to maintaining the health of the person they care for:

	"Full time caring, meds, personal care, feeds and diet control, health-care" (4) *"Regular monitoring at night, morning washing & dressing of child, tailored meal plan & preparation according to set Dietician guidelines, medication management throughout the day, physical movement exercise and educational development support." (4)* Additionally, several respondents to our survey stipulated the mobility adjustments that have been required to be implemented around their house to ensure the person living with ARG1d can move around either independently or dependently, as well as cared for (4). These include wheelchair ramps, step-less access to other areas of the house, including garage and backyard, bath lifts and electronic stair seats/lifts (4). Finally, many families have shared the various emotions they have experienced throughout the diagnostic process and subsequent progression of the disease, including being "concerned", "confused", "devastated", "terrified", as well as describing the experience as "surreal", "heartbreaking" (1). Considering the current circumstances where many families know that a working treatment is out there, and in most cases even having accessed it through the clinical trial program, yet currently being unable to access it, families have shared their desperation: *"I fear that I will lose [her] if she continues to decline. […] I am begging for someone to help us get my daughters back on this medication." (1)* *"I fear that she could no longer be able to walk, or be able to communicate with us. […] This isn't fair, we were so close and we know there is a medicine to help avoid this from happening." (1)* *"I fear that I may not be able to continue to work due to worsening side effects [of ARG1d]." (1)*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Arginase Deficiency can be managed through the following (5): • A protein restricted diet • A special amino acid supplement • Sufficient energy supply from food and feeds / regular feeding • Vitamin and mineral supplements • Other medications to control the level of ammonia in the blood, e.g. nitrogen scavengers In practice this generally means people living with ARG1d are on a strict diet of a very small amount of protein per day (1,5). They take special formula to receive all the nutrients missing from their daily diet, which may be

	given through an NG- or G-tube (1,5). Additionally, nitrogen scavengers are taken to minimise the nitrogen building up: *"All we could do was maintain a strict diet, and give Ravicti to slow down the disease. This was absolutely the toughest time in our life." (1)* Finally, hydration is also a crucial part of management to ensure the nitrogen scavenger medication is effective and ammonia is flushed out of the body (4). Families expressed that the management plan has clear benefits over no management and with that express a need for timely diagnosis: *"I wish he was on the proper formula plan sooner, I wish he was on nitro scavenging medications earlier. Maybe he would still be able to do some of the things or all of the things he used to do" (1)* *"Newborn screening and early treatment could've stopped or reduced the effects of this condition and might have made a big difference in [his] development. It's unfortunate that [he] was left untreated and became severely brain damaged." (1)* Nonetheless, families expressed that the current management strategies are insufficient: *"No treatment option available, just management. The disease slowly disables the ARG1d sufferer." (4)* *"Although the prescribed treatment of a low protein diet for this disorder isn't enough to completely stop the progression, we adapted well and were very strict with it. [She] followed her protein and formula intake precisely as planned. Even with this, we still couldn't get her arginine numbers under control and her liver enzymes continued to climb." (1)* Additionally, families will have an emergency regimen, to be used during e.g. childhood illnesses, to avoid a lack of energy supply and build-up of ammonia. Alternatively, given that the urea cycle takes place in the liver, a liver transplant may be considered (8). Opting for a liver transplant is often a difficult consideration, with one family commenting: *"Our fear was to let go of one set of issues and possibly get into another with a liver transplant." (1)*

	Our community shared that one family “lost a child […] following liver transplant, that was needed after elevated ammonia episode” (4). Further to this, at least two people living with ARG1d are currently on the liver transplant list in the UK.
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for people living with ARG1d and their families. In the absence of an approved disease-modifying treatment for people living with ARG1d, they and their families will continue to experience a gradual progression of the disorder. For individuals living with ARG1d, the condition impacts their physical, cognitive and mental health and eventually results in premature death. The mental health of parents and carers of people living with ARG1d is also impacted, as well as their day-to-day, social life and ability to be in paid-employment.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Pegzilarginase is the only disorder-modifying treatment option for people living with ARG1d. It has the potential to make a significant impact on the lives and outcomes of people living with ARG1d, as well as their families. Advantages of pegzilarginase raised by survey respondents included (4): - It effectively reduces arginine levels. - It improves the affected individual's physical and mental ability *"towards normality".* - It reduces the risk of developing life-threatening hyperammonaemia events. - No more dietary restrictions. Overall, families shared that it led to *"better management of the condition".* Additionally, families share that these advantages *"indirectly improve the mental well-being of the patient, family and carers"; "The true value of this treatment is in the improvement it provides to the lives of patients with Arginase Deficiency and the impact of this on family and carers" (4).* Other advantages shared anecdotally by individuals and their families who have experience with pegzilarginase through its trials include (1): - No longer requiring hospital admissions. - Ability to hold down a full-time job. - Reduction in seizures, with numerous families sharing seizures completely stopped leading them to *"fully stop her seizure medications".* - Improved mobility, posture, spasticity and strength, alongside a reduction in fatigue and "feeling ill": *"she quit falling"* and *"She could be active for longer amounts of time and her gait was much smoother".* - Increased functional communication, length of sentences, "*vocalising a variety of nouns and verbs*", clarity and speech. - Increase in sustained attention, catching up to friends, learning more quickly and "*not feeling singled out*". - Feeling like dreams about the future are within grasp again *"She has always dreamed of one day being married and having her own family"* and *"Her dream of being a ballerina was that much closer as she was finally able to get back into ballet and dance".*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Disadvantages of pegzilarginase raised by survey respondents included (4): - The requirement to use medication for a long period of time, likely a full life-time. - The requirement to travel to a specialised site; one family in the UK is currently receiving pegzilarginase under a compassionate use programme after having been part of the PEACE trial. They need to travel to the site weekly to receive the infusion which they regard as *"somewhat time consuming and would be beneficial if this new drug could be administered at home". (4)* - The risk unavailability of the product poses to families. This disadvantage was shared on the backdrop of the medication having become unavailable in the USA, where parents and carers have seen their children make substantial progress, only to regress shortly after treatment was paused in anticipation of regulatory approval: *"Less than one month after being off the medication, my daughter was admitted to the hospital in January and twice in the month of February."*, "*[She] is a 10-year old female child that stopped walking after 10 years in front of not only her school classmates, teachers but friends and family."* and *"I fear that I may not be able to continue to work due to worsening side effects [of ARG1d]" (1).* Continuous and sustained access to treatment will be paramount for people living with ARG1d and their families.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	ARG1d is a genetic condition with a reported higher prevalence in communities where consanguineous marriage is more prevalent. Special consideration must be given to communities where consanguineous marriage is/was common.

Other issues

13. Are there any other issues that you would like the committee to consider?	Families who participated in the PEACE trial, the phase 3 randomised, double-blind, placebo-controlled, multi-centre trial in which pegzilarginase was compared to placebo in people living with ARG1d, shared that they had concerns around some of the outcome parameters used. Specifically, the two-minute walking test was brought up as an outcome in which they felt some individuals may have achieved insufficient progress in the views of assessors. However, they ask reviewers to consider that a number of individuals enrolled in the trial had limited mobility to begin with. While outcomes may not be regarded as clinically relevant, observed improvements were meaningful to the individuals living with ARG1d and their families.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• ARG1d is an ultrarare, autosomal recessive, progressive inherited metabolic disorder, associated with considerable impact on physical, cognitive and mental health, as well as life expectancy. • The condition also has a profound impact on the parents and carers of those living with ARG1d, including their mental health, day-to-day life, social life and ability to be in paid-employment. • There are currently no disease-modifying treatments for ARG1d; instead, disease management currently relies on supportive care. • People living with ARG1d generally put a high demand on the healthcare system, requiring regular medical appointments with various specialist, as well as hospitalisations, including life-threatening emergency admissions, the number of which increases by age. • Pegzilarginase is the only potential disease-modifying treatment option for people living with ARG1d; research has shown the direct impact treatment has on the physical and cognitive health of people living with ARG1d, as well as direct impact on quality of life of both people living with and those caring for someone with ARG1d.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **03 July 2024** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

Part 1: Treating arginase-1 deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Arunabha Ghosh
2. Name of organisation	Willink Biochemical Genetics Unit, St Mary's Hospital, Manchester
3. Job title or position	Consultant in Paediatric Inherited Metabolic Disease
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with arginase-1 deficiency? ☐ A specialist in the clinical evidence base for arginase-1 deficiency or technology ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for arginase-1 deficiency? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is to prevent progression, which is characterised by progressive neurological disease. This manifests in particular as progressive lower limb spasticity, affecting gross motor function and mobility, as well as cognitive deficits and seizures in some patients. Episodic decompensations with

	hyperammonaemia also occur and prevention of these would also be a secondary goal of treatment.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Currently standard treatment aims to reduce plasma arginine levels to below 200 µmol/L, but this is very difficult to achieve in practice. A reduction of plasma arginine to below this treatment target could be considered clinically significant. In terms of the main goal of treatment, a stabilisation of motor function or improvement in functional mobility would be considered clinically significant. However, it would be important to consider that there may be other clinically meaningful benefits, which may be particularly of relevance in patients who are more severely disabled, where there may not necessarily be improvements in standard measures of mobility (e.g. 2 minute walk test). These could include for example: reduction of seizure frequency; reduction in hospital admissions, improved spasticity and need for medications/treatments for these.
10. In your view, is there an unmet need for patients and healthcare professionals in arginase-1 deficiency?	Yes. Standard treatment rarely results in achieving target plasma arginine levels and despite adherence to treatment, patients continue to experience a gradual progression of disease, with physical and cognitive deterioration. Episodic hyperammonaemia is relatively less common than in other urea cycle disorders but life-threatening decompensations, and decompensations with neurological sequelae, still occur.
11. How is arginase-1 deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	Diagnosis of arginase deficiency is based on the finding of elevated plasma arginine levels on amino acid analysis, in the context of a suggestive clinical history or family history. This disorder is not currently part of newborn screening programmes in the UK. It is standard practice to confirm the diagnosis by molecular genetic analysis of *ARG1*, to look for biallelic variants. Standard treatment involves:

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	- Dietary management with restriction of natural protein, with the goal of reducing plasma arginine levels to below 200 µmol/L. This usually requires a relatively extreme restriction of natural protein and up to 50% of required protein being given as essential amino acid supplements. Even despite adherence to this regimen, it is rare for the target arginine levels to be achieved. - Use of ammonia scavenging medication (e.g. sodium benzoate, glycerol phenylbutyrate) - An emergency regimen (a regimen of glucose polymer based drinks) to be used during intercurrent illnesses, and in some cases hospital admission may be required if these are not tolerated or if there is clinical deterioration, due to the risk of acute hyperammonaemia. Finally, liver transplantation may be considered in some patients if target treatment levels are not achieved and / or if there are frequent episodes of decompensation with hyperammonaemia. There are no guidelines for arginase deficiency only, but there are clinical guidelines for the management of urea cycle disorders which includes a section on management specific to arginase deficiency (Haberle et al. 2019 - 10.1002/jimd.12100). Guidelines for emergency management of decompensations is available at www.bimdg.org.uk. The pathway of care for paediatric patients is well defined in that patients in England with arginase deficiency will be referred to a paediatric metabolic disease centre, and are treated in an outpatient setting with paediatric metabolic clinical and specialist dietetic input. Patients are generally seen 4-6 monthly for clinical and dietetic assessments and monitoring of parameters including plasma amino acids (and arginine), and routine laboratory evaluations.

	In my experience, during discussions with clinicians and dietitians at other metabolic centres, the approach to treatment is comparable. I am not best placed to comment on the pathways of care for adult patients. This technology would not change the referral pathway for these patients but it is likely that additional resources will be required (see below), with some inpatient management initially and subsequently a move to home treatments. Some elements of standard care may be modified or no longer required. For example, there is a potential for relaxation of the severe dietary protein restriction, and for reduction or potentially cessation of ammonia scavenging medication.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Patients will still require access to specialist metabolic services, including a clinician and specialist metabolic dietitian. The treatment should only be used under the direction of a specialist paediatric or adult metabolic service. Pegzilarginase is given by subcutaneous injection and it is likely that treating centres would opt to administer at least the first few doses in hospital, to monitor for hypersensitivity reactions. Thereafter, the preferred option would be, where possible, to enable patients to receive treatment at home, which could be with community nursing report, or self-administration, which will require investment and planning. Investment into the following areas would be required: - Nursing time to support administration of medication in hospital - Availability of day case hospital bed and ancillary equipment - Availability of community nursing staff to support with administration of injections at home

	- Nursing time for training of patients/caregivers to administer injections at home - If home administration of treatment is possible in the long term this would necessitate delivery of vials to the home through a home care company; provisions for appropriate storage at home (medical fridge); ancillary equipment e.g. needles, syringes, gauze - Monitoring of plasma arginase levels in patients on this treatment requires specialised specimen collection tubes which would need to be sourced and provided to the clinical centres, and validation of the plasma amino acids analyses in these tubes needs to be conducted at the relevant metabolic laboratories
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It is not possible to comment on whether this technology will impact on length of life based on currently available data. I would expect the technology to increase health-related quality of life more than current care. Despite standard treatment, it is typical for there to be progression of neurological disease in these patients, leading to motor and cognitive deterioration and impacts on physical and psychological health. Pegzilarginase has the potential to prevent progression and may even lead to improvements in function. In addition, it may be possible for there to be relaxation of the extremely restrictive dietary regimen, or to reduce/stop additional medications such as ammonia scavengers.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Some individuals may have profound disability secondary to severe hyperammonaemic decompensation. The pathogenesis of the neurological disease in this situation is distinct from the neurological disease typical of arginase deficiency, and would not be expected to respond to treatment with pegzilarginase.

	For patients with profound disability and severely impaired mobility due to arginase deficiency, pegzilarginase may not lead to measurable improvements in mobility. However, it would be important to consider whether there may still be meaningful benefits from treatment such as improvement of tone/spasticity, reduction in seizure frequency, prevention of hyperammonaemia. Given the trend in clinical trial data for there to be a degree of improvement in functional mobility, rather than simply stabilisation of disease, patients with moderate to severe disability could still be considered candidates for treatment.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There are practical implications for the use of pegzilarginase: - The medication would need to be administered lifelong - Administration of a subcutaneous injection would likely be done in hospital for at least a number of initial doses, to monitor for hypersensitivity reactions. For patients this means travel to a specialist centre for dosing, which may be some distance away from the patient's home. From the healthcare professional point of view, this will require a day case admission bed and nursing time - In the longer term it would be preferable if patients and families could be supported to receive treatment at home, rather than travelling to a specialist centre regularly. This could be achieved with support from homecare nursing teams, community nursing teams, and it would be a reasonable goal to try to enable patients and caregivers to administer the medication themselves. This will require training of patients and caregivers, arrangements for delivery of medication to the home, appropriate storage (e.g. medical fridge), provision of ancillary equipment - Plasma amino acid monitoring will need to be done with specialised specimen collection tubes which will need to be supplied to treatment centres and the relevant laboratories will have to validate their assays using these tubes - More frequent plasma amino acid monitoring may be required during the first few weeks of treatment initiation, until a stable dosing level is achieved

	However, there is a potential for some elements of standard care to be modified, reduced or stopped after treatment with pegzilarginase - Liberalisation of the protein intake in the modified diet may be possible while on pegzilarginase therapy. This is a very difficult diet to maintain, with extreme levels of protein restriction, necessitating additional essential amino acid supplementation in most patients, which are generally unpalatable. It may be possible to increase the amount of natural protein allowed in the diet and reduce or stop the need for essential amino acid supplementation. - Treatment with ammonia scavenging medications (e.g. sodium benzoate, glycerol phenylbutyrate) could potentially be reduced or stopped While there are some practical and logistical aspects to delivering the therapy, I would anticipate that the treatment would be acceptable to patients and, if elements of standard treatment, particularly the diet, can be liberalised, the treatment regimen incorporating pegzilarginase may be considered to be easier to use overall. Without pegzilarginase, the alternative to standard treatment would be liver transplantation, which has been considered for some individuals with persistently high arginine levels. Pegzilarginase treatment would be expected to be more acceptable to the patient population that transplantation.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would expect that starting criteria would be as per the marketing authorisation, though there may be a clinical decision in individual situations that the treatment may not be expected to be of clear clinical benefit (see Q14). I would expect that stopping rules could be informal but based on non-response (failure to produce a reduction in plasma arginine levels to below the treatment

	target) or evidence of significant progression of neurological disease despite treatment.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The QALY calculation may not have fully taken into account the burden of current standard care, with an extremely restrictive and rigorous diet, and medications. There is a potential that these could be liberalised with pegzilarginase therapy. Other potential impacts on quality of life may include reduced hospital admissions with decompensations; reduced need for physiotherapy/OT/home adaptations for mobility issue and ability to remain in mainstream education and/or employment.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Pegzilarginase represents a step change in the management of the condition. Standard treatment is burdensome and treatment targets are very rarely attained, such that progression of disease despite treatment is common, resulting in significant disability in the long term. The potential for this treatment to stabilise or even result in a degree of improvement of function ability, as suggested by clinical trial data, clearly addresses a major unmet need of this patient population.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Infusion reactions may require a longer period administration of injections in hospital, and additional pre-medications.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	The trials include UK patients and the standard of care treatments for patients is comparable with UK clinical practice. The most important outcome measures include plasma arginine levels, as a surrogate outcome measure, and measures of motor ability. These were

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	measured in the trials (motor ability measured using GMFCS classification; GMFM-D and GMFM-E, and 2MWT). However, for patients who are more severely disabled at baseline, these may not be the most appropriate outcome measures, but there may still be measurable and meaningful clinical benefit. Other outcome measures of interest may therefore include: seizure frequency; measures of swallowing dysfunction; requirement for medication / treatments for dystonia. The use of plasma arginine as a surrogate marker is reasonable given the implication of hyperargininaemia in the pathogenesis of neurological disease in arginase deficiency. While there is limited data on the relationship between arginine levels over time and long term outcomes, there is evidence of a limited clinical improvement with reduction of arginine levels with standard therapy.(10.1002/jimd.12564) I am not aware of any adverse effects that have come to light since the clinical trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. How do data on real-world experience compare with the trial data?	Real-world experience with pegzilarginase is limited as this product has only been licensed for a relatively short period of time and to my knowledge there is not yet published real world data available. [redacted]

	[redacted]
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	Arginase I deficiency is inherited in an autosomal recessive manner and is reported to be more prevalent in communities with a higher prevalence of consanguineous marriages. It would be important that there is equity of access to specialist teams and treatment for patients from these communities.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Standard treatment is extremely restrictive and difficult to adhere to, and even with treatment, reduction of plasma arginine to target levels is almost never attained.
Progression of disease despite standard care is common.
Pegzilarginase reduces arginine levels to within target levels and has the potential to stabilise disease or even produce improvements in functional mobility in some patients.
Prevention of progression of disease would represent a meaningful change in health-related quality of life.
There may be additional benefits such as the potential to liberalise modifications to the extremely restrictive diet, or reduce or stop medications.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **03 July 2024** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating arginase-1 deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Salford Royal Foundation
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with arginase-1 deficiency? ☐ A specialist in the clinical evidence base for arginase-1 deficiency or technology ☒ Other (please specify): Metabolic Support UK
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I was chief investigator for the Phase three trial for the product under discussion
8. What is the main aim of treatment for arginase-1 deficiency?	Prevent progression of the disability (by preventing progression of neurological disease, reducing episodes of high ammonia and reducing blood arginine level)

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reducing arginine level below the target of 200 or reducing it by 100% from base line
10. In your view, is there an unmet need for patients and healthcare professionals in arginase-1 deficiency?	Yes
11. How is arginase-1 deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are no guidelines agreed nationally in the UK. Treatment is aimed at reaching the internationally agreed target of blood arginine below 200 micromoles. Majority of the patients are managed by the specialist metabolic centres in the UK. Although there is no defined pathway the approach is similar. Low protein diet is used to achieve the target blood arginine level (which is usually not successful). Ammonia scavenger therapies are used where patients have high ammonia. Supportive care is provided for learning difficulties and reduced mobility including botox, tendon release and baclofen pump. Technology will help to achieve the target blood arginine level and as result reduce progression of the neurological disease and reduce episodes of high ammonia.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	As it is injection given either under the skin or intravenous, patients will initiate therapy in the hospital at specialist centres. Once stable, the infusion will be delivered at home by the home care nurses. Family members will be encouraged to learn and be independent with the infusion.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Specialist metabolic centres. Metabolic Specialist centres in NHS are trained to start treatment i.e. ERT including new therapies for the patients. There are home care nurse services which are used to deliver treatment at home.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The clinical trial data form phase 3 was not long enough to confirm this but I truly believe that this technology has a very good chance of changing the course of the disease for these very unfortunate patients due the very debilitating disease. Yes Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who have very significant non reversible disabilities and do not have high ammonia may not benefit by this.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	At the initiation of therapy more frequent blood tests would be required for arginine and ammonia level to get the optimum dose. Once the treatment is optimised it should not be anymore burdensome.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would be useful to have formal stop and start rules. They should get agreed with all the specialist centres. I am not aware of such rules so far. Additional testing would be in the form of patient reported outcomes which are not measured as a part of standard of care now.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes: it is a step change
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Allergic reactions to the technology is possible and I do not expect for this to have any major impact on the quality of life and management of the condition.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, except that the liver disease in adults is much more pronounced and osteoporosis has also been noticed in our cohort. The most important outcome for immediate benefit would be blood arginine level and its impact on allowed amount of protein intake and ammonia. Impact on mobility Yes they were measured in the clinical trial

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	It is expected to have positive impact on mobility and reducing neurological progression and it would be long term outcome. No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. How do data on real-world experience compare with the trial data?	Comparable, our centre experience with this disease is currently in publication. There are some more emerging complications of the disease that we are reporting.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Current standard of care for these patients is not sufficient and patients' progression of the disease is relentless even if they were diagnosed early in life.

None of our adult cohort patients have a target level for blood arginine of less than 200 micromole/L

All patients have learning difficulties and have spastic paraparesis.

There are emerging complications of the disease in adult cohort like osteoporosis, need of multiple tendon release surgeries, need for baclofen pump, pancytopenia, worsening epilepsy.

Hepatic adenomas are other liver complications are under reported.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with arginase-1 deficiency or caring for a patient with arginase-1 deficiency. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **31 July 2024** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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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Patient expert statement

Part 1: Living with this condition or caring for a patient with arginase-1 deficiency

Table 1 About you, arginase-1 deficiency, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with arginase-1 deficiency? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with arginase-1 deficiency? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Self-nomination via Metabolic Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with arginase-1 deficiency? **If you are a carer (for someone with arginase-1 deficiency) please share your experience of caring for them**	My 20-year-old daughter, referred to as "the patient", has arginase-1 deficiency, and was diagnosed at the age of 7, with her first evident episode of arginase-1 deficiency, although many symptoms was present from birth (developmental and cognitive delay, stumbling walk etc). **Declining Health & Mental-State Over Time** From early life to now, the patient has gone from being able-bodied, very physically active, enjoying and wanting to be engaged in outdoor activities and adventures, and socialising; to having declining physical mobility ability, spastic paraplegia, wheelchair bound, and having reduced neurological, mental and cognitive abilities, and losing the confidence to socialise, and no longer enjoying being outdoors. **Full-time Care** The patient's condition requires full-time care and support to manage normal and basic daily life routines (i) Getting dressed, washing and bathing (ii) very strict daily diet management to maintain metabolic stability (protein, calories, fluids) (iii) taking medications on-time and the right dosage (iv) movement within the house and outdoors. **Daily Diet Management Critical for Metabolic Stability** The patient's daily diet must be strictly controlled and calculated for every meal and feeds, in terms of protein, calories and fluids, and requires supplements during daytime and nighttime, via electronic pump connected to gastro-PEG tube. Supplements and supplies are provided by NHS to manage this strict diet.

	Regular Hospital Management Needed & Admissions The patient requires constant and regular follow-up from the hospital metabolic teams, as well as emergency treatment as mentioned below. For hospital admission relating to any other illness, we must consider ensuring the patient can be admitted to the hospital where her metabolic team is based, as ANY type of medical intervention must take into account the patients arginase-1 condition and managed accordingly. **Triggers of Metabolic Instability – Hyperammonemia** With age, the patient seemingly has more frequent and regular symptoms and onset of Hyperammonaemia, ie. elevated levels of ammonia in the blood, that can lead to **coma and fatality** if not treated immediately. **On average the patient has monthly symptoms of hyperammonaemia.** We have experienced the patients common causes and triggers of hyperammonemia are: 1. Illness and infections 2. Stress & Anxiety 3. Lack of sleep 4. Dehydration 5. Menstrual cycle onset (currently causing a monthly hyperammonemia and implementation of emergency medical plan and often needing immediate hospital A&E treatment) 6. Introduction of new medications (happened with the introduction of biological medications)

	At the onset of the symptoms of Hyperammonaemia, we take immediate action to implement an Emergency Management plan at home (stop protein intake, prepare and start to continuous sos25 (glucose) feeds, via gastro-PEG feed controlled by Electronic Pump, and move straight to Hospital A&E department for investigations and treatment, and patient is normally taken immediately to Resus room. The patients Metabolic Emergency plan document (kept inside the patient's medical travel bag, and with patient at all times) is presented on arrival to A&E, triage team and medical A&E doctors). Ultimately if the patient deteriorates in A&E Resus, (clinical picture and symptoms and/or elevated ammonia in bloods), the immediate IV treatment with specialist scavenger medications is started, with regular monitoring of vital signs and labs/bloods) **Medical Emergencies & Life-Threatening Events** The arginase-1 deficiency condition has led to several serious medical emergencies and life-threatening events to the patient due to hyperammonaemia (elevated ammonia levels), requiring urgent admission to Hospital Emergency Department & treatment in resus. During these medical emergencies the patient had the following serious symptoms that can ultimately lead to **coma and fatality** had they not have been treated promptly: a) Loss of eyesight **/ cortical blindness** (temporary) b) Seizures c) Confused, d) Drowsy,

	e) Sleepy, f) Slurred speech g) Uncontrollable frustration h) Erratic behaviour and shouting, lashing out (video recordings taken), i) Pulling hair and pulling clothe off (video recordings taken) **<u>Loss of Eye-sight – Cortical Blindness</u>** On two occasions the arginase-1 deficiency condition has also led to extremely traumatic temporary loss of eyesight 'cortical blindness' for the patient (where the patient was asking if she was still alive). **<u>Travelling</u>** Whenever the patient is travelling, we must with the patient many medical supplies including (i) her diet control supplements and supplies (ii) electronic feed pump (ii) medications (iii) be aware of nearest hospitals in case of medical emergency.
7a. What do you think of the current treatments and care available for arginase-1 deficiency on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. No treatment available; only scavenger medications to help to prevent hyperammonaemia (elevated ammonia levels). b. Widely recognised that no current treatment available under the NHS. We are aware from families of many patients who have been on Pegzilarginase globally (on the trials and some now receiving the treatment), that Pegzilarginase has demonstrated to treat arginase-1 deficiency.
8. If there are disadvantages for patients of current NHS treatments for arginase-1 deficiency (for example, how they are given or taken, side effects of treatment, and any others) please describe these	No current NHS treatment available, thus patient exposed to all risks and symptoms of the condition as mentioned in #6 above as follows, with disadvantages as follows: a) Risk of Hyperammonaemia leading to <u>coma and fatality</u> not eliminated b) Risk of Cortical Blindness c) Decline of Mental state and Physical mobility not stopped

9a. If there are advantages of pegzilarginase over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pegzilarginase help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	(a) Advantages in order of importance i. Will stop the frequency of medical emergency admissions and threats to life including cortical blindness, coma and fatality – remove risk to life ii. Will stop all the condition related health and medical symptoms mentioned in #6 above – improve quality of health and life, iii. Will stop neurological mental decline – improve mental health and quality of life, iv. Will stop physical mobility deterioration and decline, improve ability to stand and walk again – improve physical health and quality of life v. Will stop seizures - improve health quality of life vi. Will stop the needs for strict daily management of diet calculation and control and stop need for daytime and nighttime electronic pump feeds and supplies - improve quality of life vii. Will stop the need for supplies from NHS of dietary supplements - improve mobility and quality of life viii. Will stop the need for full-time care - allow independence and quality of life ix. May prevent the need for **liver transplants**, that can be a long-term adverse effect of arginase deficiency (b) Advantages listed above in (a) in order of importance with reason mentioned at the end of each advantage

	(c) Overcome the risk of i. Life-threatening Hyperammonaemia leading to coma and fatality ii. Cortical Blindness iii. Decline of Mental state and Physical mobility iv. Reduce reliance of carers and allow independence v. Reduce the risk of need for liver transplant in long-run
10. If there are disadvantages of pegzilarginase over current treatments on the NHS please describe these. For example, are there any risks with pegzilarginase? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None
11. Are there any groups of patients who might benefit more from pegzilarginase or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Pegzilarginase will benefit patients will impact on physical mobility, as it will improve physical mobility (based on information and feedback from families of patients who received Pegzilarginase). Overall, it benefits ALL Pegzilarginase patients.
12. Are there any potential equality issues that should be taken into account when considering arginase-1 deficiency and pegzilarginase? Please explain if you think any groups of people with this condition are particularly disadvantage	None

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Pegzilarginase is the only treatment available for Arginase-1 deficiency, giving hope to patients and their families to i. Remove risk of life-threatening events (coma, fatality) ii. Improve the mental and physical health of patients and live and enjoy a normal quality of life iii. Reduce the strain on family carers iv. Reduce strain on NHS v. Can lead to need for liver transplants, which has its own complications with need for long term medications, and creates further demands on NHS for treatment

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- 1. **Arginase-1 Deficiency leads to life-threatening health issues**, requiring lifelong specialized medical management by rare disease metabolic teams, and frequent ER admissions – Pegzilarginase can remove this risk to life and dependency
- 2. **Arginase-1 Deficiency has a severe adverse patient quality of life impact**, leading to mental decline, and decline in physical mobility of patients leading to losing the ability to walk, and a huge strain on family members as carers – Pegzilarginase can stop this mental and physical decline, aid to improvements, and lessen the strain on carers
- 3. **Arginase-1 Deficiency patient management requires daily dietary management** via supplies and supplements to be administered, as well as rare disease (scavenger) medications – Pegzilarginase can eliminate this daily diet control, eliminate dependency and reliance on supplies and supplements, allowing patients to be free of these daily restrictions, and allow normality of life
- 4. **Arginase-1 Deficiency patients require full-time carers and management** - Pegzilarginase can eliminate the huge patient dependency on carers, and allow patients to move towards a normal quality of life with higher degree of independency
- 5. **Arginase-1 Deficiency patients may need liver transplants if the condition is not manageable** - Pegzilarginase can eliminate the need for liver transplants (liver transplants require further medical management needs and medication, from the NHS)

Thank you for your time.

Patient expert statement

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Single Technology Appraisal

Pegzilarginase for treating arginase-1 deficiency [ID4029]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with arginase-1 deficiency or caring for a patient with arginase-1 deficiency. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **31 July 2024** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with arginase-1 deficiency

Table 1 About you, arginase-1 deficiency, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with arginase-1 deficiency? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with arginase-1 deficiency? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): a sibling and carer of three people with arginase-1 deficiency
3. Name of your nominating organisation	Metabolic Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with arginase-1 deficiency? **If you are a carer (for someone with arginase-1 deficiency) please share your experience of caring for them**	I am the eldest of five; three of us have arginase-1 deficiency (ARG1d). All of us were normal, healthy children until around three or four years of age when three of us started to show symptoms. I watched each of them go from being a healthy child who was growing up to slowly starting to notice symptoms; the change in walking and learning difficulties. Each of them slowly deteriorated over time. They are now 32, 28 and 22 years old. My siblings were not diagnosed with ARG1d until seven years ago. Their diagnosis prior to that was spastic paraplegia. As there are no diet restrictions for spastic paraplegia, their protein was never restricted. None of them were ever good eaters, so they were on high calorie, high protein drinks. We also did not have an emergency protocol. If they were unwell, we just thought they were really sick. They probably had many episodes of high ammonia, and we never knew. I suspect that the lack of the right diagnosis and thus the right diet restriction and treatment did a lot of damage. Their care needs now are extremely high. They go to day centres, but the care outside of that is non-stop: they require fulltime personal care. Each of them is a wheelchair user, none of them can walk. For all of them, their speech deteriorated with time, my brother lost his speech, and my two sisters have speech difficulties but they can still speak and have gone to speech therapy. On average, we have three or four hospital appointments every week. The only specialist that is the same for all three of them is from the metabolic clinic. Besides that, they are under numerous other clinics, all seeing different specialist. Each of them has had numerous surgeries to address issues with their legs, muscles and bones and my brother is currently on the waiting list for further orthopaedic surgery. My siblings were diagnosed as a result of my request to be genetically tested for spastic paraplegia when I wanted to start a family. They told me there was no test

	for spastic paraplegia, but did send me to a genetic counsellor. The genetic counsellor confirmed the absence of a test, but did suggest we get the bloods of one of my siblings researched. About a year later they came back and said they had not found anything but that the bloods had been send to some other research institutes and that results would be shared if any were ever found. Five years later, they called again to let us know about the ARG1d diagnosis. After we received the ARG1d diagnosis, my partner and I, we already had twins, decided not to have any more children. I got pregnant again, an unplanned pregnancy, and decided not to have the testing done while I was pregnant. Unfortunately, it was later confirmed that my daughter does also have ARG1d. My daughter is now two years old and on a restricted protein diet. She currently does not have any ARG1d symptoms, except for highly elevated arginine levels. Last year, we made the difficult decision to put her on the liver transplant list. As the consultants are aware of our family situation and the disorder onset at about three years of age, we first started discussing a liver transplant when my daughter was six months old. Even though my daughter is on the restricted protein diet, which my siblings did not have originally, we have struggled to control her arginine levels. She is on the lowest safe amount of protein. With that, her arginine levels are generally around 450, where the doctors aim for below 200. Occasionally, her levels will go up to 800-900 and we have had to go below the safe amount of protein to bring her arginine levels back down. Besides that, she is also on ammonia scavengers. While we have hopes for pegzilarginase, we cannot wait and hope it will become available so we have moved forward by putting her on the liver transplant list. For as long as I can remember, I have cared for my siblings alongside my parents: I cared for them while I was going through school, college and university. I went to university and qualified as an accountant and worked for a year but had to stop to help my parents because they could not do it on their own. Now, I look at my parents and think that they should be at the age where they are retiring. Instead, my parents are fulltime carers and my dad is having to get up in

	the middle of the night to change my sibling's pads because they have become incontinent. ARG1d affects all of us in our family. When I was younger, I did not understand what was happening. I often wondered why this was happening and why them and not me? Now, I see the same happening with my twins. They have asked me how old they will be when they will need to start using a wheelchair and they are carers now too. They help with the care without being asked. It is our normal.
7a. What do you think of the current treatments and care available for arginase-1 deficiency on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The current treatment options are poor. It is all the doctors have available to them, but it is just poor. It comes down to diet control and ammonia scavengers. The diet can control it to an extent, for example, when my siblings were first diagnosed their levels were at 800 and after dietary restrictions were brought in, they lowered to 500. The low protein diet is very demanding for caregivers as it means everything has to be weighted and counted. As we care for several family members with ARG1d who are all on a different protein allowance, everyone's portion looks different. Besides that, especially my siblings also struggle with the flavour of the food. My daughter has only ever known low protein food, though she struggles seeing other people eat things she cannot have; but my siblings know what regular milk, rice, pasta and bread taste like. It is just not the same.
8. If there are disadvantages for patients of current NHS treatments for arginase-1 deficiency (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As per the above, the low protein diet is based on the weight of the person with ARG1d which is very demanding for caregivers. Additionally, accessing low protein food can also be challenging. None of the staple food items can be bought in the supermarket. All are prescribed. There have been numerous occasions where the pharmacy has not been able to supply bread or milk. As for the ammonia scavengers, they severely constipate my daughter.
9a. If there are advantages of pegzilarginase over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	One of my siblings, who is currently 32, was on the PEACE trial for two years. Through her we were able to observe the impact of pegzilarginase. At the time of the trial, she was the only one eligible. My other sister had just undergone surgery and was therefore not on a consistent diet which was a requirement of the trial. My brother was unable to give verbal consent, which was another requirement of the

	trial. My daughter was not yet born and once she was born, she was still too young to enrol. Pegzilarginase works better than the current treatment options available on the NHS. In my sister, it was able to bring her arginase levels down to zero like any other person. This is something diet had never been able to do. It took away a lot of stress and worry about her arginase levels, knowing that they were now normal. For my sister, a lot of fluid and swelling in her legs went down. Her ankles used to be very stiff but once treatment started, they became lean and could move around. She used to always sleep in a foetal position and now she could lie straight. Her personal care also became easier and less painful for her because her muscles were not as stiff anymore. My sister's speech also improved. She spoke a lot more clearly and generally was a lot happier. From speaking to other families, we know that some families saw symptoms reserve, with physical improvements most commonly observed. We know of one family whose child was 8 or 9, who went from walking with aids to independently walking as part of the trial.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	The reduction in arginase levels as that causes all the problems associated with ARG1d.
9c. Does pegzilarginase help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	As part of the trial we had to keep my sister on a low protein diet. We are not sure whether that would still be needed if she were to receive pegzilarginase outside of a trial setting, but it definitely took away the fear associated with the low protein diet still causing high arginase levels.

10. If there are disadvantages of pegzilarginase over current treatments on the NHS please describe these. For example, are there any risks with pegzilarginase? If you are concerned about any potential side effects you have heard about, please describe them and explain why	We observed substantial weight gain in my sister when she was on the trial. Within six months, she started gaining weight. Consultants were adamant it was not related to pegzilarginase as there were no other reports. We cut everything out of her diet but she was still gaining weight and went from a size 10 to a size 20. We also had to get her a new wheelchair. Once the drug stopped, she also lost all the weight again. However, weighing it up, we would rather see her gaining weight but stabilising everywhere else than continuing to worsen.
11. Are there any groups of patients who might benefit more from pegzilarginase or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The younger a person is when they start receiving pegzilarginase after an ARG1d diagnosis, the better it will be for them.
12. Are there any potential equality issues that should be taken into account when considering arginase-1 deficiency and pegzilarginase? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	Not that I know of.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	The diagnosis of ARG1d needs to be improved. It is only because I went for genetic testing that we eventually found out that spastic paraplegia was not the correct diagnosis for my siblings. All families affected by ARG1d or spastic paraplegia should have access to genetic counselling for family planning purposes.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- ARG1d is a life-changing condition.
- The current treatment options available on the NHS do not work. It is not enough for people with ARG1d.
- Pegzilarginase does what it is supposed to do. It brings the arginase levels down and keeps them down which has downstream effects on all symptoms of ARG1d.
- Caring for anyone with ARG1d is extremely difficult for the carers and for the person living with it.
- Click or tap here to enter text.

Thank you for your time.

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NHS commissioning expert statement

Pegzilarginase for treating arginase-1 deficiency [ID4029)

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☐ **x** commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick	☐ **x** yes

here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Current treatment of the condition in the NHS	
8. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NHS England commissioning policies for this intervention or this patient group. The BIMDG have developed a metabolic formulary, linked to the BNF which sets out the treatment regimes for this cohort.
9. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NHS England commissions an inherited metabolic disorders specialised service for adults and children which includes treatment of urea cycle disorders. The service aims to identify and diagnose patients, provide high quality diet and/or drug treatment and link in other clinical specialties as required.

10. What impact would the technology have on the current pathway of care?	This intervention if approved will represent a step change in care for this patient group as there is a significant burden of disease and limited existing treatment options
The use of the technology	
11. To what extent and in which population(s) is the technology being used in your local health economy?	This intervention is not formally commissioned by the NHS so any use to date will have been within the context of clinical trials
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Current care is largely supportive and this intervention would require iv or sc administration
• In what clinical setting should the technology be used? (For example,	The treatment would be used within the commissioned metabolic centres

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Drug companies are normally expected to provide drug specific training for health care organisations, including homecare companies. Infusions may require additional day case capacity or homecare capacity. These are costs associated with these options that are not currently in the system.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Any starting or stopping rules may be linked to continuing clinical benefit from the drug, mobility, plasma arginine and side effects. If the guidance includes any starting or stopping rules they would be included in a Blueteq form at commissioned centres
13. What is the outcome of any evaluations or audits of the use of the technology?	NHSE has not undertaken any audits of the use of this technology
Equality	
14a. Are there any potential equality issues that should be	No specific equality issues

taken into account when considering this treatment?	
14b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
15. To what extent does the population included in the key trials reflect the current population with the condition in the NHS in England? What is the current distribution of patients by the Gross Motor Function Classification System (GMFCS)? (what % of patients would currently be in these	We will hopefully have data later in the year for the number of patients, split by adult and paediatric, with urea cycle disorders known to services in England.

health states?) in the NHSE in England? What is the current split between children and adults in the population eligible for treatment in the NHSE in England?	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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Pegzilarginase for treating arginase-1 deficiency. [Review of ID4029]

A Highly Specialised Technology evaluation

Produced by	School of Health and Related Research (SCHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
	Sue Harnan, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
	Sunhong Kwon, Research Associate, SCHARR, University of Sheffield, Sheffield, UK
	Sa Ren, Research Associate, SCHARR, University of Sheffield, Sheffield, UK
	Ruth Wong, Information Specialist, SCHARR, University of Sheffield, Sheffield, UK
	Spyros Batzios, Consultant in Paediatric Metabolic Medicine, Great Ormond Street Hospital NHS Foundation
	Charlotte Dawson, Consultant in Adult Inherited Metabolic Disorders, University Hospitals Birmingham, UK
	Sergei Korenov, Consultant in Paediatric Metabolic Medicine, Central Manchester University Hospitals NHS Foundation Trust, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK

Date completed	13/06/2024

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare. However, Dr Batzios was involved in the PEACE study and provided unpaid clinical advice to Immedica.

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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

Ruth Wong critiqued the company's search strategy. Sue Harnan summarised and critiqued the clinical effectiveness data reported within the company's submission. Sa Ren critiqued the statistical aspects of the submission. Matt Stevenson and Sunhong Kwon critiqued the health economic analysis submitted by the company and performed the exploratory and sensitivity analyses. Matt Stevenson led the team. All authors were involved in drafting and commenting on the final report.

CONTENTS

List of tables

List of figures

List of Boxes

Abbreviations

2MWT	2 Minute Walk Test
ARG1-D	Arginase 1 deficiency
BSID-III	Bayley Scales of Infant and Toddler Development
CI	Confidence interval
CS	Company submission
CSR	Clinical Study Report
EAG	External Assessment Group
GMFC-MLD	Gross Motor Function Classification in Metachromatic Leukodystrophy
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
GMFM-E	Global Motor Function Measure, Part E
HAC	Hyperammonaemic crisis
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
ICER	Incremental cost-effectiveness ratio
IDM	Individualised disease management
ITC	Indirect treatment comparison
LTE	Long-term extension
MAS	Modified Ashworth Scale
MCID	Minimal clinically important difference
MLD	Metachromatic leukodystrophy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
pArg	Plasma arginine
PAS	Patient Access Scheme
PedsQL	Paediatric Quality of Life Inventory
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RoB	Risk of Bias
SAE	Serious adverse event

SF-36	36-Item Short Form Health Survey
SLR	Systematic literature review
SMR	Standardised mortality rate
TEAE	Treatment emergent adverse events
UCDC	Urea Cycle Disorders Consortium
USA	United States of America
VABS-II	Vineland Adaptive Behaviour Scales, Second Edition
WRS	Wilcoxon Rank Sum
ZBI-12	Zarit Burden Interview Short: 12 items

1. EXECUTIVE SUMMARY

1.1 Overview of the EAG's key issues

The EAG concludes that pegzilarginase appears to have a robust effect on plasma arginine (pArg) within the first 24 weeks of treatment, but that the effect on clinical outcomes (motor, neurocognitive and quality of life (QoL)) in the short-term are less certain since results were not both clinically and statistically significant or were not tested for statistical significance. There was some uncertainty around the generalisability of the minimal clinically important difference used to arginase 1 deficiency and underpowering may have affected outcomes. Short-term outcomes may have been affected by underpowering and there was some risk of bias from baseline imbalances in patient characteristics between arms in PEACE. In the long-term, numerical effects on pArg, 2 minute walk test, Gross motor Function Measures D and E appeared to be maintained through to weeks 96 or 120, though outcomes were uncertain due to the lack of a comparator arm and small numbers at later time points. Long term effects on neurocognition and QoL were more mixed and uncertain. Results for hyperammonaemic crisis favoured pegzilarginase numerically but were subject to limitations regarding the analyses performed, and at risk of bias due to imbalances at baseline in age. One clinical advisor to the EAG noted that chronic hyperammonaemia may cause harm without hospitalisations.

The majority of the issues identified by the EAG are related to uncertainty around key parameters values and assumptions which is a consequence of the lack of data. In this situation, the EAG could not confidently state which of multiple plausible assumptions are correct and have provided sensitivity analyses so that the NICE Appraisal Committee can deliberate on its preferred base case having an indication of how this could affect the EAG's base case results. The EAG's base case analysis includes three changes from the company's base which generated a more favourable incremental cost-effectiveness ratio (ICER) (expressed in terms of cost per quality-adjusted life year (QALY) gained) for pegzilarginase treatment compared with individualised disease management (IDM). The company's and EAG's deterministic weighted ICERs are £308,375 and £299,636, respectively. The probabilistic ICERs including QALY weighting are £311,119 in the company's base case (after EAG-correction) and £297,516 in the EAG's base case. All these values are substantially higher than the £100,000 threshold used by NICE in Highly Specialised Technology (HST) appraisals. The EAG highlights that its base case should be viewed in context of the considerable uncertainty in the decision problem and with reference to the sensitivity analyses undertaken and that some sensitivity analyses can greatly increase the ICER. Table 1 summarises the key issues identified by the EAG. Amendments made for Issues 1 to 3 are included in the EAG's base case, whilst Issues 4 to 15 are explored in sensitivity analyses. The EAG could not adapt the model for Issue 16.

Table 1: The EAG's key issues

Issue Number	Summary of issue	Report section
1	Identification of an error in calculating the transition probabilities for IDM	4.5.2.1
2	Uncertainty around the likely starting GMFM DE score for patients in GMFCS-I	4.5.2.2
3	Uncertainty around the decrease in GMFM DE score as patients age	4.5.2.3
4	Uncertainty around the appropriateness of assuming that patients on pegzilarginase treatment remain in the same GMFCS state after 3 years of treatment	4.5.2.4
5	Uncertainty around the cognitive improvement associated with pegzilarginase treatment	4.5.2.5
6	Uncertainty around the utility gain associated with an improved diet due to pegzilarginase treatment	4.5.2.6
7	Uncertainty around pegzilarginase drug wastage assumed within the company's model	4.5.2.7
8	Uncertainty around the starting distribution of patients across GMFCS states	4.5.2.8
9	Uncertainty around the assumption that almost all patients die by 35 years of age	4.5.2.9
10	Uncertainty around transition probabilities for IDM as not all patients start at the upper GMFM DE score associated with each GMFCS state	4.5.2.10
11	Uncertainty around the distribution of peak ammonia levels during a HAC	4.5.2.11
12	Uncertainty around the assumed discontinuation rate	4.5.2.12
13	Uncertainty around the disutility for carers	4.5.2.13
14	Uncertainty around life expectancy for patients receiving pegzilarginase treatment	4.5.2.14
15	Uncertainty around whether QALY losses attributed to carers should be included in the incremental QALY gains when calculating the weights for QALYs	4.5.2.15
16	Responders and non-responders not considered in the model	4.5.2.16

GMFCS: Gross Motor Function Classification System; GMFM DE: Gross Motor Function Measure D and E; IDM: individualised disease management; QALY: quality-adjusted life year

The EAG's preferred assumptions are:

- Correction of an error relating to the transition probabilities for IDM
- Amending the starting Gross Motor Function Measure (GMFM) DE score for patients in Gross Motor Function Classification System (GMFCS) state I
- Changing the rate of decline in GMFM DE score as patient age.

However, the EAG highlights that there are multiple alternative assumptions to that used by the company that are plausible. These have not been incorporated into the EAG's base case because the

EAG is not confident that the company's assumptions are incorrect. Instead, these have been explored in sensitivity analyses.

1.2 Overview of key model outcomes

The company's model assumes that pegzilarginase treatment increases quality-adjusted life years (QALYs) by increasing life expectancy for patients with arginase 1 deficiency (ARG1-D), maintaining patients in less severe Gross Motor Function Classification System (GMFCS) states and improving health related quality of life (HRQoL) for some patients through a less restrictive diet.

The company's model assumes that pegzilarginase treatment increases costs due to the acquisition price of pegzilarginase, which has a Patient Access Scheme (PAS) in the form of a simple discount ([redacted]). Whilst there will be annual cost reductions due to fewer hyperammonaemic crises in patients receiving pegzilarginase treatment and reduced costs due to patients being in better GMFCS states, the extension of life for patients results in more non-drug costs for patients receiving pegzilarginase treatment.

The modelling assumptions that have the greatest effect on the company's base case ICER relate to whether treatment with pegzilarginase stops disease deterioration after 3 years, with the weighted deterministic ICER rising to £629,638 when it was assumed that progression was 20% of the rate associated with IDM. Assumptions relating to: improvement in cognitive impairment related to pegzilarginase treatment; the distribution of patients across GMFCS states; the assumed age of death for patients treated with IDM; and assuming that carer disutility is taken from the burden of illness (BOI) survey pooling patients in GMFCS-IV and GMFCS-V all can increase the weighted deterministic ICER by more than £20,000.

1.3 Summary of EAG's preferred assumptions and resulting ICER

The components of the EAG's base case are shown in Table 2. The abbreviated results for the sensitivity analyses run using the EAG's base case as a starting point are shown in Table 3. The EAG highlights that each of the sensitivity analyses presented should be deliberated by the Appraisal Committee and a preferred set of assumptions defined, for which the EAG can produce an Appraisal Committee ICER. The EAG is confident that the ICER (including QALY weighting) for pegzilarginase treatment at the current PAS price is more than £100,000 per QALY gained.

Table 2: The EAG's base case including QALY weighting

Scenario	Incremental cost (£)	Incremental QALYs gained	Weighted cost per QALY gained (£)	Change from company's base case (£)
Deterministic model				
Company's base case	[redacted]	[redacted]	308,375	-
EA1 (Correction of error in IDM transition probabilities)	[redacted]	[redacted]	308,782	407
EA2 (Assumed starting GMFM DE score for patients in GMFCS-I)	[redacted]	[redacted]	306,515	-1860
EA3 (Using lower 95% CI for decrease in GMFM DE score when ageing one year)	[redacted]	[redacted]	300,737	-7638
EAG base case (EA1, EA2 and EA3 combined)	[redacted]	[redacted]	299,636	-8739
Probabilistic model				
Company's base case	[redacted]	[redacted]	311,119	-
EAG base case (EA1, EA2 and EA3 combined)	[redacted]	[redacted]	297,516	-13,603

CI: confidence interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Measure; IDM: individualised disease management; LYG: life year gained; QALY: quality-adjusted life year

Table 3: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results

Scenario	Incremental cost (£)	Incremental QALYs	Weighted cost per QALY (£)	Change from EAG's base case (£)
EAG's base case	[redacted]	[redacted]	299,636	-
SA1a (risk of transition to the next worse GMFCS state is 10% of that associated with IDM)	[redacted]	[redacted]	441,714	142,078
SA1b (risk of transition to the next worse GMFCS state is 20% of that associated with IDM)	[redacted]	[redacted]	629,638	330,002
SA1c (remain in same health state after 2 years of pegzilarginase treatment)	[redacted]	[redacted]	340,294	40,659
SA1d (remain in same health state after 4 years of pegzilarginase treatment)	[redacted]	[redacted]	276,387	-23,249
SA2 (distribution of cognitive impairment independent of treatment)	[redacted]	[redacted]	326,613	26,977
SA3 (no utility gain from improved diet)	[redacted]	[redacted]	309,247	9,611
SA4a (full pegzilarginase wastage)	[redacted]	[redacted]	318,306	18,670
SA4b (no pegzilarginase wastage)	[redacted]	[redacted]	289,600	-10,036
SA5 (starting distribution aligned with the European BOI study)	[redacted]	[redacted]	333,486	33,850

Scenario	Incremental cost (£)	Incremental QALYs	Weighted cost per QALY (£)	Change from EAG's base case (£)
SA6a (assuming nearly all patients died before 50 years of age for the calibration)	[redacted]	[redacted]	320,392	20,756
SA6b (assuming a starting age of 13 years for the calibration)	[redacted]	[redacted]	297,581	-2055
SA7 (using time in GMFCS health state based on midpoint GMFM DE scores)	[redacted]	[redacted]	307,896	8260
SA8 (adding a continuity correction to the peak ammonia levels data for HAC)	[redacted]	[redacted]	306,991	7355
SA9 (assuming no discontinuation of pegzilarginase treatment whilst alive)	[redacted]	[redacted]	289,501	-10,135
SA10a (assuming a carer disutility of 0.062 for patients in GMFCS-III and above)	[redacted]	[redacted]	287,990	-11,646
SA10b (assuming carer disutility from the BOI survey pooling GMFCS-IV and GMFCS-V)	[redacted]	[redacted]	325,422	25,786
SA11 (assuming double the SMR associated with pegzilarginase treatment)	[redacted]	[redacted]	317,596	17,960
SA12 (removing QALY losses for carers when calculating the QALY weight)	[redacted]	[redacted]	291,639	-7,997

BOI: burden of illness; CI: confidence interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Measure; IDM: individualised disease management. LYG: life year gained; SMR: standardised mortality rate; QALY: quality-adjusted life year

2 BACKGROUND

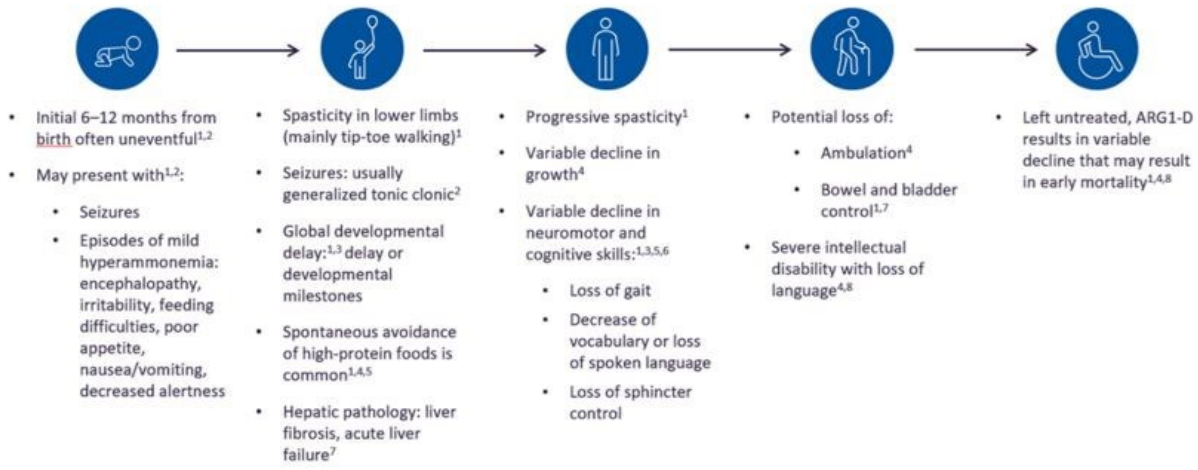
This report critiques the company submission (CS)[1] for pegzilarginase for the treatment of arginase-1 deficiency (ARG1-D). The main text is divided into three main sections: a background section, where the disease is discussed and the decision problem set out; a clinical effectiveness section, where the data related to the benefits associated with treatment are detailed and critiqued; and a cost-effectiveness section where the model submitted by the company is detailed and critiqued, and where the cost-effectiveness estimates for pegzilarginase are reported in terms of the incremental cost per QALY gained, along with exploratory analyses conducted by the External Assessment Group (EAG).

2.1 Critique of company's description of underlying health problem

In Section B.1.3 of CS,[1] the company provides a good description of arginase 1 deficiency (ARG1-D) which is an ultra-rare disease characterised by markedly elevated plasma arginine (pArg) levels. High pArg concentrations are significantly correlated with worse motor skills and are also associated with poorer global functioning and memory deficits.[2] Patients may experience clumsiness, tripping, falling, and slower growth. The disease is progressive, so patients gradually lose developmental milestones and become spastic.[3] The company provides a graphic showing the impact of persistently high pArg levels which is reproduced (with an amendment to a reference) in Figure 1. The disease is inherited, progressive, causes early death, and has a substantial impact on patients' health-related quality of life (HRQoL).[4-6] It is very rare for patients to achieve control of pArg levels with current standard of care.

The company estimates that there is a maximum of 33 patients with the disease in England.

Figure 1: The progressive impact of persistently high pArg levels (reproduced from CS, Figure 4)



ARG1-D: arginase 1 deficiency.
Sources: [1]Carvalho *et al.*[7]; [2]Scaglia and Lee[3] ; [3]Sun *et al.*[8]; [4]Crombez *et al.*[9]; [5]Cai *et al.*[10]; [6]Bakhiet *et al.*[11] ; [7]Schlune *et al.* [12]; [8]Prasad *et al.*[13].

The company also reports the Gross Motor Function Classification System (GMFCS) which is used within the company's model. Figure 6 of the CS is reproduced in Figure 2, which is stated to be sourced from Palisano *et al*.[14] and applicable to patients aged 6 to 12 years of age.

Figure 2: The company's representation of the GMFCS (reproduced from CS, Figure 6)

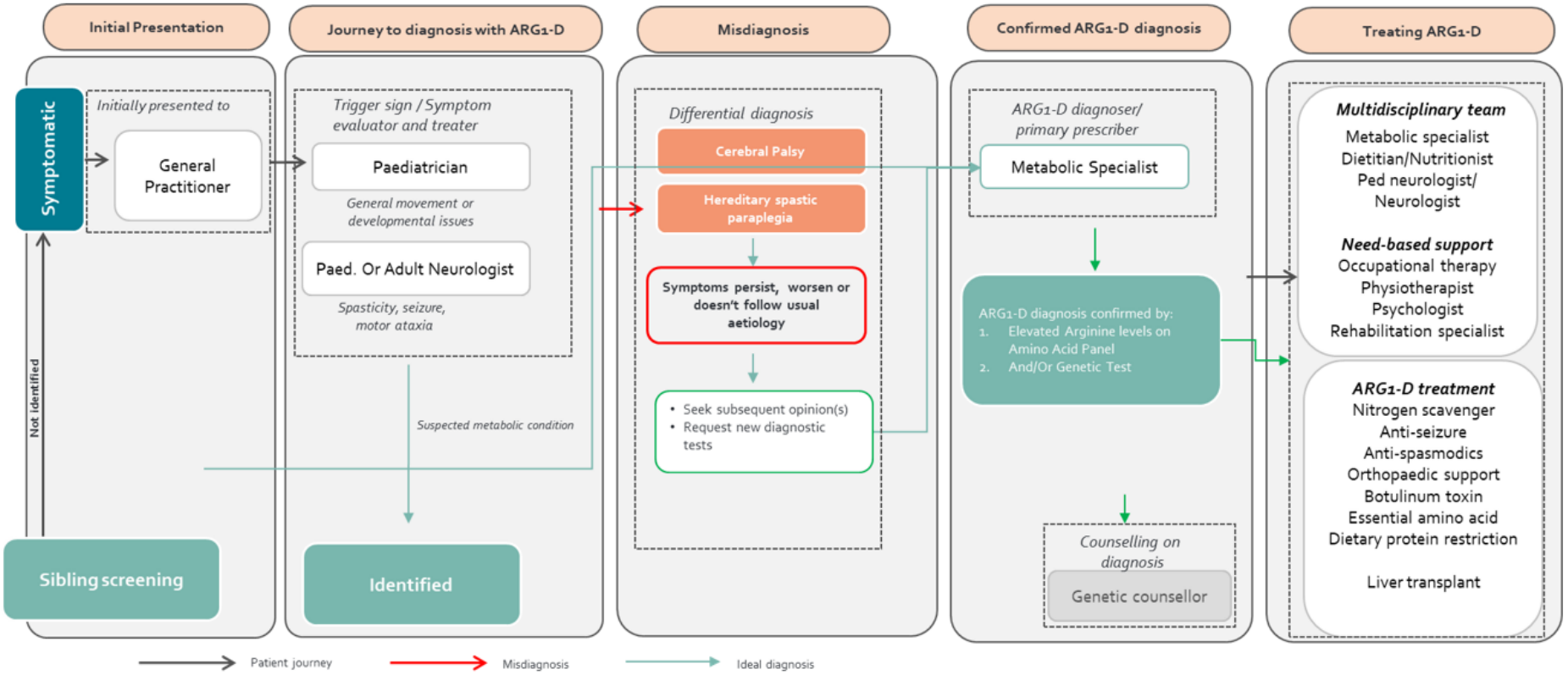
2.2 Critique of company's overview of current service provision

The company states that neither the National Institute for Health and Care Excellence (NICE) nor NHS England provide guidance on the treatment of ARG1-D. The British Inherited Metabolic Disease Group provides guidelines on the emergency treatment of urea cycle disorders, which would include ARG1-D, but does not provide details on treatment thereafter. Given this situation, the company established a clinical care pathway for ARG1-D patients based on conversations with clinical experts in the UK (see Figure 3). Clinical advisors to the EAG were generally content with this pathway, but noted that a minority of patients may present with hyperammonaemia or may be identified through a sibling with ARG-1 D.

The company has termed current care individualised diseased management (IDM) which the EAG has also used. A fundamental component of IDM is adherence to a strict protein-restricted diet with other components including amino acid supplements and nitrogen scavengers.

The company anticipates that if pegzilarginase was recommended then it would be an option in the bottom right box in Figure 3 entitled 'ARG1-D treatment', with the current treatment options used in addition to pegzilarginase, as required.

Figure 3: The company's representation of the current clinical pathway (reproduced from CS, Figure 10)



ARG1-D: arginase 1 deficiency.

2.3 Critique of company's definition of the decision problem

A summary of the main components of the decision problem is provided in Table 1 of the CS. As the EAG does not have any major concerns with the company's deviations from the final NICE scope,[15] the components of Table 1 in the CS which are in the scope are discussed in Sections 2.3.1 to 2.3.4 rather than tabulated with one additional element of the scope discussed in Section 2.3.5.

2.3.1 Population

The population covered in the company's submission is all patients aged 2 years or older with ARG1-D which is aligned with the Medicines Healthcare products Regulatory Agency marketing authorisation of pegzilarginase,[16] and the final NICE scope.[15]

2.3.2 Intervention

The intervention is pegzilarginase, a modified, cobalt-substituted, pegylated recombinant form of the human enzyme arginase 1, this aligns with the final NICE scope.[15] Pegzilarginase is intended to be used alongside IDM and can be administered by either intravenous (IV) infusion or subcutaneous (SC) injection. The intervention is available in 3mL single-use vials, containing 0.4mL of 5mg/mL for injection or infusion. The initial dose is administered by IV infusion and is 0.1/mg/kg/week, this dose can be increased or decreased in 0.05mg/kg increments, although the company (and the summary of product characteristics[17]) notes that doses greater than 0.2mg/kg/week have not been used in clinical studies. The SC route should only be considered after at least eight weeks of treatment, once a stable dose has been established, and the risk of hypersensitivity reactions is assessed as low.

2.3.3 Comparators

The company defined the comparator as IDM, which could include dietary protein restriction, essential amino acid supplementation and/or the use of nitrogen scavengers. The company prefers to use the term IDM rather than established clinical management as it states that this better aligns with the terminology used in the published literature, UK clinical practice and in the pivotal PEACE study.[18-21] The EAG does not have concerns with the nomenclature change.

2.3.4 Outcomes

The outcomes considered by the company include: pArg concentration; level of ornithine and guanidino compounds; mobility; adaptive behaviour; neurocognitive function; adverse effects of treatment; and HRQoL. The outcomes in the CS are in line with those in the final NICE scope.[15]

2.3.5 Economic analysis

The final NICE scope[15] discusses the reference case in the NICE manual for health technology evaluations.[22] The company's economic analysis adheres to these recommendations.

3 CLINICAL EFFECTIVENESS

Chapter 3 describes and critiques the methods (Section 3.1) of the company's systematic literature review (SLR), and the key studies associated with pegzilarginase (Section 3.2 and Section 3.3). It also describes ongoing studies (Section 3.4), the company's evidence synthesis (Section 3.5), the EAG's additional work on clinical effectiveness (Section 3.6) and the EAGs summary and conclusions relating to the clinical evidence (Section 3.7).

3.1 Critique of the methods of review(s)

3.1.1 Searches

The company performed a systematic literature review to identify all clinical effectiveness and safety studies of pegzilarginase or comparator treatments of patients with ARG1-D aged 2 years and older.

The EAG has identified limitations in the company search strategy related to: (i) the sources searched and (ii) the replication of a published search strategy (Bin Sawad *et al*., 2022; Bin Sawad *et al.*, 2022b).

The company searched the following electronic bibliographic databases in December 2023: MEDLINE (via PubMed), EMBASE (via Embase.com), Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL via Cochrane Library), Database of Abstracts of Reviews of Effects (DARE, via the Centre for Reviews and Dissemination (CRD)), NHS Economic Evaluation Database (via CRD) and the Health Technology Assessment (HTA) database (via The International Network of Agencies for Health Technology Assessment, INAHTA). In addition, the company searched bibliographies of relevant systematic reviews to identify other new studies for inclusion.

The electronic database search was supplemented with grey literature from the Clinicaltrials.gov registry in December 2023 to identify ongoing, completed, or unpublished trials. The company searched three HTA agencies in December 2023: NICE; Scottish Medicines Consortium (SMC); and the All Wales Medicines Strategy Group (AWMSG).

The EAG notes that the company did not search the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (EUCTR). Whilst the company searched CENTRAL which indexes all the trials from ICTRP and ClinicalTrials.gov, there will be delays of eight weeks before appearing on CENTRAL and thus it is recommended that the original sources are searched to ensure maximum coverage. Additionally, the company could also have searched several key conference abstracts such as the European Conference on Rare Diseases; or the

Rare Disease Summit; or the International Congress on Rare Diseases and Orphan Drugs; and the World Orphan Drug Congress. Whilst there is therefore a risk that ongoing or recently completed but unpublished papers may not be retrieved, the EAG is confident that the manufacturer of pegzilarginase will know of all studies relevant to this drug.

The company performed an updated SLR search of two published systematic reviews.[23, 24] Comparison of the company's updated search with the published searches shows that the latter are more sensitive since they have used the multiple-purpose field searching (.mp.) as opposed to the title and abstract field searches.

Whilst there is therefore a risk that all relevant papers may not be retrieved, the EAG is confident that the manufacturers of pegzilarginase will know of all studies relevant to this drug.

3.1.2 Inclusion criteria

The inclusion criteria for the review are described in CS Appendix D and are reproduced here as Table 4. The EAG agrees that the criteria appear to be appropriate. Outcomes were defined in very broad terms and are therefore likely to have captured all outcomes listed in the final NICE scope across a wide range of study designs. Only studies published in 2020 onwards were included, since the review was an update of two reviews conducted by Sawad *et al.* in 2022.[23, 24] One of these[23] was of high relevance to the clinical efficacy review, and is likely, in the opinion of the EAG, to have captured relevant intervention and comparator studies since it aimed to identify (amongst other objectives) any intervention for ARG1-D, and had no date limits. The EAG is therefore satisfied that the update was appropriate, and that all relevant studies would have been identifiable by the inclusion criteria and the update strategy.

Table 4: Inclusion criteria of the company's systematic review update (reproduced from CS, Appendix D)

Criteria	Description
Population	***Inclusion criteria:*** Paediatric and adult patients with ARG1-D
Interventions	No restrictions
Comparators	No restrictions
Outcomes	Efficacy and safety - Change in plasma arginine concentration - Achievement of plasma arginine level below 200 µmol/L - Achievement of plasma arginine level between 40-115 µmol/L - Clinical response, defined as either a mobility response or an adaptive behaviour response

Criteria	Description
	- Seizure frequency - Neurocognitive function - Adverse events Quality of life - Generic patient-reported outcomes measures - Disease specific patient-reported outcomes measures - Utility measures - Caregivers burden Economic burden - Comparison of benefits and costs between interventions and comparators - Results expressed in incremental costs, incremental cost-effectiveness ratios, quality adjusted life years, life years gained, or any other measure of effectiveness reported together with costs - Costs associated with treating ARG1-D - Total healthcare costs (both direct and indirect costs) - Direct costs (e.g., costs related to drugs, adverse events, inpatient/outpatient services, hospitalizations) - Indirect and societal costs (e.g. costs related to caregiver absenteeism and presenteeism, patient productivity loss, out-of-pocket costs) - Resource utilization (e.g. health system use, medication use, time spent on activities related to treating ARG1-D)
Study design	***Inclusion criteria*** - Case reports - Controlled and un-controlled clinical trials - Retrospective and prospective observational studies - Cross-sectional and case-control studies - Systematic and targeted literature reviews - Quality of life instrument application/validation studies - Cost effectiveness analyses - Cost utility analyses - Cost benefit analyses - Cost consequence studies - Cost minimization analyses - Budget impact models - Burden or cost of illness studies, including observational studies of resource utilisation ***Exclusion criteria*** - Comments, editorials
Language	Only studies published in English will be included
Time	2020 onwards

ARG1-D: arginase 1 deficiency

3.1.3 Study selection and data extraction

The company screened references from the two systematic reviews and from the update searches. Screening was conducted by two researchers independently, with disagreements resolved through discussion. This is a high-quality study selection strategy. However, the EAG notes that Bin Sawad *et al*. 2022[23] identified a limited number of studies that reported clinical outcomes for comparator treatments, and these have not been included in the CS. The Bin Sawad *et al*. review did not list which papers contained effectiveness assessments, and the company did not document the inclusion or exclusion of papers listed in these systematic reviews (see clarification response, question A31), so the EAG was unable to determine whether the company considered them for inclusion and then excluded them for valid reasons. This leaves some degree of uncertainty about the completeness of the review of evidence on comparators. However, the EAG was satisfied with the company's rationale for not conducting an indirect treatment comparison (ITC) (see Section 3.5).

Data extraction processes were not described, in the CS and are therefore of unknown quality. There were some errors and discrepancies noted by the EAG in the CS, which were clarified by the company. The EAG extracted data for the long-term extension (LTE) study directly from the CS, as this contained the latest data-cut (see clarification response, question A17). The EAG encourages the company to carefully check data in the EAG report to ensure it is the latest available.

3.1.4 Quality assessment

The CS reports quality assessment of PEACE using the CRD list of questions, and the assessment of Studies 101A and 102A using the Downs & Black checklist. The EAG agrees that these were appropriate tools to choose. The EAG critiques the company's scores and the studies in Section 3.2.5.

3.1.5 Synthesis

The company did not perform synthesis as part of the SLR. A pooling of some outcomes (pArg, 2- & 6-minute walk tests, Gross Motor Function Measure (GMFM) D and GMFM-E) from PEACE and Study 102A was provided in the company's clarification response to question A21. The analysis pooled patients from Study 102A and the PEACE study using a mixed effect model repeated measures (MMRM) model. Pegzilarginase-pegzilarginase arm patients from PEACE contributed to the on-treatment arm of the pooled analysis alongside Study 102A patients, and patients from the placebo arm of the PEACE study contributed to the placebo arm of the pooled analysis. In the company's clarification response to question A21, the company states "*The MMRM model for each endpoint included baseline values, treatment group, study (Study 102A and PEACE), visit and interaction*

between visit and treatment groups as covariates in the model. The study factor was included to adjust the study differences between Study 102A and PEACE (22)."

EAG critique of the synthesis methods

The EAG acknowledges that the study differences have been adjusted for in the pooled analysis, but it is unclear whether the adjustment has been done properly due to a lack of details provided in the CS.

3.1.6 Critical appraisal of the methods of the SLR

The EAG appraised the quality of the SLR using AMSTAR 2. The scores are provided in Appendix 1. Overall, the SLR was of reasonable quality in terms of the search and study selection process. However, it could have been improved by reporting that a protocol was designed *a priori* and pre-registered (e.g., on PROSPERO), by reporting that data extraction was performed in duplicate, by providing reasons for exclusions of studies included in the previous SLRs by Bin Sawad *et al*.,[23, 24] and by providing a more robust discussion of aspects of risk of bias of the included studies, such as the impact of baseline imbalances, and the open-label nature of the LTE of PEACE (see Section 3.2.1.1) and Study 102A. A discussion of the reasons for the heterogeneity between responses in pegzilarginase-pegzilarginase patients and pegzilarginase-placebo patients (see Section 3.2.2) would also have improved the review, as would a statement about how conflicts of interest were handled when performing the review.

3.2 Results of the company's SLR

The SLR identified three studies of relevance to the appraisal, PEACE, 101A and 102A.

3.2.1 Studies of pegzilarginase included in the efficacy systematic review

The designs of the studies are summarised in Table 5. More details, including the inclusion and exclusion criteria, are provided in the CS (PEACE in Section 2.3.1.1 and Table 6 of the CS; Studies 101A and 102A in Section 2.3.2.1 and Table 12 of the CS), but for the sake of brevity the EAG does not reproduce all this information here, but instead focusses on key elements.

PEACE was a multi-centre, multi-national double-blind Phase 3 randomised controlled trial (RCT). Study 101A was a Phase 1/2 dose-finding study. Study 102A was a Phase 2 open-label extension of Study 101A to test long-term safety and efficacy. All studies included patients aged 2 years and over. Pegzilarginase was administered intravenously (IV) in all studies initially, but patients could switch to subcutaneous (SC) delivery in 102A and PEACE. All studies were multinational (including Europe and North America), but primarily recruited from the United States of America (USA). Of note, four UK

sites were involved in PEACE (out of 19, nine of which were in the USA), and one UK site was involved in Studies 101A and 102A (out of eight, five of which were in the USA).

3.2.1.1 Study design of PEACE

The schema for the PEACE trial is reproduced in Figure 4. PEACE comprised a screening period of 3-4 weeks, prior to randomisation, then an initial double-blind period of 24 weeks, and the primary efficacy endpoint analysis was based on this period. Randomisation was stratified by prior history of hyperammonaemia and was 2:1 pegzilarginase to placebo. The inclusion criteria are listed in Table 7 of the CS. Concomitant medications were allowed, but disease management had to be stabilised throughout the 3-4 weeks screening period, including prescribed protein and essential amino acids and ammonia scavengers. Botulinum toxin and surgical procedures were prohibited during the double-blind period and the company confirmed neither were administered to any patient throughout the double-blind and LTE periods (clarification response, question A12).

Pegzilarginase was administered intravenously at a starting dose of 0.10 mg/kg and dose adjustments were allowed based on pharmacodynamic response. Placebo patients received individualised disease management (IDM) plus an IV infusion of the drug vehicle. Sites were instructed to minimise changes to dietary protein intake to within 15% of baseline because protein intake can alter pArg.

The 24-week double-blind period was followed by an open-label LTE where patients in the placebo arm switched to pegzilarginase, but patients and personnel remained blinded for the first 8 weeks of this period. All patients then remained on pegzilarginase treatment for up to approximately 150 weeks. Therefore, all data in the LTE relate to patients who were being treated with pegzilarginase, albeit those in the pegzilarginase-pegzilarginase arm were on treatment for 24 weeks longer than those in the pegzilarginase-placebo arm.

EAG critique of the PEACE trial design

Clinical advisors to the EAG were satisfied with the trial design. They considered the selection criteria to be appropriate, though they noted that the most ill patients would be missed (as they excluded patients with extreme mobility deficit), as would patients with no symptoms (as they included only patients with a baseline deficit in at least one of two-minute walk test (2MWT), GMFM-D or GMFM-E). The impact of these exclusions on estimates of efficacy is unknown but the clinical advisors were not concerned. The EAG notes that 24 weeks was a short timescale within which to demonstrate clinical benefits in outcomes such as changes in walk tests and neurocognitive outcomes and would have preferred to see a longer double-blind period, since the LTE had no comparator arm and no comparison to disease

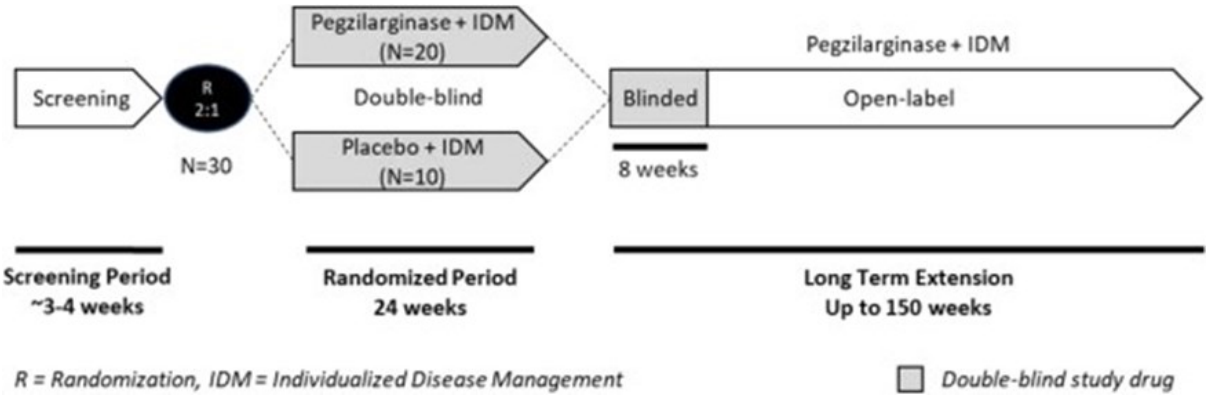
natural history was attempted. The primary outcome was a surrogate outcome (pArg). Clinical advisors to the EAG noted that pArg levels do not have a consistent relationship with clinical severity of the disease but also noted that it is one marker of disease used to monitor patients and is more closely linked to hyperammonaemic crises (HACs). The EAG agrees that stratification at baseline according to prior history of HACs may balance disease severity across groups at baseline, but it was unclear if other patient characteristics may have been equally or more important, and no justification was provided in the CS or CSR for selecting this factor over other factors. As discussed in Section 3.2.3, there were imbalances at baseline in factors and at least one (age) that clinical advisors thought might be an important prognostic factor or potentially a treatment effect modifier.

Table 5: Summary of the trial designs of PEACE, 101A and 102A (reproduced from CS, Table 5)

Study	**CAEB1102-300A (PEACE) (NCT03921541)**	**CAEB1102-102A (NCT03378531)**	**CAEB1102-101A (NCT02488044)**
Study design	A Randomised, Double-blind, Placebo-controlled Phase 3 Study of the Efficacy and Safety of Pegzilarginase in Children and Adults With Arginase 1 Deficiency	A Phase 2 Open-label, Multicentre Extension Study to Evaluate the Long-Term Safety, Tolerability and Effects of Intravenous AEB1102 in Patients With Arginase I Deficiency Who Previously Received Treatment in Study CAEB1102-101A.	A Phase 1/2 Open-label Study in Patients with Arginase I Deficiency to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous AEB1102
Population	Patients aged 2 years and older with ARG1-D	Patients aged 2 years and older with ARG1-D	Patients aged 2 years and older with ARG1-D
Intervention(s)	Pegzilarginase plus IDM	Pegzilarginase plus IDM	Pegzilarginase plus IDM
Comparator(s)	Placebo plus IDM	None (Study 102A is a single-arm study)	None (Study 101A is a single-arm study)
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	Yes
Rationale if study not used in model	*Not applicable. PEACE presents the pivotal, regulatory, clinical*	*Not applicable. Study 102A provides long-term efficacy and safety data*	*Not applicable. Data used for the statistical model of the relationship*

	evidence in support of pegzilarginase in ARG1-D.	*in support of pegzilarginase in ARG1-D.*	*between GMFCS and GMFM*
Reported outcomes specified in the decision problem	• Plasma arginine concentration • Level of ornithine and guanidino compounds • **Mobility** • Adaptive behaviour • **Neurocognitive function** • Adverse effects of treatment • **Health-related quality of life**	• Plasma arginine concentration • Level of ornithine and guanidino compounds • **Mobility** • Adaptive behaviour • **Neurocognitive function** • Adverse effects of treatment • **Health-related quality of life**	• Plasma arginine concentration • Level of ornithine and guanidino compounds • **Mobility** • Adaptive behaviour • **Neurocognitive function** • Adverse effects of treatment • **Health-related quality of life**
All other reported outcomes	Not applicable	Not applicable	Not applicable

Figure 4: Overview of trial design of PEACE (reproduced from CS, Figure 12)



3.2.1.2 Study design of Study 101A and 102A

Studies 101A and 102A included the same patients (in 102A, minus two who withdrew during 101A) with an interval between the two. The median duration of time between the last dose of pegzilarginase in Study 101A and the first dose in Study 102A was [redacted] weeks (range: [redacted] weeks). Study 101A was a Phase 1/2 open-label study to investigate the safety, pharmacokinetics, and pharmacodynamics of intravenous pegzilarginase. It aimed to find an appropriate dose (based on stopping rules) for pegzilarginase by administering single ascending doses at 2-week intervals, then continuing that dose for 8 weeks. Study 102A was a Phase 2 open-label, multicentre extension study to evaluate the long-

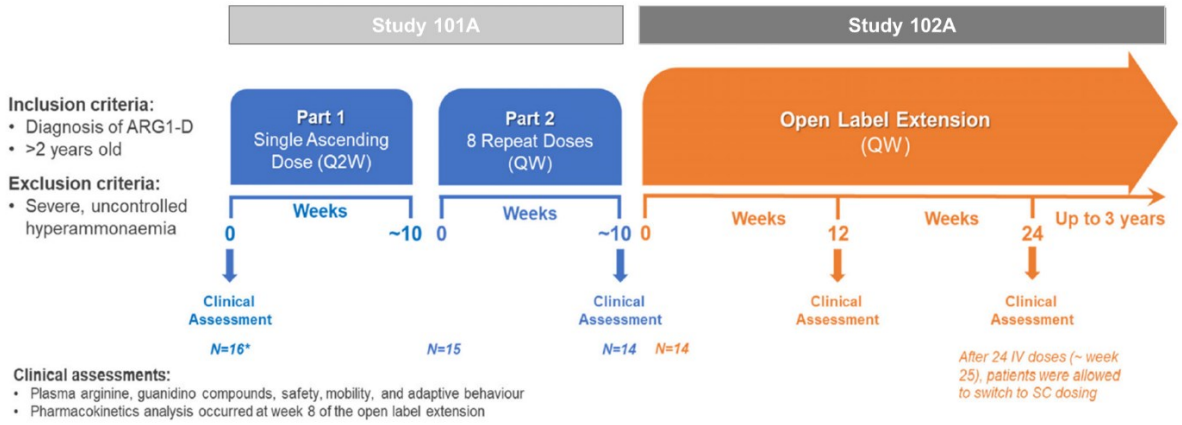
term safety, tolerability, and effects of intravenous pegzilarginase. Outcomes and endpoints are described in more detail in Section 3.2.4.

EAG critique of studies 101A and 102A study design

The EAG agrees that Study 102A is of higher relevance to the efficacy evaluation and the company appropriately focused on the results from this study. The EAG therefore focusses on study 102A from hereon in, except where it is necessary to refer to Study 101A to provide details of relevance to 102A. The study design appears to be appropriate for a Phase 2 study.

The EAG notes that patients in Study 102A may have some residual benefit from treatment during Study 101A for patients who only had a short gap between the two (median [redacted] weeks, range: [redacted] weeks). Therefore, outcomes at 24 weeks may be expected to be superior to those seen at 24 weeks in PEACE.

Figure 5 Overview of study design of Study 101A and 102A (reproduced from CS, Figure 13)



3.2.2 Participant flow and analysis populations

3.2.2.1 Participant flow and analysis populations in PEACE

In PEACE, 44 patients were screened and consented, of which 32 were considered eligible and were randomised to pegzilarginase (n=21) or placebo (n=11). One pegzilarginase patient withdrew after having received at least one dose and within the double-blind period for personal reasons. Efficacy and safety analyses used the full analysis set (FAS) of all who were randomised and completed at least one dose of blinded study treatment.

The company's response to clarification question A13 explains that the 12 patients who were screen failures met exclusion criteria as follows: hyperammonaemic history (n=1), other medical condition

judged by investigator to interfere with study assessments (n=1); or did not meet inclusion criteria as follows: provision of informed consent (n=4), arginine elevation ≥250 μM (n=2), able to complete the study assessments and had a baseline deficit in at least one component (n=4). In response to the EAG's question about how this might affect the generalisability of study results to the population eligible for treatment, the company stated that only a small number of patients are expected to have a similar hyperammonaemic history or a medical condition, based on the prevalence in the sample of 44 (10% of total ARG-1D population in recruitment countries). They noted that patients with any pArg level were eligible at under the license and therefore provided an analysis comparing patients with baseline pArg < and ≥250 μM from study 102A (where this criterion did not apply) and noted findings consistent with PEACE. They also stated that patients with no baseline deficits in Study 102A suffered from a ceiling effect, but that the lack of deterioration was positive in the context of a progressive disease, and that the baseline characteristics of the four patients who did not give informed consent were unknown, but the small number was unlikely to affect generalisability.

3.2.2.2 Participant flow and analysis populations in studies 101A and 102A

In Study 101A and 102A, analyses were performed on the FAS, defined as all patients enrolled who received pegzilarginase (n=16 and n=14 respectively). The company clarified that across Studies 101A and 102A, 3 patients withdrew in total, 2 from 101A for personal reasons (to focus on high school and due to the sudden death of a family member) and one from 102A due to parental discontent with the medical care received from the hospital, but they did not cite discontent with pegzilarginase.

EAG critique of participant flow and analysis populations in PEACE and Studies 101A and 102A

The generalisability of the PEACE results to patients eligible for treatment under the licence, with respect to screening failures, is subject to some uncertainty. However, the EAG's clinical advisors were not concerned about the spectrum of patients recruited and the EAG notes that Studies 101A and 102A had less restrictive inclusion criteria and were largely consistent with PEACE results.

The EAG agree the FAS is appropriately defined. The withdrawal of one patient due to personal reasons in conjunction with withdrawals from Studies 101A and 102A suggests that some withdrawal from treatment is inevitable, e.g., for practical reasons such as time constraints or carer commitment. The EAG notes that treatment at home may reduce practical limitations, but that even home administration requires some time and carer commitment.

3.2.3 Baseline characteristics in PEACE and 101A

3.2.3.1 Baseline characteristics in PEACE

Baseline characteristics of patients in the FAS for PEACE are presented in Table 6. The company stated that characteristics were "*generally comparable*" between arms, but noted some exceptions ("*slightly younger age, lower pArg levels, and less moderate/severe spasticity among patients randomised to pegzilarginase vs placebo*", p56 of the CS). They also noted a younger age (10.5 years (range: 2 to 29 years)) compared to a European Burden of Illness (BOI) study ([redacted] years (range: [redacted] – [redacted] years[25])) and a UK study[26] (16.0 years (range: 12 – 28 years)). They also noted the high pArg levels at baseline despite IDM, and that 56.2% had GMFCS Level ≥II, similar to the European BOI study.

EAG critique of baseline characteristics in PEACE

The EAG agrees that the pegzilarginase group compared to the placebo group has a lower mean age (9.6 years (standard deviation (SD) 6.16) compared to 12.9 years (SD 6.8)), pArg levels (365.4μM (SD 93.7) compared to 471.7μM (SD 79.9)) and fewer moderate to severe spasticity levels than placebo patients (6 (28.6%) compared to 6 (54.5%)). The EAG further notes that there are also differences in the mean age at diagnosis (2.8 years versus 4.2 years respectively) and 2MWT (109.0 meters (SD 55.8) versus 99.9 meters (SD 49.0) respectively), the latter being notable since placebo patients were on average older and might reasonably be expected to walk further. One of the EAG's clinical advisors thought that age might affect estimates of efficacy (with older patients having more severe disease), but that mean pArg and spasticity were less of a concern, since pArg is elevated in all patients due to the inclusion criteria (≥250μM) and is not perfectly correlated with clinical outcomes. The EAG discusses the effects that age and severity may have had on outcomes in Section 3.3. The clinical advisors indicated that otherwise the baseline characteristics appeared to be in line with what they would expect in UK clinical practice, though they noted that data in the UK was limited.

Table 6: Patient demographics and baseline characteristics for the PEACE FAS (reproduced from CS, Table 11, with a correction of the label relating to baseline pArg levels as per clarification response, question A16)

	Pegzilarginase (n=21)	**Placebo (n=11)**	**Overall (n=32)**
Age at enrollment (years)			
n	21	11	32
Mean (SD)	9.6 (6.16)	12.9 (6.77)	10.7 (6.47)
Median	8.0	12.0	10.5
Min, Max	2, 28	5, 29	2, 29
Age categories (years), n (%)			
2 - <6	5 (23.8)	1 (9.1)	6 (18.8)
6 - <12	8 (38.1)	4 (36.4)	12 (37.5)
12 - <18	7 (33.3)	4 (36.4)	11 (34.4)
≥18	1 (4.8)	2 (18.2)	3 (9.4)
Sex, n (%)			
Female	9 (42.9)	4 (36.4)	13 (40.6)
Male	12 (57.1)	7 (63.6)	19 (59.4)

	Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Race, n (%)			
Asian	3 (14.3)	3 (27.3)	6 (18.8)
Black/African American	0	2 (18.2)	2 (6.3)
White	10 (47.6)	4 (36.4)	14 (43.8)
Other	6 (28.6)	0	6 (18.8)
Multiple Race	1 (4.8)	1 (9.1)	2 (6.3)
Missing	1 (4.8)	1 (9.1)	2 (6.3)
Age at onset of manifestations, years			
n	11	10	21
Mean (SD)	1.6 (2.5)	2.5 (2.0)	1.9 (2.4)
Median	1.0	2.0	1.0
Min, Max	1, 10	0, 7	0, 10
Age at diagnosis, years			
n464.7	17	9	26
Mean (SD)	2.8 (4.1)	4.2 (3.1)	3.3 (3.8)
Median	0.7	4.6	2.6
Min, Max	0, 15	0, 11	0, 15
Baseline pArg, µM[a]			
n	19	11	30
Mean (SD)	365.4 (93.7)	471.7 (79.9)	402.0 (101.8)
Median	368.2	483.7	398.2
Min, Max	202, 572	294, 573	202, 573
Level of spasticity, n (%)			
Any	13 (61.9)	8 (72.7)	21 (65.5)
Lower-limb	13 (61.9)	8 (72.7)	21 (65.6)
Upper-limb	1 (4.8)	3 (27.3)	4 (12.5)
Moderate to severe	6 (28.6)	6 (54.5)	12 (37.5)
History of seizures, n (%)			
Yes	7 (33.3)	4 (36.4)	11 (34.4)
No	14 (66.7)	7 (63.6)	21 (65.6)
History of hyperammonaemia, n (%)			
Yes	12 (57.1)	6 (54.5)	18 (56.3)
No	9 (42.9)	5 (45.5)	14 (43.8)
GMFCS level at baseline, n (%)[b]			
I	9 (42.9)	5 (45.5)	14 (43.8)
II	9 (42.9)	4 (36.4)	13 (40.6)
III	0	0	0
IV	3 (14.3)	2 (18.2)	5 (15.6)
V	0	0	0
Baseline GMFM-E score, points[c]			
n	21	11	31
Mean (SD)	48.3 (19.93)	46.5 (24.56)	47.7 (21.25)
Median	53.0	56.0	54.0
Min, Max	5, 71	0, 72	0, 72
Baseline 2MWT, metres[d]			
n	20	11	31
Mean (SD)	109.0 (55.76)	99.9 (49.00)	105.8 (52.82)
Median	122.0	102.0	118.0

	Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Min, Max	2, 202	0, 171	0, 202
Baseline GMFM-D score, points[e]			
n	21	11	31
Mean (SD)	28.0 (9.6)	29.5 (12.4)	28.5 (10.4)
Median	30.0	33.0	32.0
Min, Max	1, 38	0, 39	0, 39

Key: 2MWT: 2-Minute Walk Test; FAS: full analysis set; GMFCS: Gross Motor Function Classification System; GMFM-D: Gross Motor Function Measure-88, Part D; GMFM-E: Gross Motor Function Measure-88 Part E; Max: maximum; Min: minimum; pArg: plasma arginine; SD: standard deviation.
Notes: Percentages are based on the total number of patients in the FAS.
a One patient had pArg <250 μM (screening, 242 μM; baseline, 202 μM) but was considered eligible for the study based on documented historical pArg levels.
b No patients at GMFCS Level V were enrolled due to inability to complete functional mobility assessments.
c Baseline GMFM-E was assessed in 10 of 11 patients in the placebo group; one patient was not assessed at baseline because of severe disability and wheelchair dependence.
d Baseline 2MWT was assessed in 20 of 21 patients in the pegzilarginase group; one patient was not assessed at baseline due to young age.
e Excludes one patient (placebo) with missing baseline value.
Sources: Table 1, Sanchez Russo *et* al. (2024) (59); Table 14 & Table 15, PEACE CSR (84).

3.2.3.2 Baseline characteristics in Studies 101A and 102A

Studies 101A and 102A had similar baseline characteristics (see CS, Table 15). Of note, Study 102A had a higher mean age ([redacted] years (SD [redacted])) compared to PEACE and lower pArg levels (309.2μM (SD 97.60)). Otherwise, baseline characteristics were similar.

3.2.4 Study endpoints, analysis methods and MCIDs in PEACE and Study 102A

3.2.4.1 PEACE endpoints, analysis methods and MCIDs

The primary endpoint was plasma arginine (pArg), with key secondary outcomes of (2MWT (a measure of distance walked in 2 minutes) and Global Motor Function Measure, part E (GMFM-E) (a measure of ability to walk, run, and jump). Other secondary outcomes were changes in ornithine and guanidino compounds (GC), GMFM-D (a measure of ability to stand) and Vineland Adaptive Behaviour Scale, Second Edition (VABS-II) (a measure of adaptive behaviour). Tertiary outcomes were responder analyses, neurocognition and memory tests Bayley Scales of Infant and Toddler Development (BSID-III and Wechsler tests), Modified Ashworth Scale (MAS) (a measure of spasticity), Paediatric Quality of Life Inventory (PedsQL) (a measure of paediatric quality of life), 36-Item Short Form Health Survey (SF-36) and Zarit Burden Interview Short: 12 items (ZBI-12) (a measure of carer burden). Each outcome is described in more detail at the start of each relevant section of the results (Sections 3.3.1 – 3.3.5).

For the primary outcome and one secondary outcome (GCs and ornithine) missing change from baseline values were imputed as zero. A MMRM analysis was used. Missing data for key secondary and secondary endpoints were not imputed. Tertiary outcomes were analysed using summary statistics.

Several other outcomes were measured in the trial but not reported in the CS. The EAG considers the most relevant of these in Section 3.3.5.

The company used minimal clinically important differences (MCIDs) to interpret change from baseline data. No MCIDs for ARG1-D were available, so they used MCIDs from other conditions as follows: 2MWT, 9% mean change from baseline, based on cerebral palsy data; GMFM-E, increase of ≥1.8 to ≥4.0 points (according to baseline GMFCS classification), based on cerebral palsy data; GMFM-D, increase of ≥1.5 to ≥3.3 (according to baseline GMFCS classification), based on cerebral palsy data.

3.2.4.2 Study 102A endpoints, analysis methods and MCIDs

The company reported the following endpoints from Study 102A: pArg, ornithine, guanidino compounds, 6MWT, GMFM-D, GMFM-E, MAS, a responder analysis, Wechsler intelligence batteries, VABS-II, PedsQL and ZBI-12. The MCIDs used were the same as in PEACE, except for the 6MWT where the same value (9% change from baseline) was used but based on data from Morquio A syndrome patients.

EAG critique of study endpoints

The EAG agrees that the study covered important biochemical, functional, and quality of life outcomes of interest to clinicians and patients. Clinical advisors to the EAG were satisfied with the selection of outcomes. The EAG notes that the primary outcome is a surrogate which the EAG's clinical advisors noted does not have a consistent relationship with clinical manifestations of the disease.

The EAG agree that the use of a MMRM analysis method was appropriate. No imputation for key secondary and secondary endpoints results in small numbers at later time points, and the EAG provides more critique of this methodology in section 3.2.2. Clinical advisors to the EAG noted that the MCIDs for cerebral palsy were probably not transferable since cerebral palsy is an incurable disease, whilst ARG1-D is progressive. The EAG is not aware of more suitable alternatives.

3.2.5 Critical appraisal of PEACE and Study 102A

Formal critical appraisal of PEACE and 102A was undertaken by the company as part of its SLR (see Section 3.1.4 for details). For PEACE, the EAG disagrees with some scores provided by the company, as outlined in Table 6. In particular, the study arms were imbalanced at baseline. This is discussed in more detail in Section 3.2.3. There were also several relevant outcomes that were not reported in the CS but were measured in the trial. The EAG has included a description of the relevant outcomes in section 3.3.5, thus reducing the risk of reporting bias. The EAG notes that the 15% change to protein

intake rule was not adhered to in all cases (34.4% broke protein intake restrictions in the pegzilarginase group, and 18.2% in the placebo group) during the double-blind period, and that this would be more likely to disadvantage treatment with pegzilarginase; the company noted that pArg level reductions were maintained despite the additional protein intake (roughly equivalent to [redacted]), and cited this as evidence of the efficacy of the treatment. The EAG concludes, however, that there is some risk of bias associated with the PEACE RCT, mainly related to the imbalance in baseline characteristics.

For Study 102A, the EAG notes that where items scored poorly, this was due to the inherent limitations of open-label studies (blinding), and studies in rare diseases (small sample size), and of being a single-arm study (adjustments for confounders). Nevertheless, it is worth noting that Study 102A is subject to these limitations, as well as having no comparator arm meaning it is unclear what effect the treatment had compared to IDM. The EAG notes that most patients were children or teenagers and that it was unclear what changes over time may have been seen without treatment since there may be opposing influences of improvements due to growth and deterioration due to disease. This also affects the long-term data reported in PEACE. However, when asked generally about the impact of age and growth on neurocognitive and mobility outcomes, two paediatric clinical advisors out of three did not think growth would affect outcomes, whilst the third deferred to the paediatricians.

Table 7: Quality assessment of PEACE as assessed by the company, with EAG critique (adapted from CS, Appendix D, Table 70)

	Company's quality assessment		EAG's quality assessment	
Study question	**CS Score**	**Rationale**	**EAG's response**	**EAG Score**
Was randomisation carried out appropriately?	Yes	Patients were randomised to treatment following completion of all screening assessments and confirmation of study eligibility in a 2:1 ratio to receive weekly intravenous infusions of pegzilarginase plus individualised disease management (IDM) or placebo plus IDM during the 24-week, double-blind period. Randomisation was performed using a computer-generated randomisation schedule. Randomisation was stratified by the severity of prior history of hyperammonaemia.	The EAG agree with this score.	Yes
Was the concealment of treatment allocation adequate?	Yes	All site personnel involved in the study, including patients, families, caregivers, investigators, expert assessors of relevant endpoints, and all sponsor and contract personnel were blinded to the patient's randomised treatment assignment. Each site had an unblinded pharmacist, and an unblinded physician where required, to manage protocol-defined dose adjustments.	Allocation concealment relates to blinding of patients, enrollers and personnel involved in randomisation BEFORE the patient is randomised, not after randomisation. Therefore, some of the rationale provided is irrelevant. However, the EAG agrees with the score provided.	Yes

		Laboratory results for arginine, ornithine, and guanidino compounds (GCs) during the 24-week double-blind period were not provided to the investigator or other blinded individuals until all patients had completed the blinded portion of the study and formal unblinding of the 24-week double blind period had occurred.		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	As described in Section B.2.3, baseline characteristics were generally comparable across treatment groups, albeit with a few exceptions (slightly younger age, lower plasma arginine (pArg), and less moderate/severe spasticity among patients randomised to pegzilarginase vs placebo).	The EAG disagrees with this score. Patients in the placebo group were older and more severe than those in the pegzilarginase group at baseline. There is a potential for this to have affected study results and no adjustments were performed to account for these differences, presumably due to small patient numbers. More robust stratification at baseline and a larger sample size may have avoided these imbalances.	No
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	All site personnel involved in the study, including patients, families, caregivers, investigators, expert assessors of relevant endpoints, and all sponsor and contract personnel were blinded to the patient's randomised treatment assignment to minimise potential biases in the assessment of safety and clinical outcomes. Each site had an unblinded pharmacist, and an unblinded physician where required, to manage protocol-defined dose adjustments.	The EAG agrees that these people were blinded but noted that more patients in the pegzilarginase arm (34.4%) broke protein intake restrictions than in the placebo group (18.2%) during the double-blind period. The EAG asked the company if this may indicate that blinding was subverted. The company responded that they did not think this was the case (clarification response, question A11) and put the difference down to an easing of protein aversion as a result of treatment with pegzilarginase.	Yes

Were there any unexpected imbalances in drop-outs between groups? **If so, were they explained or adjusted for?**	No	One patient randomised to pegzilarginase withdrew consent at Week 6 for personal reasons unrelated to pegzilarginase. Otherwise, all patients who completed the double-blind period entered the long-term extension portion of the study.	The EAG agrees.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All of the outcomes measured are fully documented in the clinical study report.	The EAG agrees that all outcomes are reported in the CSR, but with respect to the company submission, not all outcomes that were measured were reported. The EAG therefore would score this item "Yes". The EAG have reported some additional functional outcomes in this report, Section 3.3.5.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All safety and efficacy analyses were conducted on the Full Analysis Set, defined as all patients who were randomised and received at least one dose of blinded study treatment. For the primary efficacy endpoint (pArg) and one secondary endpoint (GCs and ornithine), when a final value was not available, change from baseline was imputed as zero. Missing data due to study withdrawal, death, COVID-19 were imputed as though the	The EAG would suggest that imputation methods could have been explored for the secondary and tertiary endpoints, since some of these were of central importance to the assessment of efficacy.	No

		patient did not improve from baseline: a composite estimand strategy. Missing data for key secondary and secondary endpoints was not imputed.		
Was there good data quality assurance for this study?	Yes	An electronic data capture system was used for the collection of clinical data at the investigational sites. Laboratory data was held within individual laboratories' databases, and all data (clinical, laboratory, and interactive response system) was merged into a data analysis database.	The EAG agrees.	Yes

Abbreviations: CS, company submission; CSR, clinical study report; EAG, external assessment group; GC, guanidino compounds; pArg, plasma arginine

3.3 Clinical effectiveness of pegzilarginase

In these sections, the EAG brings data from PEACE (the double-blind period as well as the LTE results for both pegzilarginase-pegzilarginase and placebo-pegzilarginase patients), Study 102A and the pooled analysis together, to provide an overview of all available data.

3.3.1 Clinical effectiveness in biochemical outcomes

pArg data are reported in Table 8 and Figure 6. In PEACE, the between-group difference in mean change from baseline at 24 weeks was −76.7% (95% confidence interval [CI]: −67.1%, −83.5%, $p<0.0001$), where a decrease from baseline indicates an improvement in pArg levels. In the LTE, the mean change from baseline in the pegzilarginase arm remained similar to that seen at week 24 ([redacted] n=21) through to week LTE96 ([redacted]), though numbers in the analysis were small at this time point (n=[redacted]).

Upon switching after the 24-week double-blind period, the placebo-pegzilarginase patients pArg levels also fell by LTE week 24, though by a numerically higher amount than the pegzilarginase-pegzilarginase group after the same time on treatment (24 weeks) ([redacted] compared to [redacted] n=21), respectively). This fall was maintained through to week 96 of the LTE, though numbers in the analysis were small at this time point (n=[redacted]). [redacted] remained on treatment at week 120.

In Study 102A, the change from baseline in pArg levels at 24 weeks was [redacted]. The fall was maintained at week 144, with a mean change from baseline of [redacted], indicating that the reduction in pArg was maintained, and was numerically higher at week 240 ([redacted]) though numbers in the analysis were small at this time point (n=[redacted]).

In its response to clarification question A21, the company provided data from a pooled analysis of PEACE and Study 102A (see

Figure 7). At Week 24, pegzilarginase demonstrated a [redacted] reduction (versus 76.7% in PEACE) in mean pArg compared to placebo (p<0.0001).

Data for ornithine and GCs can be found in Figure 17 of the CS. The company states that "*At Week 24, patients treated with pegzilarginase had a clinically relevant and statistically significant 106.9% increase in mean ornithine (70.2 µM, 15 of 21 patients) compared to the placebo group (31.9 µM, 10 of 11 patients) (95% CI: 1.567, 2.731; p<0.0001) (59, 84)"* (CS, p.81), and that these levels were maintained in the LTE (CS, p.91). They also highlighted that GCs are thought to contribute to seizures in patients with ARG1-D, and that plasma levels of GCs statistically significantly decreased from baseline with pegzilarginase to week 24 and reductions were maintained in the LTE.

EAG critique of clinical effectiveness in biochemical outcomes:

The study met its primary endpoint: The EAG notes that the effect of pegzilarginase on these biomarkers was large and statistically significant in the first 24 weeks of treatment, in comparison to placebo. Large effects were also seen when placebo patients crossed over to pegzilarginase in the LTE, and in Study 102A, but the fall was smaller in absolute numbers in Study 102A ([redacted]) compared to the two arms of PEACE ([redacted] (SD [redacted], n=21) and [redacted]. The effect on other biomarkers seems consistent with the effect on pArg.

The pooled analysis is consistent with PEACE: The pooled (PEACE and Study 102A) mean change from baseline compared to placebo was [redacted] which was consistent with -76.7% in PEACE.

Effects are maintained over time, but small numbers at later time points introduce uncertainty in long term effects: Effects appear to be maintained over time, based on the LTE and data from Study 102A, though numbers in the analysis were small at later time points, meaning the effects in the long term beyond 96 or 144 weeks are uncertain. There was also no comparator arm in the long term (see Section 3.2.5). The EAG's clinical advisors agreed that long-term effects are currently unclear.

Uncertainty around the use of pArg as a surrogate outcome: Clinical advisors to the EAG noted that pArg does not correlate perfectly with disease severity but is associated with hyperammonaemia.

Uncertainty around the impact of GCs on seizures: only one clinical advisor gave an opinion, but there were unsure about the impact of GCs on seizures and noted that GCs are not routinely measured in clinical practice.

Table 8: Plasma arginine: results from PEACE and Study 102A

Outcome, range, MCID or normal	Trial arm	Baseline	Week 24	LTE24 or week 48****	LTE96 or week 120****	LTE120 or week 144, **** or last reported week
PEACE trial results						
Mean pArg, µmol/L (SD) Primary outcome Range: N/A Normal: 40-115	Pegzilarginase	n=21 GM 354.0 (0.27)* Mean: 365.4 (93.7)**	n=21 GM 86.4 (1.60)* Mean: [redacted]*** MCFB: [redacted]***	[redacted] Mean: [redacted]*** MCFB: [redacted]***	[redacted] Mean: [redacted]*** MCFB: [redacted]***	NR
	Placebo-pegzilarginase	n=11 GM 464.7 (0.2)* Mean: [redacted]***	n=11 GM 426.5 (1.31)* Mean: [redacted]*** [redacted]	[redacted] Mean: [redacted]*** MCFB: [redacted]***	[redacted] Mean: [redacted]*** MCFB: [redacted]***	[redacted] Mean: [redacted]***
	Between group	Change from baseline: −76.7% (95% CI: −67.1%, −83.5%, p<0.0001)*				
Study 102A results						

Outcome, range, MCID or normal	Trial arm	Baseline	Week 24	LTE24 or week 48****	LTE96 or week 120****	LTE120 or week 144, **** or last reported week
Mean pArg, µmol/L (SD)	Pegzilarginase	309.2 (97.60)	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted] MCFB: [redacted]

Source: *From the company submission appendix M; ** from Sanchez Russo 2024; ***from the CSR

**** The LTE week number relates to PEACE trial, whilst the week number relates to study 102A

Abbreviations: µmol/L, micromoles per litre; GM, geometric mean; LTE, long term extension; MCFB, mean change from baseline; MCID, minimal clinically important difference; pArg, plasma arginine; SD, standard deviation; Wk, week;

Figure 6: Effect of pegzilarginase on pArg levels during the double-blind period (PEACE; FAS) (reproduced from CS, Figure 14)

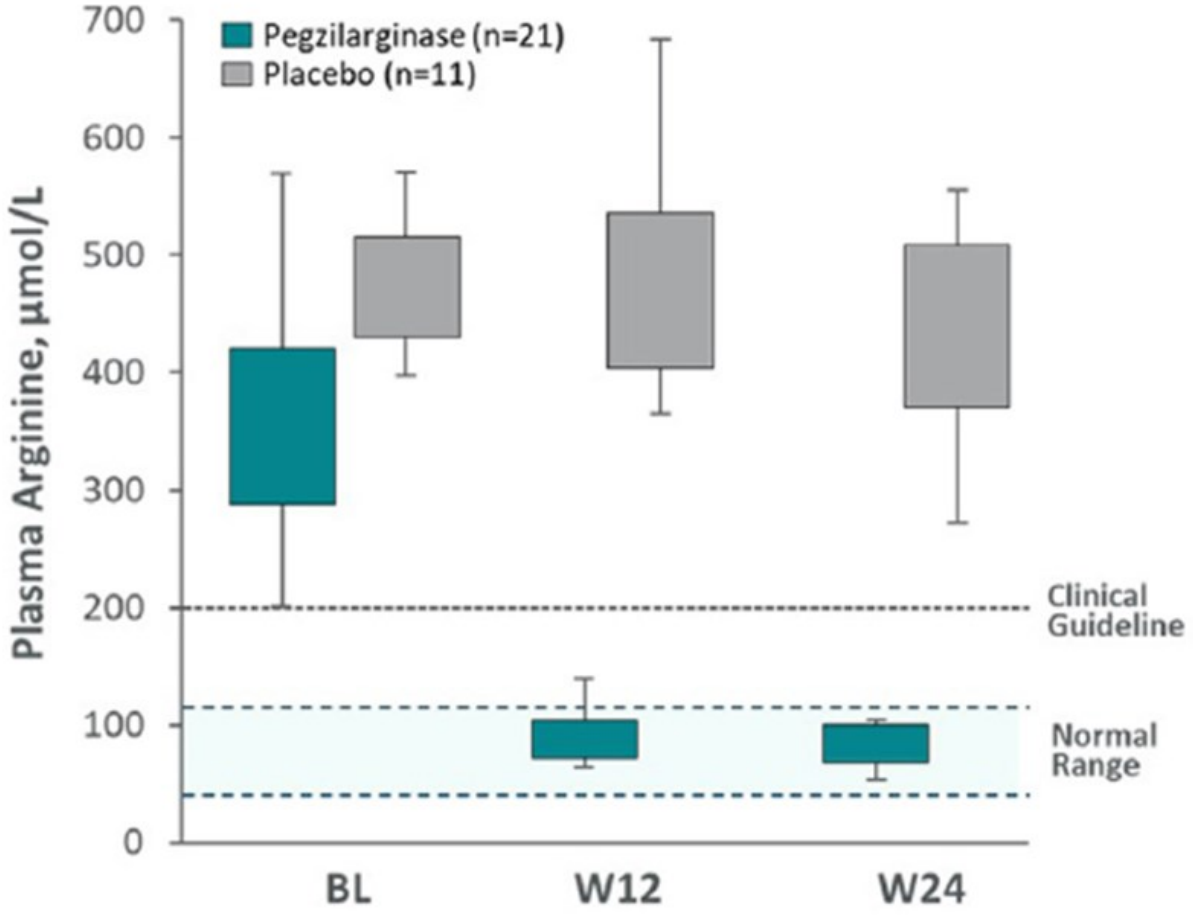


Figure 7: Pooled analysis of PEACE and Study 102A (reproduction from clarification response, Figure 7)

CI: confidence interval; GMFM-D: Gross Motor Function Measure, Part D; GMFM-E: Gross Motor Function Measure, Part E; PEG: pegzilarginase.

3.3.2 Clinical effectiveness related to mobility and spasticity outcomes

In PEACE, the main motor outcomes were 2MWT, GMFM-E, GMFM-D and MAS. In Study 102A the same outcomes were reported, except 6MWT was measured instead of 2MWT. In this section, the EAG summarises the main results and provides a critique for all outcomes together at the end of the section.

The data for the 2MWT and both GMFM scores from PEACE are reported in Table 9. Data for MAS are not tabulated in the EAG report or the CS. The EAG has not reproduced Figure 15 from the CS since the LTE data were from an interim analysis rather than the final analysis.

2MWT and 6MWT: Walk tests measure how far (usually in meters) a person walks within an allocated amount of time (in these studies, 2 or 6 minutes). For the 2MWT, the company used a MCID of 9% increase from baseline, based on work in cerebral palsy. For the 6MWT, they used a MCID of 9% based on work in Morquio A syndrome.[27]

In PEACE, at the end of the double-blind period, the 2MWT LS mean difference between the pegzilarginase and placebo group was 5.5 metres (95% CI: -15.6%, 26.7%; *p*=[redacted]), which was not statistically significant. The company highlighted that the change from baseline data in the pegzilarginase arm (12.8%) exceeded the MCID (9%). An improvement was maintained at week 96 (mean change from baseline [redacted] meters, [redacted]), through to week 120 of the LTE (mean change from baseline [redacted] meters) though numbers in the analysis were small ([redacted]) at this time point.

Upon switching to pegzilarginase, the placebo-pegzilarginase patients 2MWT had not improved after 24 or 48 weeks on treatment (mean change from baseline [redacted] and [redacted] meters) but had improved by LTE96 ([redacted]), and this was maintained/increased through to LTE120 (mean change from baseline [redacted] meters), though numbers in the analysis were small ([redacted]) at this time point.

In Study 102A, the company noted that the 6MWT showed a clinically meaningful improvement ([redacted] change from baseline) by week 48 which was sustained to week 144 (range for weeks 48-144 time points [redacted].

In the analysis pooling PEACE and Study 102A, reported in the clarification response to question A21, the LS mean difference at 24 weeks between the treatment groups was [redacted] (95% CI: [redacted] *p*=[redacted]), which was similar to the result observed in PEACE (*p*=[redacted]).[21, 28, 29]

GMFM-E: GMFM-E is a measure of ability to walk, run and jump via assessment of 24 activities. The range in scores is 0-72, where higher values indicate higher ability. The company used MCIDs derived in cerebral palsy, which varied depending on the patient's baseline GMFCS level (I-III, no values for level IV), and ranged from ≥1.8 to ≥4.0 points.

In PEACE, at the end of the double-blind period, the GMFM-E LS mean difference between the pegzilarginase, and placebo groups was 4.6 (95% CI: -1.1, 10.2; [redacted], which was not statistically significant. The company highlighted that the mean MCID across all patients exceeded the highest of the range of MCIDs derived by GMFM class (≥1.8 to ≥4.0 points). An improvement was maintained at week 96 (mean change from baseline [redacted] points, n=10), through to week 120 of the LTE (mean change from baseline [redacted] points) though numbers in the analysis were small (n=[redacted]) at this time point.

Upon switching to pegzilarginase, the placebo-pegzilarginase patients had very small improvements up to week 96 (MCFB range [redacted]), but greater numerical improvements were seen at week 120 (MCFB: [redacted]), though numbers in the analysis were small (n=[redacted]) at this time point.

In Study 102A, the company did not note any clinically meaningful improvements, but did note numerical improvement up to week 144 (mean change from baseline [redacted]). The EAG notes from the CSR[30] that for patients with GMFCS level I there was a clinically meaningful improvement at week 72 (mean change from baseline [redacted]) but the number in the analysis was small at this point ([redacted]). For patients with GMFCS level II-III, mean change from baseline from weeks 12 through to 144 [redacted] (range [redacted]) to [redacted]. [redacted]

In the analysis pooling PEACE and Study 102A, reported in the clarification response to question A21, the LS mean difference at 24 weeks between the treatment groups was 4.6 with a *p*-value of [redacted] (*p*-value improved compared to PEACE [*p*=[redacted]], but still not statistically significant).

GMFM-D: GMFM-D is a measure of ability to stand via assessment of 13 activities. The range in scores is 0-39, where higher values indicate higher ability. The company used MCIDs derived in

cerebral palsy, which varied depending on a patient's baseline GMFCS level (I-III, no values for level IV), and ranged from ≥1.5 to ≥3.3 points.

In PEACE, at the end of the double-blind period, the GMFM-D LS mean difference between the pegzilarginase, and placebo group was 2.3 (95% CI 0.4, 4.2, MMRM *p*=0.021, Wilcoxon Rank Sum (WRS) *p*=[redacted]). The company stated that the MMRM *p*-value is most appropriate since it accounts for multiple measures. Although the results were statistically significant, the company did not note a clinically meaningful improvement. An improvement was maintained at week 96 (mean change from baseline ([redacted]) points, n=10), though was small at week 120 of the LTE (mean change from baseline [redacted] points) though numbers in the analysis were small (n=[redacted]) at this time point.

Upon switching to pegzilarginase, the pattern of improvement was similar to that seen in GMFM-D, in that improvements were small [redacted]) up to week 120, when a more notable improvement was reported ([redacted] though numbers in the analysis were small (n=[redacted]) at this time point.

In Study 102A, the company did not note any clinically meaningful improvements. The EAG notes from Table 27 of the CSR[30] that for patients with GMFCS level I there were no clinically meaningful mean improvements at any follow-up week. For patients with GMFCS level II-III, mean change from baseline from weeks 12 through to 144 were difficult to interpret as the MCID for level II patients is different to level III patients and these patients were grouped together. However, the level III MCID was [redacted] at several time points (weeks [redacted]). [redacted].

In the analysis pooling PEACE and Study 102A, reported in the company's response to clarification question A21, the LS mean difference at 24 weeks between the treatment groups was [redacted] with a *p*-value of [redacted] (*p*-value worsened compared to PEACE result [[redacted]]).

Modified Ashworth Scale: MAS is a measure of spasticity. The scoring scale ranges from 0 (no spasticity) to 4 (total rigidity). No MCID was stated by the company.

In PEACE, MAS was introduced as an outcome in a protocol amendment and was only measured for [redacted]/32 ([redacted]) patients. For the double-blind period, the company states "*The mean (SD) change from*

baseline in the MAS lower body scores for patients in the pegzilarginase and placebo groups was [redacted] ([redacted]) and [redacted] ([redacted]), respectively. These improved scores indicate that [redacted] of patients ([redacted] of [redacted] patients) with baseline spasticity in the pegzilarginase group demonstrated improvements, compared to [redacted] ([redacted] of [redacted] patients) in the placebo group." (CS, p.88).

For Study102A, the company states "*At Week 24, the mean (SD) MAS score per impacted muscle group was [redacted] ([redacted]) (n=[redacted]), representing a mean (SD) decrease of [redacted] ([redacted]). At Week 48, the mean (SD) MAS score impacted per muscle group was [redacted] ([redacted]) (n=[redacted]), representing a mean (SD) decrease of [redacted] ([redacted]). Improvements in spasticity continued through up to Week 262, with mean (SD) MAS scores per muscle group of [redacted] ([redacted]), [redacted] ([redacted]) and [redacted] ([redacted]) at Week 96, Week 144 and follow-up, respectively (96).*" (p101-102 of the CS).

Heat maps of mobility outcomes (responder analysis): The company provided a heat map (Figure 8) of responses based on the MCIDs. This included all patients from PEACE and Study 102A, but only included patients with GMFCS Levels I-III as MCIDs were not available for those with GMFCS Level IV. The EAG asked for the outcomes for those with GMFCS Level IV and these were provided in the company's response to clarification question A22 (Figure 9), although they are of limited value as the baseline values for patients were not also provided, so it is not possible to determine if the placebo patients improved from baseline (except for the outcome 2MWT, as the MCID applied to patients with GMFCS-IV, and responders/non-responders are colour-coded in the heat maps).

Amongst the GMFCS level 1-3 patients, proportionately [redacted] in Study 102A and the pegzilarginase arm of PEACE [redacted]

Amongst pegzilarginase GMFCS IV patients (n=3), values at week 24 are [redacted] compared to pegzilarginase GMFCS I-III patients in all outcomes but appear to be [redacted] over time in the LTE period. Two patients [redacted]. Amongst the placebo GMFCS IV patients (n=2), one patient ([redacted]) has values of [redacted] throughout the placebo and pegzilarginase period of treatment for all outcomes, whilst the other ([redacted]) shows [redacted]

Table 9: Clinical efficacy results for key motor outcomes from PEACE and Study 102A

Outcome, range, MCID or normal	Trial arm	Baseline	Week 24	LTE24 or week 48*	LTE48 or week 96*	LTE96 or week 120*	LTE120 or week 144*	EOS
PEACE trial results								
Mean 2MWT, meters walked in 2 minutes **Key secondary outcome Range:** N/A **MCID:** 9% change from baseline, from CP patients	Pegzilarginase	109.0 ± 55.7	115.9 ± 51.8 7.3-metre increase (+12.8%) from baseline	Mean MCFB:	Mean MCFB:	Mean MCFB:	Mean MCFB:	Mean MCFB:
	Placebo-pegzilarginase	99.0 ± 49.0	102.3 ± 51.1 2.7-metre difference (+4.1%) from baseline	Mean MCFB:	Mean MCFB:	Mean MCFB:	Mean MCFB:	Mean MCFB:
	Between group	LS mean difference: 5.5 metres; (95% CI: -15.6%, 26.7%; *p*=)						
Mean GMFM-E (SD)	Pegzilarginase	48.3 (19.9)	52.0 (21.3)	n= Mean MCFB:	n= Mean MCFB:	n= Mean MCFB:	n= Mean MCFB:	n= Mean MCFB:

Key secondary outcome Range: 0-72 **MCID (CP):** ≥1.8 to ≥4.0 points depending on baseline GMFCS classification			MCFB: 4.2 (7.7)	[redacted]	MCFB: [redacted]	[redacted]	[redacted]	[redacted]
	Placebo-pegzilarginase	46.5 (24.6)	46.1 (25.7) MCFB: -0.4 (6.2)	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]
	Between group	LS mean difference: 4.6 (95% CI: -1.1, 10.2; *p*= [redacted]						
Mean GMFM-D (SD)** **Secondary outcome Range:** 0-39 **MCID (CP):** ≥1.5 to ≥3.3 points depending on baseline GMFCS classification	Pegzilarginase	n=21 28.0 (9.61)	n= 20 Mean 30.5 (10.09) MCFB: 2.7 (3.88)	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]
	Placebo-pegzilarginase	n=11 Mean [redacted]	n= 11 Mean 28.2 (13.28) MCFB: 0.4 (0.97)	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]	n= [redacted] Mean [redacted] MCFB: [redacted]
	Between group	LS mean difference: 2.3 (95% CI 0.4, 4.2) MMRM *p*-value: 0.021 WRS *p*-value: [redacted]						

Study 102A results					
Mean 6MWT, meters walked in 6 minutes **Range**: N/A **MCID:** 9% change from baseline, from Morquio A syndrome patients[27]	Pegzilarginase	n= [redacted]	322.6 (161.4) metres MCFB: [redacted] ([redacted]) metres	346.2 (177.3) MCFB: [redacted] ([redacted]) Mean % change from baseline: [redacted])	Remainder of study through to Week 144 MCFB range: [redacted] - [redacted]
Mean GMFM-E (SD) **Range:** 0-72 **MCID (CP):** ≥1.8 to ≥4.0 points depending on baseline GMFCS classification	Pegzilarginase	[redacted]	[redacted]48.9 (24.6) points MCFB: [redacted] ([redacted])	[redacted]53.6 (20.7) points MCFB: [redacted] ([redacted])	[redacted] Week 144 [redacted] [[redacted]] points MCFB: [redacted]
Mean GMFM-D (SD)**	Pegzilarginase	[redacted]	[redacted]29.1 (11.0) points	[redacted]31.8 (8.4)	[redacted] Week 144: [redacted] [[redacted]] MCFB: [redacted]

Range: 0-39 **MCID (CP):** ≥1.5 to ≥3.3 points depending on baseline GMFCS classification			[redacted] MCFB: [redacted] ([redacted])	points [redacted] MCFB: [redacted] ([redacted])	

* The LTE week number relates to PEACE trial, whilst the week number relates to study 102A

** Data for GMFM-D score have been taken from the updated corrigendum in the CSR, as per the company response to clarification question A17.

Abbreviations: 2MWT, 2 minute walk test; 6MWT, 6 minute walk test; CI, confidence interval; CP, cerebral palsy; EOS, end of study; GM, geometric mean; GMFCS, Gross Motor Function Classification System; GMFM, gross motor function measure; LS, least squares; LTE, long term extension; MCFB, mean change from baseline; MCID, minimal clinically important difference; n, number; NR, not reported; SD, standard deviation; Wk, week.

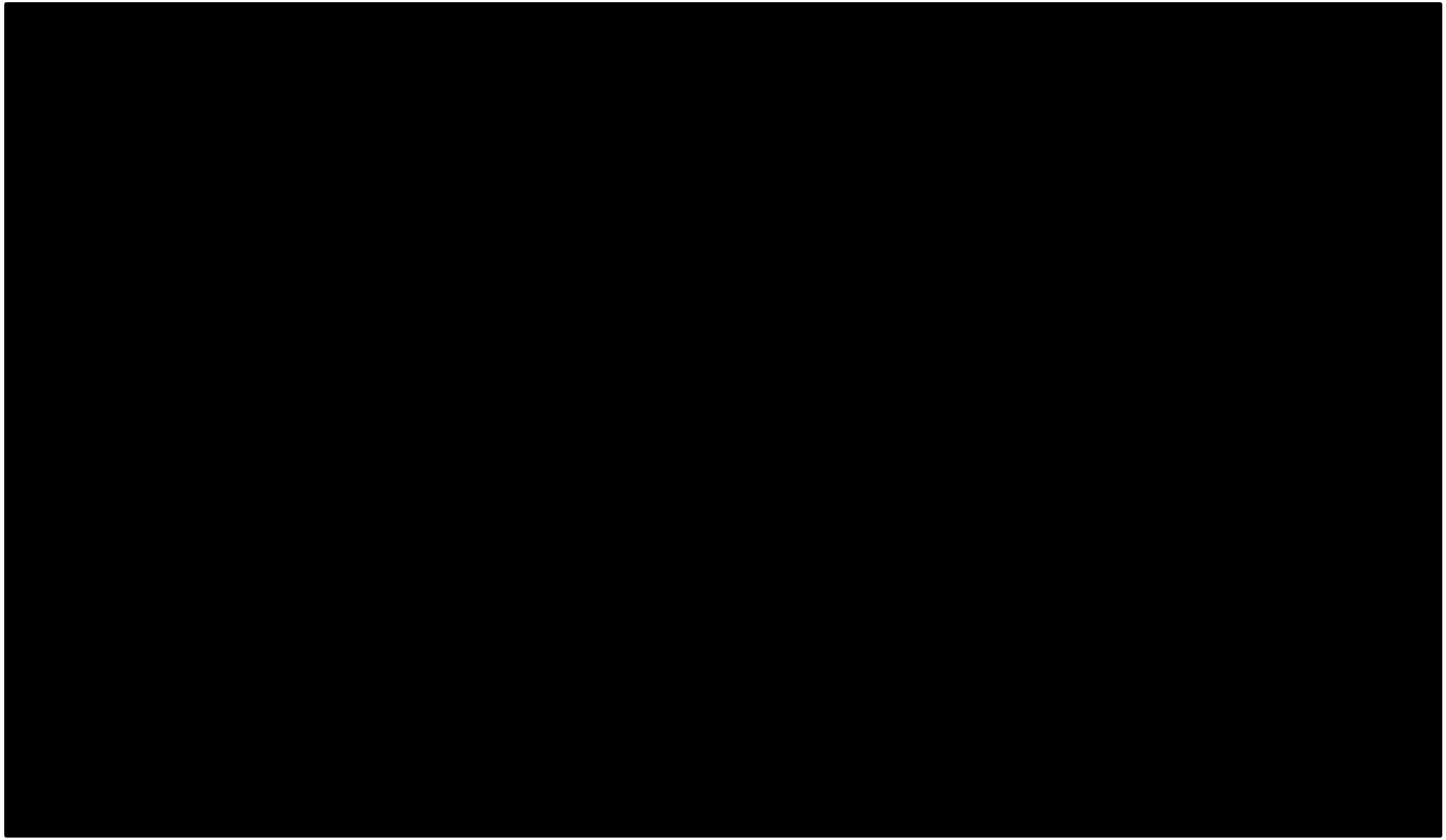
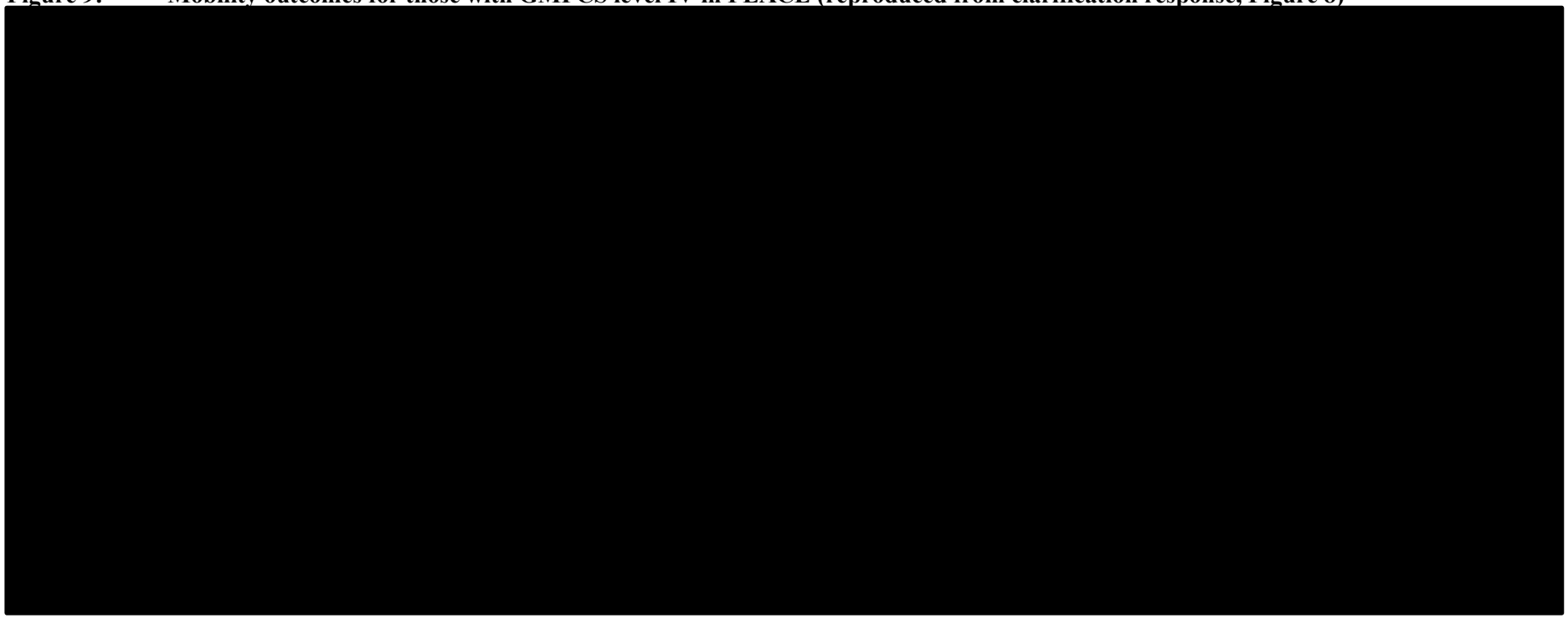


Figure 9: Mobility outcomes for those with GMFCS level IV in PEACE (reproduced from clarification response, Figure 8)



EAG critique of mobility and spasticity outcomes: Overall, the evidence on the impact of pegzilarginase on mobility and spasticity is subject to some limitations and uncertainties.

Lack of statistically significant, clinically meaningful changes in the double-blind period: Only one outcome reported a statistically significant result in the double-blind period (GMFM-D) and this outcome did not reach the MCID. For the GMFM-E, the mean change from baseline at 24 weeks exceeded the MCID, as did the between-group difference in mean change from baseline, but the between-group difference was not statistically significant. For the 2MWT, the pegzilarginase arm exceeded the MCID, but the between-group difference was narrowly short of 9% at 8.7% (when naively calculated by the EAG from available data) and was not statistically significant. Pooling results did not improve the statistical significance of results; all three mobility outcome *p*-values were non-significant. However, numbers in the analysis are still likely to have been small (n<50) and underpowering may be an issue.

However, these mobility results were positively viewed by the EAG's clinical advisors, and it is notable that the longer-term results from PEACE and Study 102A indicate that these outcomes may improve further over time, though small numbers at later time points and a lack of a comparator arm introduce some uncertainty in these results.

Effect of baseline imbalances in patient characteristics: Baseline imbalances may have affected outcomes. The older mean age (12.9 years (SD 6.8) in placebo patients compared to 9.6 years (SD 6.16) in pegzilarginase patients) at baseline of patients in the placebo arm may have caused a worse natural history course over the double-blind period than would have occurred for the younger aged pegzilarginase arm patients, accentuating the difference between arms and favouring pegzilarginase. However, the extent of this confounding is unclear.

Placebo-pegzilarginase patients' response after switching to pegzilarginase: For 2MWT and both GMFM outcomes, the placebo-pegzilarginase patients mean change from baseline at 24 weeks on treatment (LTE24) was much smaller than the pegzilarginase patients at week 24 on treatment, and notable changes were not seen until much later (LTE96 or 120). When asked about why these patients have poorer responses, the company responded that the six-month delay in treatment allowed *"for further deterioration from baseline during the double-blind period"* (clarification response, question A8). The EAG notes that, based on baseline and week 24 values, this is true on average for GMFM-D and -E, but not for the 2MWT, and where there was a deterioration, this was quite small (mean GMFM-E 46.5 (SD 24.6) at baseline compared to 46.1 (SD 25.7) at week 24; mean GMFM-D 29.5 (SD 12.42)

at baseline compared to 28.2 (SD 13.28) at week 24). The EAG's clinical advisors stated that the slower response may be because these patients were older at baseline with worse mean GMFCS, and had started treatment later in their disease course, meaning there was more disease progression to clear before improvements could be seen. Interestingly, Figures 4 and 5 of the company's clarification response show that, whilst slower, mean changes from baseline for GMFM-E and D reached higher values in the placebo-pegzilarginase group eventually, though numbers were fairly small.

However, clinical advisors were also of the opinion that patients with the most severe disease were unlikely to see their symptoms resolve completely, and this is reflected in patient [redacted] (see Figure 9).

The EAG concludes that the reasons for the differences in response to pegzilarginase seen between the two arms is unclear, but may plausibly be due to chance alone, or due to a slower but potentially not lower response in more severe and/or older patients. The EAG notes, however, that there may be a limit to improvements in those with very severe GMFCS scores.

Potential ceiling effect: The company states on page 122 of the CS that: "*As patients randomised to pegzilarginase had less severe disease at baseline and were close to the upper limit of the scale, it was more challenging for pegzilarginase to demonstrate a significant benefit across clinical outcomes versus placebo*." The EAG notes that there is some evidence to support this, from Figures 3-5 of the company's clarification response, where mean changes from baseline in the placebo-pegzilarginase group (who had worse disease on average at baseline) are higher for GMFM-D and -E. Of further interest in relation to this issue, the company conducted subgroup analyses (see Section 3.3.7) by age, sex, region (USA and ex-USA) and GMFCS classification (Level I and Levels >II) and whilst most were underpowered, the company did note that "*patients treated with pegzilarginase with more severely restricted mobility (GMFCS Level ≥II) had greater gains in both the 2MWT and GMFM-E compared to patients classified as GMFCS Level I (See Figure 39 and Figure 40, Appendix E) (84). These differences may reflect a lesser capacity to capture improvements in clinical benefit with these assessment tools in patients with near-normal baseline scores*." (CS, p.107). The EAG concludes that a ceiling effect is plausible.

MCIDs derived from different conditions: Clinical advisors to the EAG noted that the MCIDs from cerebral palsy may not be generalisable to ARG-1 deficiency, since cerebral palsy is a long-term incurable condition whilst ARG-1 deficiency is progressive. The EAG are not aware of any more suitable alternative MCIDs.

MCID for 2MWT: The company cites an MCID of 9% for the 2MWT, and notes that the pegzilarginase patients exceeded this. However, the EAG could not locate the MCID for the 2MWT in the reference indicated by the company (Oeffinger *et al*.[31]), though this reference does provide MCIDs for GMFM-D&E. The MCID for the 6MWT was also 9% but was derived in a different study[27] in patients with Morquio A syndrome.

Data on MAS in PEACE: The introduction of MAS as a protocol amendment means the group of patients was small (n=[redacted] total). Results in the CS and in the CSR appear to only relate to [redacted] subjects in total (sum of n=[redacted] and n=[redacted] noted in the text relating to "improved scores"), making it difficult to draw any meaningful conclusions about the effect of pegzilarginase on spasticity from these results. Since an MCID was not reported for this outcome, it is unclear whether the results, which appear numerically small [redacted] on a scale ranging from 0 to 4) are clinically meaningful.

Calculation of mean change from baseline: The EAG notes that the mean values provided at baseline are for all patients, whilst the mean change from baseline estimate is based on only patients who had data at the timepoint being analysed. This seems a sensible approach given the combined effects of a) the small number of patients, b) baseline values being very variable (range [redacted] meters), and c) patients missing at later time points being thought to be largely missing at random due to time of enrolment. However, the analysis method selected introduces some uncertainty, especially if c) is untrue, and patients were missing for reasons associated with the effect of treatment, e.g., due to poor outcomes.

Effects of growth on mobility outcomes: The EAG asked clinical advisors if age and growth may affect results, two paediatric clinical advisors thought this was probably not the case and one deferred to paediatricians to answer.

Conclusion: The EAG was not able to draw a conclusion as to whether pegzilarginase has a clinically meaningful effect on mobility outcomes due to results not reaching statistical and/or clinical significance. Underpowering may be an issue. In the longer-term, numerical increases in outcomes over time are consistent with the positive experience of clinical advisors and may indicate effects increase over time, especially in the context of a disease that is progressive in nature. However, small numbers of patients at later time points and the lack of a comparator arm introduce some uncertainty in long-term effects.

3.3.3 Clinical effectiveness in neurocognitive outcomes

Two outcomes related to neurocognition: VABS-II, and intelligence measured according to BSID-III (children aged 2-3.5 years) or Weschler tests (children and adults >3.5 years).

3.3.3.1 VABS-II

The company's response to clarification question A24 describes the Vineland adaptive behaviour scale II (VABS-II) as a measure of adaptive behaviour across four domains (communication, daily living skills, socialisation including play, leisure, interpersonal relationships and coping skills, and motor skills). The first three of these domains combine into the composite score reported in the CS, known as the VABS-II adaptive behaviour composite score. A score between 86-114 indicates adequate adaptive behaviour.

The results are reported in Table 10. The mean baseline values in both arms indicated a "low" or "moderately low" level of adaptive behaviour. In the double-blind period the between group LS mean change from baseline was [redacted], 95% CI: [redacted], [redacted]; *p*=[redacted], indicating a statistically non-significant change, though this was numerically in favour of pegzilarginase.

Additional time points and updated data were reported in the CSR compared to the CS. In the LTE, mean change from baseline values indicated an initial improvement ([redacted] at LTE24 and [redacted] at LTE96) then worsening by the end of study timepoint in the pegzilarginase arm (mean change from baseline at end of study: [redacted]). A similar pattern in the placebo arm was observed when they switched to pegzilarginase (mean change from baseline [redacted] at LTE24, [redacted] at LTE96, and [redacted] at end of study). In both arms, the number of patients in the analysis at the end of the study was small ([redacted] and [redacted] respectively), meaning that the results are uncertain.

In Study 102A, the CS (p.104) states that: "*Based on the adaptive behaviour composite scores for individual patients, at the last on-treatment visit (144 weeks of treatment)* [redacted] *patients were assessed to be stable,* [redacted] *patients had declined, and* [redacted] *had improved on study*."

3.3.3.2 Intelligence batteries

Different intelligence tests were applied according to patient age: BSID-III (children aged 2-3.5 years) or Weschler tests (children and adults >3.5 years, provide full-scale intelligence quotient (FSIQ) scores). FSIQ scores can range from 40-160, with a score of 90-109 considered 'average' in the general population.

The results are reported in Table 10. For patients completing the Weschler tests, the baseline mean values in both arms were extremely low indicating below average intelligence. Both treatment arms improved in the double-blind period, with a numerically larger improvement in the placebo group that was not statistically significant, and the company cautioned that the numbers at week 24 were insufficient for a robust analysis. One patient completed the BSID-III and the company stated in their clarification response[32] (question A26) that "*there was no meaningful observed change in the neurocognition and memory of this patient.*"

In Study 102A, the CS (p.103) states that: "*scores were assessed for* [redacted] *patients.* [redacted] *patients (*[redacted]*) had stable scores,* [redacted] *patients (*[redacted]*) had improved FSIQ scores, and* [redacted] *had scores fluctuating between stable to worsening over the study*."

EAG critique of neurocognitive outcomes

No statistically significant difference between arms: There were no statistically significant differences between arms in the double-blind period for either outcome. Underpowering may be an issue, but results remain uncertain.

Inconsistent results between the two outcomes: Whilst differences were not statistically significant, when considering the numerical changes seen, it is unclear to the EAG whether it is clinically plausible that VABS-II would change without a similar change in intelligence measures. When asked, one clinical advisor (two others did not respond) responded to the EAG to note that VABS-II may be affected without a similar effect on intelligence since VABS-II includes a motor component. It is unclear which domains drove the change in VABS-II as data were only provided for the composite score.

Minimal clinically important differences not provided: The company did not provide MCIDs for these tests, and it is therefore difficult to know if the numerical changes seen during the double-blind period were meaningful to patients. However, one clinician (two did not respond) noted that a small improvement in motor and/or cognitive skills can be meaningful for patients who have a low baseline. This advisor also noted that quantified MCIDs are useful for research but don't always translate well into clinical practice.

Uncertainty in the long-term outcomes for patients: The long-term effects are uncertain since there were small numbers of patients beyond LTE96 in both arms.

Effects of growth on neurocognitive outcomes: Though different tests are applied according to age, there may still have been room for improvements due to age within an age band, e.g., 2.5 to 7.6 years. The EAG asked clinical advisors if age may affect results, two paediatric clinicians thought this was probably not the case and one deferred to paediatricians to answer.

EAG clinical advisors own experience with the treatment: Clinical advisors to the EAG were, however, of the opinion that in their experience the drug has affected neurocognition positively. If an improvement in both outcomes is plausible, the non-significance of results seen and the inconsistency between outcomes in the trial may be accounted for by underpowering.

Conclusion: The EAG was not able to draw a conclusion regarding the effects of pegzilarginase on neurocognition since the trial results were uncertain and the clinical advisors did not have extensive experience of the effects of the treatment on patients.

Table 10: Clinical efficacy results for neurocognitive outcomes from PEACE

Outcome, range, MCID or normal	**Trial arm**	**Baseline**	**Week 24**	**LTE24**	**LTE96**	**LTE 120**	**EOS**
Mean VABS-II (SD) Secondary outcome Composite score adequate range 86-114 moderately low 71-85 low 20-70 higher better	**Pegzilarginase**	[redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	NR	[redacted] MCFB: [redacted]
	Placebo-pegzilarginase	[redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	NR	[redacted] MCFB: [redacted]
	Between group	(LS mean difference: [redacted], 95% CI: [redacted]; *p*=[redacted])					

Mean Wechsler (SD) Tertiary intelligence batteries WAIS-IV (16 years and older) WISC-V (6 to 16 years 11 months) WPPSI-IV (2.5 to 7.6 years) BSID-III (2 to 3.5 years)	**Pegzilarginase**	[redacted]	[redacted]MCFB: [redacted]	[redacted]MCFB: [redacted]	[redacted]MCFB: [redacted], [redacted]	NR	[redacted]MCFB: [redacted]
	Placebo-pegzilarginase	[redacted]	[redacted]MCFB: [redacted]	[redacted]MCFB: [redacted]	[redacted]MCFB: [redacted] ([redacted])	NR	[redacted]
	Between group	NR					

Range 40-160, with a score of 90-109 considered 'average' in the general population						

CI: confidence interval; EOS: end of study; LS: least squares; LTE: long term extension; MCFB: mean change from baseline; MCID: minimal clinically important difference; SD: standard deviation; NR: not reported; n: number; VABS-II: Vineland Adaptive Behavior Scale: Second Edition; WAIS-IV: Wechsler Adult Intelligence Scale: Fourth Edition; WISC-V: Wechsler Intelligence Scale for Children: Fifth Edition; Wk: week; WPPSI-IV): Wechsler Preschool and Primary Scale of Intelligence: Fourth Edition; BSID-III: Bayley Scales of Infant and Toddler Development: Third Edition

3.3.4 Clinical effectiveness in QoL outcomes

Three quality of life measures were used in PEACE: (i) the PedsQL; (ii) the SF-36 and (iii) the ZBI-12. The results for PEACE are reported in Table 11. Two outcomes were measure in Study 102A: PROMIS and PedsQL.

3.3.4.1 PedsQL

PedsQL has four domains (physical, emotional, social, and school), each with a score ranging 0-100 where higher is better. These can be combined to create 3 summary scores: total health, physical health, and psychosocial health. The summary scores were not part of the original statistical analysis plan but were analysed in a *post hoc* amendment.

At the end of the double-blind period, in each of the four domains, results favoured pegzilarginase either by demonstrating improvements from baseline that were superior to improvements/deteriorations seen in the placebo arm, or by having a smaller deterioration from baseline than placebo. In the LTE, not all domains showed sustained improvements at all time points, though small numbers at later time points introduce uncertainty. Upon switching to pegzilarginase, placebo-pegzilarginase patients saw improvements across all domains at LTE24, but these were not always sustained at LTE48 and there were very few data points beyond that.

The *post hoc* analysis of the summary scores at the end of the double-blind period reported statistically significant between-group differences in favour of pegzilarginase treatment for total ([redacted]) and psychosocial ([redacted]) health, but not for physical health [redacted]), though results were numerically in favour of pegzilarginase (difference in mean change from baseline between groups not reported).

Only two patients completed the PedsQL in Study 102A and results were only partially reported in the CS.

3.3.4.2 SF-36

The 36-Item Short Form Health Survey (SF-36) assesses 8 health concepts: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue); and general health perceptions.

Whilst the SF-36 was a protocol-defined outcome, it was only applied to adult patients. Only 4 patients completed the tool, and the company did not summarise the results, but provided the score for each SF-36 question for each patient.

3.3.4.3 ZBI-12

ZBI-12 is a measure of caregiver burden, comprising two domains (personal strain and role strain). The total score ranges 0-48, where higher scores indicate greater burden. Results numerically favoured pegzilarginase at the end of the double-blind period, but were not maintained in the long term, though patient numbers were small which introduces uncertainty. Upon switching to pegzilarginase, placebo-pegzilarginase patients eventually saw improvements in caregiver burden by the end of the study, but the number of patients included in the analysis was unclear.

3.3.4.4 PROMIS

PROMIS (a set of paediatric disease non-specific patient or parent proxy-reported outcome measures of multiple health domains) was only collected in Study 102A. The company stated: *"When data from all PROMIS tools is combined (n=[redacted]), a decrease in pain was reported in [redacted] of [redacted] patients ([redacted]) and a decrease in fatigue in [redacted] of [redacted] patients ([redacted]), with [redacted] patients having a reduction in both. Anxiety was reported as increased in [redacted] of [redacted] patients ([redacted]) and improved in [redacted] of [redacted] patients ([redacted]). No other obvious trends were observed over time."* (Cs, p.104)

Table 11: Quality of life outcomes from PEACE

Outcome, range, MCID or normal	Trial arm	Baseline	Week 24	LTE24	LTE48	LTE96	LTE 120	EOS
PedsQL Tertiary endpoint Range 0-100 for each scale (physical functioning, social functioning, emotional functioning, school functioning), higher better	**Pegzilarginase**	[redacted]16 Physical: [redacted] Emotional: [redacted] Social: [redacted] School: [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: - [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: - [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: - [redacted]		[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: - [redacted]
	Placebo-pegzilarginase	[redacted] Physical: [redacted] Emotional: [redacted] Social: [redacted] School: [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: [redacted]	[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: - [redacted] School MCFB: [redacted]	[redacted]		[redacted] Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: [redacted]

Mean PedsQL (SD) Post-hoc analysis Parent-reported * Total Scale Score Physical Health Summary Score Psychosocial Health Summary Score	**Pegzilarginase**	[redacted] Total: [redacted] Physical: [redacted] Psychosocial: [redacted]	[redacted] Total MCFB: [redacted] Physical: [redacted] Psychosocial: [redacted]	NR				
	Placebo-pegzilarginase	[redacted] Total: [redacted] Physical: [redacted] Psychosocial: [redacted]	[redacted] Total MCFB: [redacted] Physical: [redacted] Psychosocial: [redacted]					
	Between group	Total: [redacted] Physical: [redacted] Psychosocial [redacted]						
SF-36 (patients ≥19 years) Tertiary outcome	[redacted] Individual patient data provided as raw scores for each question. No summary scores provided. No LTE data provided.							

Mean ZBI-12 (SD) Tertiary outcome Range 0-48 (higher = more burden)	**Pegzilarginase**	[redacted]	[redacted] MCFB:	[redacted] MCFB: [redacted]	[redacted] MCFB:	n= [redacted] MCFB: [redacted]	NR	Week 150 [redacted] MCFB:
	Placebo-pegzilarginase	[redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB: [redacted]	[redacted] MCFB:	[redacted] MCFB:	NR	Week 150 [redacted] MCFB:

EOS: end of study; LTE: long term extension; MCFB: mean change from baseline; MCID: minimal clinically important difference; SD: standard deviation; NR: not reported; n: number; Wk: week

EAG critique of QoL outcomes

PedsQL summary scores analysed as a post-hoc amendment and unclear in the longer term: The evidence on the impact of the treatment on quality of life is most compelling from a *post hoc* analysis of the PedsQL total and psychosocial summary scores during the double-blind period, where statistically significant results were observed. However, this analysis was *post hoc* and could be subject to "data dredging." In addition, the company did not report an MCID for these measures. The effect in the longer-term was uncertain due to small patient numbers at later time points.

Data on adults was not summarised or statistically analysed: The data from adult patients were not summarised or statistically analysed, so the effect on these patients is unclear.

Data on carers not statistically analysed and unclear in the longer term: The effect on carer quality of life numerically favoured pegzilarginase treatment at the end of the double-blind period, but since these were tertiary outcomes no statistical tests were performed, and effects were unclear in the long term due to small patient numbers at later time points.

Clinical advisors to the EAG were positive about the effects of treatment: Whilst the trial results were subject to limitations, the EAG's clinical advisors were positive about the effects on their patients, and one cited improvement at school for their patient.

3.3.5 Other outcomes measured but not reported in the CS

The CSR shows that the following outcomes were measured but not reported in the CS

- Functional Mobility Scale (FMS) and Gillette Functional Assessment Questionnaire (GFAQ)
- Caregiver and Clinician Global Impression of Change (GIC)
- Caregiver and Clinician Global Impressions of Severity
- Fine motor function (9-Hole Pegboard).

The EAG has consulted the CSR to obtain relevant data. The results for the FMS were described as follows:

"[redacted]" (PEACE CSR,[33] p.112) and in the LTE

“[redacted]”
(PEACE CSR, p.170).

The results for the GFAQ were: “[redacted]” (PEACE CSR, p.116) and in the LTE “[redacted]”
(PEACE CSR, p.176).

The Caregiver and clinician GICs were both summarised as follows: “[redacted]” (PEACE CSR, p.127). The EAG could not locate LTE data in the CSR for these outcomes.

The 9-hole pegboard results were summarised as: “[redacted]”
(PEACE CSR, p.128). In the LTE, “[redacted]” and the EAG notes that changes from baseline [redacted] (PEACE CSR, p.181 and Table 48).

EAG critique of outcomes not reported in the CS

The EAG notes that these outcomes are not inconsistent with other motor outcomes in PEACE in that there is a poor or no response in the double-blind period. In the LTE, some small improvements were noted in some outcomes which may be significant in the context of a progressive disease, but small numbers in analyses at later time points and the lack of a comparator arm make the interpretation of the results uncertain.

3.3.6 Adverse events

In this section, the EAG concentrates on the PEACE trial, but notes that results from Study 102A were consistent with the findings in PEACE.

The company states that treatment exposure was similar across treatment arms in the double-blind period and in the LTE, and dosing compliance was high [redacted].

Data summarising AEs can be found in Tables 22-24 of the CS. Most patients reported at least one treatment-emergent adverse event (TEAE) (90.6%) in the double-blind period, and all (100%) did in the LTE period where patients were on treatment for longer. Most TEAEs were mild or moderate, [redacted] patients required dosing reductions (all in the LTE), and none required treatment discontinuation. However, there were 20 events in 8 patients in the pegzilarginase arm during the double-blind period that required dose interruptions compared to only 2 events in 1 patient in the placebo arm. Both arms reported TEAEs that required dose interruptions in the LTE ([redacted] events in [redacted] patients in the pegzilarginase-pegzilarginase arm and [redacted] events in [redacted] patients in the placebo-pegzilarginase arm). The events in the double-blind period that led to interruptions were: [redacted]

There were serious TEAEs in both arms in the double-blind period, and proportionately more occurred in the placebo arm than the pegzilarginase arm (36.4% compared to 19.0%, respectively). In the LTE, the same trend toward [redacted] was apparent. However, only [redacted] serious TEAEs were considered to be potentially related to the treatment across both periods. Only one is described in the CS (hyperammonaemic encephalopathy) and this resolved in a week.

Events occurring in ≥15% patients in any arm in the double-blind period included vomiting (29% in the pegzilarginase arm and 27% in the placebo arm), nausea (5% and 27%, respectively), abdominal pain (5% and 27%, respectively), hyperammonaemia (10% and 27%, respectively), ammonia increase (14% and 18%, respectively) and cough (19% and 9%, respectively), alongside pyrexia, decreased appetite, alanine aminotransferase increase, aspartate aminotransferase increase, amino acid level increase, headache, and rhinorrhoea at lower proportions. In the LTE, these AEs generally continued, alongside the emergence of others (e.g., diarrhoea, blood potassium decrease, oropharyngeal pain).

3.3.6.1 AEs of special interest

There were three AEs that were protocol-defined as being of special interest. These were: hypersensitivity reactions; injection site reactions and hyperammonaemia events (which the EAG assumes is synonymous with HACs).

Hypersensitivity reactions were mild to moderate in severity and occurred only in the double-blind period and only affected two patients. Both resolved with treatment. Subcutaneous injection site reactions occurred in [redacted] patients, and all resolved spontaneously or with standard care.

HACs were defined in the protocol as occurring: "*where ammonia levels were >100 μM, patients were symptomatic, patients required treatment in a hospital or emergency room, and are summarised by a sponsor-defined MedDRA query, which included the MedDRA preferred terms of hyperammonaemia, hyperammonaemic crisis, and hyperammonaemic encephalopathy that met these conditions*" (CS, p.115).

The company states that fewer patients in the pegzilarginase arm experienced HACs during the double-blind period compared to the placebo arm (14.3% versus 36.4%) and were associated with precipitating factors such as infection. In the LTE, fewer patients experienced HACs in the pegzilarginase-pegzilarginase arm than in the placebo-pegzilarginase arm ([redacted] versus [redacted]). The company states these rates are consistent with rates seen in ARG1-D, and that events were transient and managed with normal care. The company further noted that although quantitative assessment was not possible, a clinician noted a decline in HACs with treatment.

EAG critique of adverse events

Most events were mild to moderate: The EAG notes that many AEs were considered unrelated to the treatment and were largely mild to moderate in nature.

Unclear effect of treatment on HACs due to lack of statistical analysis and results in the LTE: HACs were numerically different in the placebo arm compared to the pegzilarginase arm, but an analysis was not conducted to test the statistical significance of this difference. Furthermore, a similar difference persisted into the LTE period, where it would be expected that patients in the placebo arm may experience fewer HACs if pegzilarginase were protective against them. Clinical advisors to the EAG noted that HACs are more common as patients get older (though one also noted that patients become more tolerant as they age, but did not state at what age this tolerance develops), and the EAG therefore notes that it is possible that placebo arm patients, who were on average approximately 3 years older at baseline, may have experienced more HACs during the double-blind period because of their age rather than due to an absence of treatment. However, the analysis done was based on the number of patients

experiencing an event, rather than number of events, and was not done at multiple time points. As such it is not clear whether a protective effect may have developed over time in the placebo-pegzilarginase arm in the LTE. In summary, it is unclear to the EAG from these data whether the treatment has an effect on HACs.

Definition of HACs limited: Clinical advisors to the EAG noted that the definition of a HAC used in the trial would miss some events that would be a burden to patients. One also noted that patients can become tolerant to high levels of ammonia and may not present as unwell or need hospital treatment, but that chronic hyperammonaemia may still cause long term harm. They also noted that ammonia tolerance increases with age but did not state when this tolerance develops.

HACs could have been an outcome in the trial: One clinical advisor noted that HACs are increasingly being recognised as a significant symptom of this disease in comparison to other urea cycle disorders. The EAG notes that HACs were not a key focus of the trial, which probably reflects the understanding of the disease at the time of the trial conceptualisation.

3.3.7 Subgroup analyses

The company conducted pre-planned subgroup analyses on pArg, 2MWT and GMFM-E, as described in Section B.2.7 of the CS. Age (< and ≥18 years), sex (male and female), region (US and ex-US) and GMFCS classification (level I and Level >I) were considered. There were too few patients aged ≥18 years (n=3) to conduct an analysis according to age, and the company reported that across the other subgroups results were consistent with findings in the primary analysis. They did however highlight that patients with GMFCS > Level I had greater gains in 2MWT and GMFM-E than those with Level 1 and attributed this to the ceiling effect observed in Level 1 patients whose baseline measurements were generally towards the top end of the scale.

EAG critique of subgroup analyses

Ceiling effect plausible, but effects in higher GMFCS categories unclear: The EAG agrees that a ceiling effect is a plausible explanation for the difference. The EAG would have been interested to see whether the effect was different in patients with GMFCS Levels >II, >III and >IV as well, since the EAG's clinical advisors suggested that the effects of the disease may not be fully reversible with more advanced disease.

Interaction tests not performed, and underpowering may mean differences have not been detected: The EAG asked the company if interaction tests were performed to formally compare subgroups, but the company responded that the sample size was too small (clarification response, question A23). The EAG

agrees with this reason, but notes that as such, there may be differences in efficacy between subgroups that have not been detected due to low power.

Data from US appear to have much larger 2MWT response than ex-US, but not GMFM-E response: The EAG also notes that the numerical difference in the response between US and ex-US patients appears to be large for the 2MWT. The LS Mean Difference between pegzilarginase and placebo patients in the US was [redacted] compared to [redacted] in ex-US. A difference in the opposite direction was seen in the GMFM-E ([redacted] compared to [redacted] respectively). The EAG notes that 95% CIs overlapped and given the underpowering cannot draw any conclusions from these data.

3.4 Ongoing studies

The company describe an ongoing study, Study 301A (CAEB1102-301A), which is a Phase 3, open-label study of the safety, pharmacokinetics, and activity of weekly SC pegzilarginase in ARG1-D patients below two years of age. The company notes that this study is of low relevance to the current appraisal since the scope is for patients >2 years of age. The EAG agrees.

3.5 Evidence synthesis

The company reported a pooling of data from PEACE and Study 102A for the outcomes of pArg, walk-tests (2MWT and 6MWT), GMFM-D and GMFM-E. This pooled analysis is discussed in Section 3.3.

The EAG notes that the placebo-pegzilarginase patients did not contribute to the on-treatment pooling, only to the placebo group pooling. This is appropriate, to avoid double-counting patients, but does mean the results, which were generally poorer at earlier on-pegzilarginase-treatment timepoints compared to the PEACE pegzilarginase patients, are not represented in the pooling.

The company noted they conducted an SLR to identify studies of comparator ARG1-D treatments but no relevant RCTs were identified, and indirect or mixed treatment comparisons could not be conducted. They also noted a lack of a standardised comparator would be problematic. The EAG is satisfied with these explanations.

3.6 Additional work on clinical effectiveness undertaken by the EAG

The EAG obtained data from the CSR where necessary to complete data tables throughout the report, and to make sure data were the most up to date as the company confirmed the CSR had the latest data (clarification response A17) and with respect to the outcomes that were not reported in the CS (see Section 3.3.8).

3.7 Conclusions of the clinical effectiveness section

The company's systematic review had some limitations but was likely to capture all relevant pegzilarginase studies. It was less clear whether studies of comparator treatments were excluded for valid reasons, but the EAG was satisfied that an ITC would have had low value due to the lack of a standardised comparator treatment.

Three studies of pegzilarginase were identified. PEACE was a multi-centre, multi-national double-blind Phase 3 RCT, Study 101A was a Phase 1/2 dose-finding study, and Study 102A was a Phase 2 open-label extension of Study 101A to test long-term safety and efficacy. The evidence on efficacy was primarily taken from PEACE and Study 102A.

The EAG noted some limitations of the PEACE trial design, including inclusion criteria that may have missed the most and least ill patients, a double-blind period that may have been too short to demonstrate the full treatment effect and the long-term effect, a primary outcome that was a surrogate outcome that clinical advisors noted does not have a consistent relationship with functional outcomes, and a very limited stratification strategy which may have led to imbalances at baseline. Study 102A was subject to the usual limitations of single-arm, open-label studies in rare diseases (no blinding, small sample size and no comparator arm). The EAG's clinical advisors were not concerned about the inclusion criteria for PEACE, and the EAG notes that long-term results from Study 102A, which had wider inclusion criteria, were consistent with results from PEACE. Both studies included important biochemical, functional, and quality of life outcomes of interest to clinicians and patients. The EAG judged PEACE, as reported in the CS, to be at some risk of bias due to baseline imbalances and evidence of selective reporting.

There were a small number of withdrawals across PEACE and Studies 101A/102A (n=4/48), mostly for personal reasons. The EAG noted that home administration of the treatment may reduce withdrawals, but that some remain possible.

Baseline characteristics for both studies were in keeping with expectations for UK clinical practice, according to the EAG's clinical advisors, though they noted that data for the UK were limited. There were some imbalances in patient characteristics at baseline in PEACE (mean age, pArg levels, spasticity levels, mean age at diagnosis, 2MWT). One of the EAG's clinical advisors noted that imbalances in age may bias study results. The clinical advisors also noted that the MCIDs used were for different conditions which may not be transferrable to ARG1-D.

In both PEACE and Study 102A, there was a large decrease in pArg (-76.7% from baseline), and PEACE met its primary endpoint. This was supported by data from ornithine and guanidino compounds. The effect appeared to be maintained over time, but there were small numbers at later time points.

Across the mobility outcomes in PEACE (2MWT, GMFM-E, GMFM-D), no between-group differences were both statistically and clinically significant at the end of the double-blind period, though the difference in GMFM-D was statistically significant (LS mean difference 2.3 (95% CI 0.4, 4.2, MMRM p=0.021, Wilcoxon Rank Sum (WRS) p=[redacted])) and the differences in 2MWT (LS mean difference 5.5 metres (95% CI: -15.6%, 26.7%; p=[redacted])) and GMFM-E (LS mean difference 4.6 (95% CI: -1.1, 10.2; [redacted]) were clinically significant. Pooling results from PEACE and Study 102A resulted in none of the results being statistically significant, though numbers in the analysis were still small and underpowering may be an issue.

Longer-term data from PEACE and Study 102A showed further improvements over time. Data in patients in the placebo-pegzilarginase arm, who switched to pegzilarginase at 24 weeks and were older at baseline, were limited by patient numbers at later time points, but may show a slower but potentially not different response. The EAG also notes that of the mobility outcomes not reported in the CS, the FMS showed [redacted] and the 9-hole peg board also showed [redacted]. Overall, the EAG could not conclude whether pegzilarginase has a clinically meaningful effect on mobility outcomes due to the lack of statistical and clinical significance, small numbers at later time points, and the lack of a comparator arm in the longer-term but note underpowering may be an issue. Clinical advisors reported seeing improvements in patients but did not have extensive experience of using pegzilarginase.

MAS was only measured in a very small number of patients and results are uncertain.

Across the neurocognitive outcomes (VABS-II and intelligence tests), the between-group comparison numerically favoured pegzilarginase for VABS-II (LS mean change from baseline [redacted] (95% CI: [redacted], [redacted]; p=[redacted])) whereas for the intelligence batteries, results were superior in the placebo arm at 24 weeks. However, there were no statistically significant changes between arms in the double-blind period, no MICDs were reported, and there was uncertainty in the long-term outcomes, for the same reasons as given for the mobility outcomes. Clinical advisors reported seeing improvements in patients but did not have extensive experience, and underpowering may be an issue.

Across the quality-of-life outcomes, a *post hoc* analysis of summary scores for the PedsQL showed statistically significant results (between-group mean change from baseline not reported) favouring

pegzilarginase in total health and psychosocial health, but not for physical health. The individual domains were not analysed statistically but generally favoured pegzilarginase treatment. Caregiver quality of life results favoured pegzilarginase but were not analysed statistically. The EAG notes that the total scores may be subject to data dredging and that the numerical increases in the other outcomes are difficult to interpret since significance testing was not performed. LTE results were uncertain due to low numbers.

AEs were generally mild to moderate in nature. Results for HACs were unclear due to a lack of statistical significance testing, the analysis being based on number of patients not number of events and may have been affected by the older age of placebo patients, since clinical advisors noted older patients have more HACs. Clinical advisors noted the definition of a HAC used would miss some events that would be a burden to patients and that chronic hyperammonaemia may cause harm without hospitalisations.

Conclusions

The EAG concludes that pegzilarginase appears to have a robust effect on pArg within the first 24 weeks of treatment, but that the effect on clinical outcomes (motor, neurocognitive and QoL) in the short-term are less certain since results were not both clinically and statistically significant or were not tested for statistical significance. There was some uncertainty around the generalisability of the MCIDs used to ARG1-D and underpowering may have affected outcomes. Short-term outcomes may have been affected by underpowering and there was some risk of bias from baseline imbalances in patient characteristics between arms in PEACE. In the long-term, numerical effects on pArg, 2MWT, GMFM-E and GMFM-D appeared to be maintained through to weeks 96 or 120, though outcomes were uncertain due to the lack of a comparator arm and small numbers at later time points. Long term effects on neurocognition and QoL were more mixed and uncertain. Results for HACs favoured pegzilarginase numerically but were subject to limitations regarding the analyses performed, and at risk of bias due to imbalances at baseline in age. One clinical advisor to the EAG noted that chronic hyperammonaemia may cause harm without hospitalisations.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of pegzilarginase for the treatment of ARG1-D in England. Section 4.1 presents the EAG's critique of the company's review of published cost-effectiveness evidence. Section 4.2 summarises the company's submitted economic evaluation. Section 4.3 presents a detailed critique of the model and Section 4.4 provides the additional exploratory analyses undertaken by the EAG. Section 4.5 contains a discussion of differences between the company's and the EAG's preferred analyses and summarises the key uncertainties around the cost-effectiveness of pegzilarginase.

The two key components of the economic evidence presented in the CS are: (i) a report of the company's economic evaluation and (ii) a presentation of the incremental cost effectiveness ratio (ICER) expressed in terms of cost per QALY gained. The company also submitted a fully executable model programmed in Microsoft Excel®. Following the clarification process the company submitted a revised version of the model, including significant changes to the way that transition probabilities were estimated and updated regression analyses, and revised estimates of the cost-effectiveness of pegzilarginase were reported. For brevity, this report will only refer to the latest model (and results) received, unless explicitly stated otherwise. The EAG identified some limitations within the model which the EAG believed that if amended would make minimal (or zero) impact on the ICERs reported by the company; these have not been formally documented for brevity reasons, but some are mentioned in passing within this report.

4.1 EAG's comment on company's review of cost-effectiveness evidence

The company conducted one SLR in December 2023 to identify literature for: (i) published cost-effectiveness studies; (ii) HRQoL studies and (iii) cost and healthcare resource use studies. The limitations described in the clinical effectiveness review related to the sources searched (see Section 3.1.1) also apply to the cost-effectiveness searches.

The CS states that the SLR did not identify any papers reporting cost-effectiveness of any intervention for treating ARG1-D. Given this, the company constructed a *de novo* model.

4.2 Description of company's health economic analysis

4.2.1 Model scope

A summary of the company's base case model is summarised in Table 12. The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over an [redacted]-year (lifetime) horizon (calculated as 100 minus the baseline age). Unit costs are not valued at the same price year, although as the earliest was 2018/2019, the EAG was not concerned by

this small inconsistency. Health outcomes and costs were discounted at a rate of 3.5% per annum as recommended by NICE.

Table 12: Summary of company's base case model

Population	Patients with ARG1-D aged 2 years or older
Time horizon	[redacted] years, assumed to represent a patient's lifetime
Intervention	Pegzilarginase with IDM (including dietary protein restrictions, essential amino acid supplementation and/or the use of ammonia scavengers)
Comparator	IDM alone
Outcome	Incremental cost per QALY gained
Perspective	National Health Service and PSS
Discount rate	3.5% per annum for both health outcomes and costs
Price year	A mixture of 2018/19, 2021/2022, 2022/23 and 2023/24

ARG1-D: arginase 1 deficiency; IDM: individualised disease management; QALY: quality-adjusted life year

4.2.1.1 Population

The population included in the company's model relates to patients with ARG1-D, aged 2 years or older, which is aligned with the marketing authorisation of pegzilarginase.[16] This is consistent with the PEACE study. At model entry, patients are assumed to have a mean age of [redacted] years, with [redacted] of patients assumed to be female.[1]

4.2.1.2 Intervention

The intervention is pegzilarginase, which is intended to be used alongside IDM. It is administered by either IV infusion or SC injection. An initial dose is administered by IV infusion of 0.1/mg/kg/week. This dosage can be adjusted up or down by units of 0.05mg/kg to achieve therapeutic goals. The company noted that doses greater than 0.2mg/kg/week have not been studied in clinical trials. The SC route should only be considered after at least eight weeks of treatment, once a stable dose has been established and the risk of hypersensitivity reactions is assessed as low.

4.2.1.3 Comparators

The comparator evaluated in the submission is IDM, which could include dietary protein restriction, essential amino acid supplementation and/or the use of nitrogen scavengers.

4.2.2 Model structure and logic

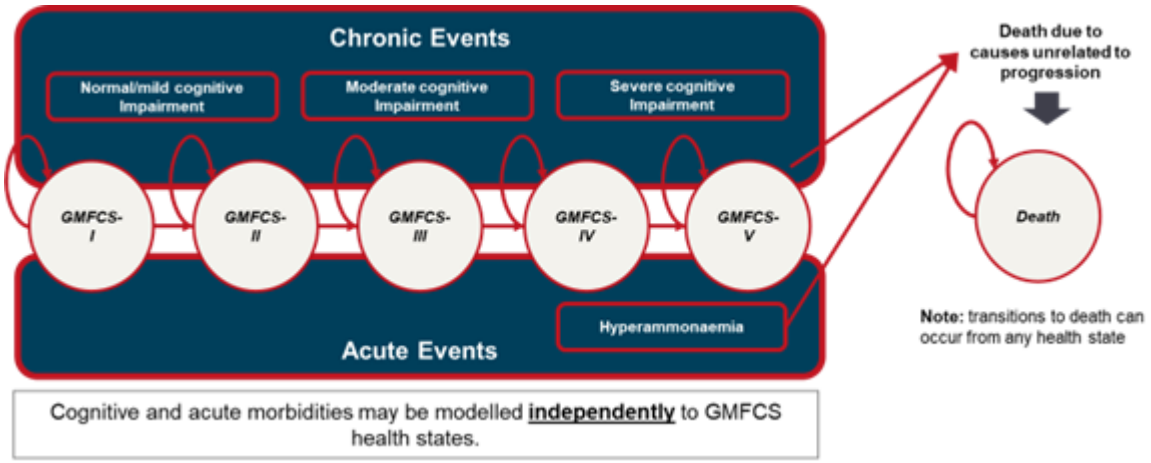
The company's model adopts a cohort-level Markov approach and simulates the lifetime of patients with ARG1-D. The cycle length is 3 months (13 weeks), and a half-cycle correction is employed. The model simulates the progression of patients through different health states which are defined by the level of motor deficit (expressed as GMFCS scores) and death. The company states that "*The GMFCS was considered the best option for categorising motor deficits as it is known that ARG1-D shares similar disease characteristics and symptoms with cerebral palsy (CP).*"

In any GMFCS state, patients can have hyperammonaemic crises (HACs) which are defined by the company as *"an event in which a subject had an ammonia level ≥100 μM with one or more symptoms related to hyperammonaemia requiring hospitalization or emergency room management."* In the model a HAC is associated with increased healthcare costs and a worsening of patient health including the possibility of death. Death related to non-ARG1-D causes can occur at any time for patients who are alive.

The model simulates the cognitive ability of patients which is categorised as mild/normal, moderate, or severe impairment; this is modelled separately to GMFCS state. The model also considers the burden on caregivers associated with each GMFCS state and the potential benefit for a patient of improved diet associated with pegzilarginase treatment.

A schematic of the company's model is shown in Figure 10.

Figure 10: The company's model structure (reproduced from clarification response, Figure 25)



GMFCS: Gross Motor Function Classification System

4.2.3 Key assumptions employed in the company's model

The company's base case model employs the following key assumptions:

- An agreed patient access scheme (PAS) discount of [redacted] is applied to the list price of pegzilarginase.
- Transition probabilities between health states were estimated from the PEACE study for the duration of follow-up. For pegzilarginase, a time-invariant transition matrix was estimated based on 96 weeks of data, which is assumed to apply for 3 years (157 weeks). For IDM, a time-invariant transition matrix was estimated based on 24 weeks of data, which is assumed to be generalisable for half a year.

- For patients treated with pegzilarginase, it is assumed after 3 years that they would remain in their current GMFCS state. For patients treated with IDM, after half a year, transition probabilities were calculated using the estimated time in a GMFCS state based on assumed GMFM DE threshold scores and GMFM DE decline per year.
- The discontinuation rate of pegzilarginase is assumed to be 1% annually.
- A standardised mortality rate (SMR) was used in the model to estimate the increased risk of death associated with ARG1-D. The SMR was estimated by calibration with the company assuming that nearly all patients with IDM die before the age of 35 years.
- The distribution of patients across cognitive impairment levels was assumed to be treatment dependent in GMFCS-I to GMFCS-III, with better severity profiles assumed for patients receiving pegzilarginase.
- It is assumed that 24.7% of patients on pegzilarginase treatment have increased utility because of an improved diet which is facilitated by pegzilarginase.
- Patients are assumed to have 2 caregivers up to 16 years of age. One caregiver is assumed for patients aged 16 years or over.
- The disutility associated with a HAC is assumed to be the same as the disutility of epilepsy/convulsions and is assumed to last for 7 days.
- The frequency of monitoring and clinician appointments is independent of treatment received but is dependent on the GMFCS of a patient. No additional monitoring costs associated with pegzilarginase are included.
- It is assumed that for the first three months, 100% of administrations would occur in the hospital setting and that, of these, 90% would be SC and 10% IV. After the first three months, 90% of patients are assumed to switch to home-based SC administration, for which no cost is assumed. The remaining 10% of patients are assumed to receive SC treatment within the hospital setting.
- 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 is assumed to be [redacted]%; for patients aged 16 years or over, the reduction is assumed to be [redacted]% with both values informed by the weight of patients in the PEACE and Phase 1/2 studies compared with an age- and sex-matched UK population
- 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 nominal threshold weight for a certain number of vials then an additional vial would not be opened.

4.2.4 Evidence used to inform the company's model parameters

The sources of evidence used to inform company's model parameters are summarised in Table 13. These are discussed in detail in the subsequent sections.

Table 13: Summary of evidence used to inform the company's base case analysis

Parameter group	Source
Patient characteristics • Age • Percentage female • Patient distribution across GMFCS states	Pooled data from PEACE, Study 101A/102A, and the European BOI survey[25] that was conducted by the company.
Weight ratio vs general population	Calculated - Ratio of pooled weight in PEACE and Study 101A/102A compared with the expected weight given the same age and sex distribution.
Transition probabilities for the initial period (3 years for pegzilarginase and 0.5 years for IDM)	Calculated using data from the PEACE study.
Longer-term transition probabilities	The model assumes that there is no change in GMFCS state in the pegzilarginase group. For IDM, assumptions were made relating to the GMFM DE score at which GMFCS state changes and the decline in GMFM DE score per year to derive transition probabilities.
HAC • Frequency of HACs on IDM • Rate ratio for pegzilarginase compared with IDM	Frequency: pooled data from the Urea Cycle Disorders Consortium Registry and the placebo arm in the PEACE study Rate ratio: the PEACE study.
Mortality • Mortality in general population • SMR • Mortality from HAC • Distribution of peak ammonia level in HACs	General population mortality: UK life tables[34] SMR for IDM: obtained via model calibration assuming nearly all patients die by 35 years of age. SMR for pegzilarginase: Highly Specialised Technology (HST) 18 (for a metachromatic leukodystrophy (MLD) treatment)[35] Mortality from HACs: Published data for urea cycle disorders[36] conditional on age and peak ammonia levels. Distribution of peak ammonia level in HACs: the PEACE study dependent on treatment arm.
Utilities	For GMFCS-II to GMFCS-V, the European BOI survey[25] mapped to EQ-5D-3L values using Hernandez-Alava *et al*.[37] For GMFCS-I, midway between the European BOI survey[25] mapped to EQ-5D-3L values using Hernandez-Alava *et al*.[37] and the general population value matched for age and sex.[38] The decrements associated with cognitive disutility are taken from HST18.[35] The utility gain from improved diet: calculated from data in HST13,[39] a vignette study,[40] and general population data.[38] Utility is assumed to decrease as patients age based on data from Ara and Brazier. [38]
Source of costs	Mainly obtained from the European BOI survey.[25] HST18[35] was used as supplementary evidence where required.

GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; SMR: standardised mortality ratio.

4.2.4.1 Patient characteristics at model entry

The model assumes that patients have a mean age of [redacted] years and [redacted]% of patients are assumed to be female. These characteristics reflect the population of patients with ARG1-D in the PEACE study (n=32), Study 101A/102A (n=16), and the BOI survey (n=16) with pooling of data. The company states that: "*This approach was chosen, firstly, because the larger data pool is likely to be more representative of clinical practice and more likely to include all GMFCS health states at baseline*" (CS,[1] page 129). The distribution of GMFCS health states at model entry is presented in Table 14.

Table 14: Distribution of GMFCS at model entry in the company's base case (reproduced from CS, Table 30)

	Proportion of patients, started in health states by GMFCS					**Source**
	I	**II**	**III**	**IV**	**V**	
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from the PEACE study, study 101A/102A, and BOI survey (n=[redacted])

GMFCS: Gross Motor Function Classification System

The dose of pegzilarginase is weight-based. 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 is assumed to be [redacted]%; for patients aged 16 years or over, the reduction is assumed to be [redacted]% with both values informed by the weight of patients in the PEACE and Phase 1/2 studies compared with an age- and sex-matched UK population. Both the age and the weight of patients change as time within the model progresses.

4.2.4.2 Initial disease progression

Transition probabilities between health states were estimated using the observed counts of GMFCS changes between visits in the PEACE study for the duration of follow-up (with last observation carried forward where there were missing data and for pegzilarginase, when plausible movements were not observed, assuming that the transition probability of moving from GMFCS-III to GMFCS-II was the mean of GMFCS-IV to GMFCS-III and GMFCS-II to GMFCS-I and that the transition probability of moving from GMFCS-V to GMFCS-IV was half that of moving from GMFCS-IV to GMFCS-III). For pegzilarginase, a time-invariant transition matrix was estimated based on 96 weeks of data, which is assumed to apply for 3 years (157 weeks). For IDM, a time-invariant transition matrix was estimated based on 24 weeks of data, which the company assumed to be generalisable for half a year (26 weeks). The transition probabilities used in the model are presented in

Table 15.

Table 15: Transition probabilities per cycle used in the company's model

Intervention	From	To					Number of patients with data
		GMFCS -I	GMFCS - II	GMFCS - III	GMFCS - IV	GMFCS -V	
IDM for 0.5 years (2 cycles)	GMFCS-I	100%	0%	0%	0%	0%	n=[redacted]
	GMFCS-II	14%	71%	0%	14%	0%	n=[redacted]
	GMFCS-III	0%	0%	100%	0%	0%	n=[redacted]
	GMFCS-IV	0%	0%	31%	69%	0%	n=[redacted]
	GMFCS-V	0%	0%	0%	0%	100%*	n=[redacted]
Pegzilarginase for 3 years (12 cycles)	GMFCS-I	100%	0%	0%	0%	0%	n=[redacted]
	GMFCS-II	8%	92%	0%	0%	0%	n=[redacted]
	GMFCS-III	0%	10%*	90%	0%	0%	n=[redacted]
	GMFCS-IV	0%	0%	14%	86%	0%	n=[redacted]
	GMFCS-V	0%	0%	0%	5%*	95%	n=[redacted]

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

4.2.4.3 Long-term disease progression

For patients receiving pegzilarginase treatment, the company assumed that after 3 years there would be no disease progression. That is, all patients would remain in the GMFCS state that they were in after 3 years if they continue to receive pegzilarginase treatment.

For patients receiving IDM, the company estimated transition probabilities in multiple steps using several sources. The first step was to estimate a relationship between GMFM DE score and GMFCS state. This was operationalised by using the 95% CIs of the observed GMFM DE scores for patients in each GMFCS state, which were [redacted] for GMFCS-I, [redacted] for GMFCS-II, [redacted] for GMFCS-III and [redacted] for GMFCS-IV. The company assumed that the thresholds at which patients changed between GMFCS states were mid-way 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], which is the midpoint of [redacted] and [redacted]. The threshold for changing between GMFCS-II and GMFCS-III was [redacted] with the threshold for changing between GMFCS-III and

GMFCS-IV being [redacted] and the company assumed that at a threshold of [redacted] patients became GMFCS-V. Once the thresholds were established, the average times taken to move through the GMFCS states were calculated based upon a linear regression of GMFM DE score and patient age, which indicated that for each additional year of age a patient's GMFM DE score would be estimated to decline by 1.45; however, the R^2-adjusted was 0.09 suggesting that age alone did not explain a great deal of the variation in GMFM DE score. The company used the value of 1.45 decrease per year to estimate the number of years it would take to progress through a GMFCS state. Thus, as the GMFM DE score threshold for arriving at GMFCS-II is [redacted], and the threshold to moving to GMFCS-III is [redacted], a decline of [redacted] in GMFM DE score is required to move from GMFCS-II to GMFCS-III, which at a decrease of 1.45 per year equates to a period of [redacted] years. The time between GMFCS-I to GMFCS-II was estimated to be [redacted] years (assuming a starting GMFM DE score of 107), the time between GMFCS-III to GMFCS-IV was estimated to be [redacted] years and the time between GMFCS-IV to GMFCS-V was estimated to be [redacted] years. The total duration between GMFCS-I and GMFCS-V was estimated to be approximately [redacted] years – the EAG notes that this is much longer than any time estimated by clinicians consulted by the company, reported in Table 3 of the clarification response, where the longest duration between GMFCS-I to GMFCS-V was estimated to be a) 5-6 years, b) "*decades*", and c) 20-25 years.

The company generates constant transition probabilities using the inverse of the mean time in state, converting from annual to cycle-specific transition probabilities (Table 16). The EAG notes that the inverse of the mean time in state should be considered as a rate rather than probability.

Table 16: Transition probabilities for patients receiving IDM

Transitioning from	Time from previous cut-off to next cut-off in years	Annual probability	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.

4.2.4.4 Discontinuation of treatment

The model does not include a stopping rule based on pArg levels as there was a lack of consensus among UK clinical experts that provided advice to the company. The company assumed that discontinuation from pegzilarginase would be low and assumed a 1% discontinuation per year. The EAG's clinical advisors agreed that it was unlikely that patients would discontinue pegzilarginase treatment where it was positively impacting on pArg levels. On discontinuation of treatment, patients revert to the disease trajectory of IDM and use the cognitive impairment distributions and HAC probabilities associated with IDM.

4.2.4.5 Frequency of HAC with IDM and the rate ratio for pegzilarginase

The clinicians consulted by the company highlighted that HACs are a major cause of mortality and morbidity in patients with ARG1-D and are associated with additional hospitalisation costs. The incidence of HACs for patients receiving IDM was estimated from pooled data using the Urea Cycle Disorders Consortium (UCDC) registry ([redacted] patient years) and the placebo arm in the PEACE study ([redacted] patient years). The estimated number of HACs for patients receiving IDM was [redacted] events per year.

The number of HACs for patients receiving pegzilarginase was estimated based on the number of HACs for patients receiving IDM ([redacted] per year) and a rate ratio which is intended to reflect the beneficial impact of pegzilarginase. During the clarification process, the company updated its method by calculating rate ratios for pegzilarginase both within the double-blind period and within the long-term extension (LTE) phase of the PEACE study compared to the number of HACs experienced by patients on placebo in the double-blinded period ([redacted] HACs in [redacted] patient years). This approach used a Poisson regression model and resulted in a rate ratio for pegzilarginase compared with IDM of [redacted] in the double-blind period and [redacted] in the LTE. The company calculated the HAC rate for pegzilarginase by multiplying the rate ratio and the HAC rate for IDM. The derived probability of HACs per cycle was [redacted] for pegzilarginase in the first 24 weeks and [redacted] thereafter, for IDM this probability was [redacted].

4.2.4.6 Cognitive impairment

The company assumed that the relationship between GMFCS state and cognitive impairment (categorised as normal/mild; moderate, or severe) observed in MLD and reported in HST18[35] was generalisable to patients with ARG1-D who were receiving IDM. However, the company had to assume a distribution amongst cognitive states for those in GMFCS-I. The assumption of the distribution amongst cognitive health states for those in GMFCS-I in the IDM arm was informed by the fact that [redacted] in the BOI study [redacted] in a severe state, and it was therefore likely that some may be in the moderate state given a larger sample size. For a cohort of patients receiving pegzilarginase treatment, the company assumed that after 52 weeks cognitive abilities would be improved and used a different distribution for those with GMFCS-I to GMFCS-III, based on the small improvement on VABS-II scores observed in the clinical studies. Whilst these distributions were arbitrary, the EAG's clinical advisors were comfortable with the values chosen. The distributions assumed by the company are shown in

Table 17.

Table 17: Distributions across cognitive impairment bands

	Cognitive impairment when receiving IDM			
Health State	**Normal / Mild**	**Moderate**	**Severe**	**Source**
GMFCS-I	90.00%	5.00%	5.00%	Assumption
GMFCS-II	53.00%	38.00%	9.00%	HST18[35] (MLD)
GMFCS-III	33.00%	42.00%	25.00%	HST18[35] (MLD)
	Cognitive impairment when receiving pegzilarginase (after 52 weeks)			
Health State	Normal / Mild	Moderate	Severe	Source
GMFCS-I	100.00%	0.00%	0.00%	Assumption
GMFCS-II	70.00%	25.00%	5.00%	Assumption
GMFCS-III	43.00%	32.00%	25.00%	Assumption
	Cognitive impairment independent of treatment			
Health State	Normal / Mild	Moderate	Severe	Source
GMFCS-IV	17.00%	28.00%	55.00%	HST18[35] (MLD)
GMFCS-V	4.00%	17.50%	78.50%	HST18[35] (MLD)

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

4.2.4.7 Mortality

A proportion of HACs are assumed to result in death. To estimate the risk of death due to a HAC, the company used data from UCDC registry which provided estimates of mortality conditional on age (between 2 and 12 years; and over 12 years of age) and four peak ammonia categories (≤200 µmol/litre; >200-500 µmol/litre; >500-1000 µmol/litre; and >1000 µmol/litre).[36]

For the distribution peak ammonia in patients receiving IDM, data were pooled from Bin Sawad *et al*.,[24] (number. of episodes =[redacted]) the UCDC registry,[41] (number of episodes =[redacted]) and the placebo arm of the PEACE study (number of episodes=[redacted]). For patients receiving pegzilarginase, the company considered all HAC episodes in patients that had received treatment for at least 24 weeks. The distributions of peak ammonia levels for patients receiving IDM and for patients receiving pegzilarginase are shown in Table 18, alongside the reported risk of death due to the HAC.[36] Table 18 also provides the weighted risk of death associated with HACs for people receiving pegzilarginase treatment and people receiving IDM conditional on age band.

Table 18: Peak ammonia levels during HAQs conditional on treatment (reproduced from the CS Table 43)

	Probability of death due to a HAC		Distribution of peak ammonia level in HACs	
	Age 2-12	Age >12	Pegzilarginase	IDM
Peak ammonia level				
≤200 µmol/L	2.1%	0.7%	[redacted]	[redacted]
>200-500 µmol/L	2.3%	0.6%	[redacted]	[redacted]
>500-1000 µmol/L	17.9%	6.3%	[redacted]	[redacted]
>1000 µmol/L	100.0%	50.0%	[redacted]	[redacted]
Mortality used in the model				
Aged 2-12 years			[redacted]	5.9%
Aged over 12 years			[redacted]	2.4%

HAC: hyperammonaemic crisis; IDM: individualised disease management

For mortality associated with ARG1-D but not from a HAC, the company states that there was "*Little evidence regarding overall survival in ARG1-D is available in the literature and mortality data were not available from the UCDC registry.*" A review of case reports was identified by the company which reported a median age at death of 17 years of age.[24] The company stated that it was "*not aware of many patients over the age of 40 in any of the centres it is in contact with throughout Europe (only one patient aged* [redacted] *in the BoI study).*"

To estimate long-term survival, the company calibrated the model such that "*nearly all*" patients receiving IDM die by 35 years of age, including deaths associated with HACs. This process assumed that (i) SMRs from MLD[35] compared to an age- and sex-matched population captured the impact of neuro-disability on mortality and were generalisable for people with ARG1-D treated with pegzilarginase, having removed the toxicity associated with the MLD treatment (atidarsagene autotemcel) and (ii) that a multiplier would be applied to the pegzilarginase SMRs to obtain the SMRs for patients treated with IDM. In its calibration, the company estimated an SMR for IDM that was 800 times greater than the SMR for pegzilarginase. With a multiplier of 800, the proportion of alive patients is 0.0008% at 35 years. The SMRs used in the model are presented in

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Table 19.

Table 19: The SMRs applied in the model

Health State	Mortality		SMR	
	Pegzilarginase	IDM	Pegzilarginase[1)]	IDM
Mortality by GMFCS				
GMFCS-I	Age- and sex- matched mortality[34]		1.16	928.0
GMFCS-II			1.32	1056.0
GMFCS-III			1.80	1440.0
GMFCS-IV			1.80	1440.0
GMFCS-V			8.14	6508.8

GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; SMR: standardised mortality ratio.
1) these were the SMRs applied to patients treated with atidarsagene autotemcel in HST18 dividing by 1.25 to remove the impact of toxicity.

4.2.4.8 Treatment-related adverse effect

The model does not include TEAEs. The EAG notes that ideally these would be included but would be unlikely to change the ICERs noticeably.

4.2.4.9 Health-related quality of life

4.2.4.9.1 Health-related quality of life associated with model health states

The company mainly uses health state utility values taken from the European BOI survey[25] which includes EQ-5D-5L responses from [redacted] patients and [redacted] carers (for patients aged less than 16 years in Portugal, UK and Spain or aged less than 18 years in France, or who could not answer themselves). EQ-5D-5L responses were mapped to EQ-5D-3L values using Hernandez-Alava *et al*.[37] For GMFCS-I, the company stated that the EQ-5D-3L value was substantially lower than in similar health states in cerebral palsy and MLD. Instead, the company used the mean of the utility value of the GMFCS-I state in the BOI survey and general population utility at [redacted] years old.[38] For GMFCS-III, the average of GMFCS-II and GMFCS-IV was used.

4.2.4.9.2 QALY losses due to cognitive disability

The model includes further decrements in HRQoL from cognitive disability which persist indefinitely whilst patients remain in each health state. The company estimated the disutility values for each cognitive impairment level, by GMFCS state, using values for MLD presented in a report for the Institute for Clinical and Economic Review,[42] as the relevant values were redacted in HST18.[35] The disutility was calculated by subtracting the utility values for moderate and severe cognitive function health states from that for the mild/normal cognitive function health state in early juvenile patients with MLD. The company assumed no loss of utility in the no impairment and mild impairment states. In calculating the values for GMFCS states (Table 20), the company assumed that: the average of gross motor function classification in metachromatic leukodystrophy (GMFC-MLD) scores 0 to 1 was

generalisable to GMFCS-I; that GMFC-MLD 2 was generalisable to GMFCS-II; that GMFC-MLD 3 was generalisable to GMFCS-III; that GMFC-MLD 4 was generalisable to GMFCS-IV; and that the average of GMFC-MLD 5 and 6 was generalisable to GMFCS-V.

Table 20: Cognitive deficit by GMFCS health state

	Disutility Associated with		
Health State	**Moderate impairment**	**Severe impairment**	**Source**
GMFCS-I	0.24	0.53	Calculated from an Institute for Clinical and Economic Review report[42] on MLD
GMFCS-II	0.28	0.57	
GMFCS-III	0.28	0.49	
GMFCS-IV	0.16	0.33	
GMFCS-V	0.17	0.28*	

*Original value -0.33; 0.28 used as the company assumes utility cannot be below -0.250
GMFCS: Gross Motor Function Classification System; MLD: metachromatic leukodystrophy.

4.2.4.9.3 Disutility associated with HACs

The company did not identify any disutility values associated with HAC. The company therefore assumed the impact of epilepsy/convulsions on HRQoL (a reduction of 0.067) was generalisable to that of a HAC. This impact is assumed to last for one week.

4.2.4.9.4 Disutility associated with a restricted diet

IDM involves dietary protein restriction. The company's clarification response[32] provides data that showed that a reasonable proportion (typically [redacted]% or greater) of people in the LTE receiving pegzilarginase had increased protein consumption of more than 15% relative to baseline. The company attributed a benefit to the patient of less strict dietary protein restriction within the model. This was estimated using a utility decrement reported in HST13[39] (volanesorsen for treating familial chylomicronaemia syndrome, where dietary fat levels must be restricted) which was informed by a vignette study.[40] The vignette study indicated a population with low triglycerides, without acute pancreatitis, but having to restrict dietary fat had a utility that was 0.078 higher compared with a population aged 46 years and with 41% female); the company assumed this loss was generalisable to patients having to restrict dietary protein compared with those who could eat protein. The company assumed that an improved diet would be associated with half of this utility gain (0.039) and applied this to 24.7% of patients, which was the difference in the proportions of patients in PEACE that increased protein consumption by greater than 15% in the pegzilarginase arm (42.9%) and the corresponding value in the IDM arm (18.2%). This resulted in an average increase in utility, across the cohort, of 0.010 due to benefits in improvements in dietary restrictions which was applied indefinitely whilst a patient was alive.

Table 21 provides a summary of the starting utility values for patients used in the company's base case. As patients get older, a utility multiplier is used to reduce utility in accordance with the Ara and Brazier algorithm.[38] The company imposed a constraint that patient utility could not drop below a minimum value of -0.250. The EAG notes that the Ara and Brazier algorithm has been superseded by one from Hernandez Alava *et al*. but believes that this change would not materially affect the ICER.[43]

Table 21: Summary of the starting utility values for patients used in the company's base case excluding age-adjustments and decrements due to HACs

	GMFCS-I	GMFCS-II	GMFCS-III	GMFCS-IV	GMFCS-V
IDM					
Mild/no cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegzilarginase + IDM					
Mild/no cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GMFCS: Gross Motor Function Classification System; IDM: Individualised Disease Management.

4.2.4.9.5 Caregiver disutility

In its response to clarification,[32] the company provided summarised data of individual carer disutilities although notes that there was a small sample size and that "[redacted]." However, the company noted that the disutilities did not monotonically increase as the severity of patients increased. As such, the company assumes that caregiver disutility values associated with patients with MLD[35] are generalisable to patients with ARG1-D.

The model assumes patients with ARG1-D have two caregivers until age 16 years and one caregiver at older ages. The values used in the model are shown in Table 22.

Table 22: Caregiver disutility values as used in the model

Health State	Disutility	Source
GMFCS-I	0.01	Average of GMFC-MLD 0 and 1 from HST18[35]
GMFCS-II	0.03	GMFC-MLD 2 from HST18[35]
GMFCS-III	0.07	GMFC-MLD 3 from HST18[35]
GMFCS-IV	0.11	GMFC-MLD 4 from HST18[35]
GMFCS-V	0.16	Average of GMFC-MLD 5 and 6 from HST18[35]

GMFCS: Gross Motor Function Classification System; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy.

4.2.4.10 Costs

This section provides a description of the resource costs included in the company's model and concludes with a summary table. Further details are provided in Section 3.5 of the CS. The model includes costs associated with: (i) drug acquisition and administration; (ii) background health state costs and (iii) the costs of HAC events.

4.2.4.10.1 Acquisition and administration costs related to pegzilarginase

In the PEACE study, dose optimisation was observed. The company estimated the average dose received through analysing a regression with the random effects model from the 20 patients who received pegzilarginase treatment. This analysis suggested an average dose of 0.14mg/kg per week for the first 24 weeks, increasing slightly to 0.16mg/kg afterwards. The threshold weights at which additional vials would need to be used were calculated but the company assumes that if a patient's weight is 10% or less above a threshold weight then an additional vial would not be opened. The company referred to this as "*assuming a margin of 10%*". The thresholds assuming the 10% margin are shown in Table 23. As the company assumes a constant weight for all patients at a given age, the number of vials required at each age can be calculated (see Table 23) For example, after 24 weeks of treatment it was assumed that patients aged between 1.50 and 7.49 years require 2 vials, whilst patients aged over 13 years would require 5 vials. In the probabilistic sensitivity analysis (PSA), the company limited the maximum dosage in their model to 0.2mg/kg per week, as higher doses have not been tested in clinical trials.

Table 23: The numbers of vials required each week by patient age and weight (deterministic analyses)

No. of vials (Total dose)	Weight threshold applying a 10% margin (kg)		Age range (years) associated with the weight threshold	
	First 24 weeks	After 24 weeks	First 24 weeks	After 24 weeks
1 (2mg)	14.9	13.5	0 to 4.49	0 to 1.49
2 (4mg)	29.9	27.0	4.50 to 10.49	1.50 to 7.49
3 (6mg)	44.8	40.5	10.50 to 12.49	7.50 to 10.49
4 (8mg)	59.7	54.0	12.50 to 100	10.50 to 12.49
5 (10mg)	74.6	67.5	-	12.50 to 100

Drug costs were calculated by multiplying the number of vials used by the cost per vial, including the PAS discount: one vial costs [redacted] and 5 vials cost [redacted].

Pegzilarginase is administered weekly. The model assumes that in the first cycle (3 months) 100% of administrations would occur in the hospital setting with 90% of hospital administrations being SC and 10% being IV. After the first cycle, 90% of patients are assumed to switch to home-based SC administration with 10% receiving SC administration in hospital. The company assumed that 1 hour of nurse time (either band 5 or band 6) was required for IV administration, which would be reduced to 15 minutes for SC injection performed in hospital. The hourly cost of a band 5 and band 6 nurse's time (excluding qualifications) was taken from the Unit Costs of Health and Social Care, using 2021/2022 prices,[44] resulting in costs for an IC infusion of £52 for an IV infusion and £13.for an SC injection. No administration costs are assumed for SC injections performed at home. The company states that it will cover the marginal costs of homecare delivery.

The mean administration costs for pegzilarginase used in the model are £218 in the first cycle and £17 in subsequent cycles.

4.2.4.10.2 Background health state costs

The CS states that *'No sources of UK health state costs in ARG1-D were identified in the SLR.'* Therefore, it used two resources for disease management costs: the European BOI survey[25] and HST18,[35] which considered treatment for MLD. In the BOI survey, the company collected data on healthcare costs, medication costs, dietary costs, professional caregiving costs and wheelchair costs, all conditional on GMFCS levels. As appropriate data were not available, the following assumptions were used:

- The costs in GMFCS-III are assumed to be the mean of the costs of GMFCS-II and GMFCS-IV, plus the costs of diet associated with ARG1-D patients in GMFCS-IV.

- Healthcare costs within GMFCS-V are assumed to be the mean of the costs from GMFC-MLD health states 5 and 6.[35]
- Medication and diet costs within GMFCS-V are assumed to be the same as in GMFCS-IV.
- Professional caregiving costs within GMFCS-V are assumed to be the same as the costs of respite care for patients with MLD.
- Wheelchair costs within GMFCS-V are assumed to be the same as MLD cost of healthcare equipment.

The health states costs extracted from HST 18[35] were valued at 2018/19 prices; however, the EAG believes that the ICER would not noticeable change if the values were inflated to current prices.

4.2.4.10.3 Cost for HAC events

No costs related to a HAC were identified by the company in either the literature or in NHS Reference Costs. The company assumed that the costs of hospitalisation would be the weighted mean of non-elective and short-stay admissions for paediatric metabolic disorders (Health Resource Group codes: PK72A, PK72B, PK2C). This value (£5984) was also used for adult patients. The company notes that this approach has the potential to underestimate costs as it does not account for intensive care unit (ICU) stays.

4.2.4.10.4 Costs of managing treatment-related adverse events

The company's model does not include costs related to TEAEs because no serious TEAEs were observed for patients receiving pegzilarginase in any study. The EAG notes that ideally this would be included but would be unlikely to change the ICERs noticeably.

4.2.4.10.5 Summary of costs

The costs used in the company's base case model are summarised in

Table 24.

Table 24: Summary of costs per GMFCS level used in the company's base case model

Cost category	GMFCS-I	GMFCS-II	GMFCS-III	GMFCS-IV	GMFCS-V
Acquisition and administration costs related to pegzilarginase					
Pegzilarginase	Dependent on age as dosing is weight-based (see Table 23). Costs range from [redacted] to [redacted]				
Administration (first cycle)	£218.33 independent of GMFCS level				
Administration (subsequent cycles)	£16.79 independent of GMFCS level				
Health state costs per year					
Healthcare costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medication costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dietary costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Professional caregiving costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs associated with a HAC					
Costs of a HAC	£5984 independent of GMFCS level				

GMFCS: Gross Motor Function Measure Classification System; HAC: hyperammonaemic crisis

4.3 The company's model validation and verification

The CS states that *'The model functionality and calculations were verified by a senior health economist not involved in constructing the pegzilarginase project, through use of an internal model quality control (QC) checklist (which can be provided on request).'* The company stated that clinical validation was difficult due to lack of data on disease progression and mortality while clinicians' opinions on disease course varied widely due to the rarity and heterogeneity of the disease. The company stated that the model was calibrated so that "*nearly all*" patients were dead at 35 years to reflect the low survival rate observed in practice.

4.4 The company's cost-effectiveness results

The CS presents base case ICERs for pegzilarginase versus IDM as reported in Table 25. Results are presented using the deterministic and probabilistic versions of the model. The company has applied QALY weighting in line with guidance from NICE.[22] In the company's base case the undiscounted QALY gain associated with pegzilarginase treatment was [redacted], resulting in a QALY weighting of [redacted].

The probabilistic ICERs are based on 1000 Monte Carlo simulations by which point the ICER had largely stabilised. Sampled values were generated by the company using either modified 95% CIs or an assumption that the standard errors of parameters were equal 20% of the mean (logged where appropriate).

The EAG notes slight limitations within the company's PSA that included: (i) sampling individual SMRs for each GMFCS state, rather than applying a single sample to all states; (ii) sampling individual probabilities of a HAC for each GMFCS state, rather than applying a single sample to all states; and (iii) patient utilities were assumed fixed for the GMFCS-IV and GMFCS-V states. The first two points may result in improbable relationships in the values across health states whereas the third will underestimate uncertainty.

The EAG noted that the total QALYs for pegzilarginase was lower in the PSA than in the deterministic analysis. In the fact check process the EAG identified that in the probabilistic analyses the incorrect starting distribution of patients across GMFCS states was referenced, with the distribution from the BOI study alone being used instead of the combined distribution from the PEACE, Phase 101A/102A and BOI studies. This error was corrected in EAG analyses by amending the formulae in E21:I25 in the sheet 'Data_baseline_char.' to reference AL21:AP25, rather than AL20:AP24. As an illustration for cell E21, the formula '=IF(ctrl_SA=2,**AL20**,O21/SUM($O21:$S21))' was amended to '=IF(ctrl_SA=2,**AL21**,O21/SUM($O21:$S21))'

The results of the PSA were presented in the CS as a cost-effectiveness plane and as cost-effectiveness acceptability curves for pegzilarginase versus IDM. These plots are reproduced in Figure 11 and Figure 12, respectively having corrected the error identified by the EAG in relation to the starting distribution used in the probabilistic analyses. Following correction of this error the deterministic ICER and probabilistic ICERs became more similar.

The company's weighted ICER is well above the £100,000 per QALY gained. In the PSA, no results produced a weighted ICER below £100,000 per QALY gained. The company's model assumes that pegzilarginase treatment increases QALYs by increasing life expectancy for patients with ARG1-D, maintaining patients in less severe GMFCS states and improving HRQoL for some patients through a less restrictive diet. Costs are increased in the pegzilarginase arm due to the acquisition price of pegzilarginase, which is significantly larger than any cost offset such as fewer HACs associated with pegzilarginase treatment. The company performed multiple scenario and sensitivity analyses, which are not presented in this section. The EAG has run the ones that it thought was key using the EAG base case as a starting point.

Table 25: The company's base case results

Treatment	Total costs (£)	Total QALYs (patient; carers)	Inc Costs (£)	Inc QALYs	ICER (£)	Weighted ICER (£)
Deterministic model						
Pegzilarginase	[redacted]	[redacted]	[redacted]	[redacted]	884,777	308,375
IDM	[redacted]	[redacted]				
Probabilistic model						
Pegzilarginase	[redacted]	[redacted]	[redacted]	[redacted]	918,250	338,263
IDM	[redacted]	[redacted]				
Probabilistic model (having corrected an error)						
Pegzilarginase	[redacted]	[redacted]	[redacted]	[redacted]	871,992	311,119
IDM	[redacted]	[redacted]				

IDM: individualised disease management; Inc - incremental

Figure 11: Cost-effectiveness plane (generated by the EAG using the company's model having amended an error)

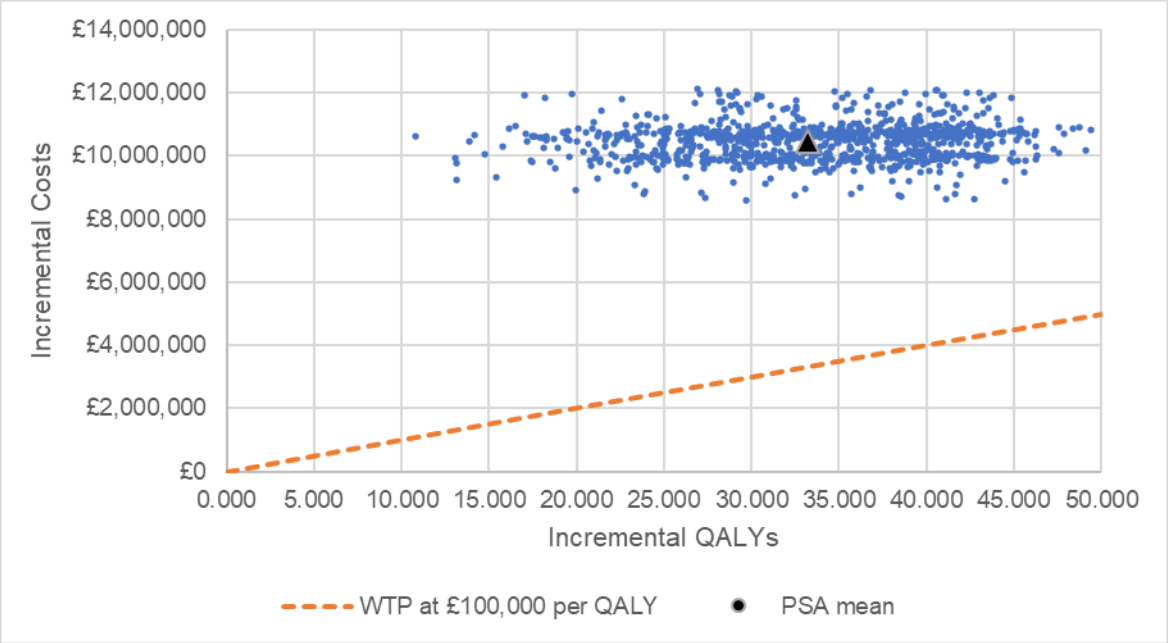
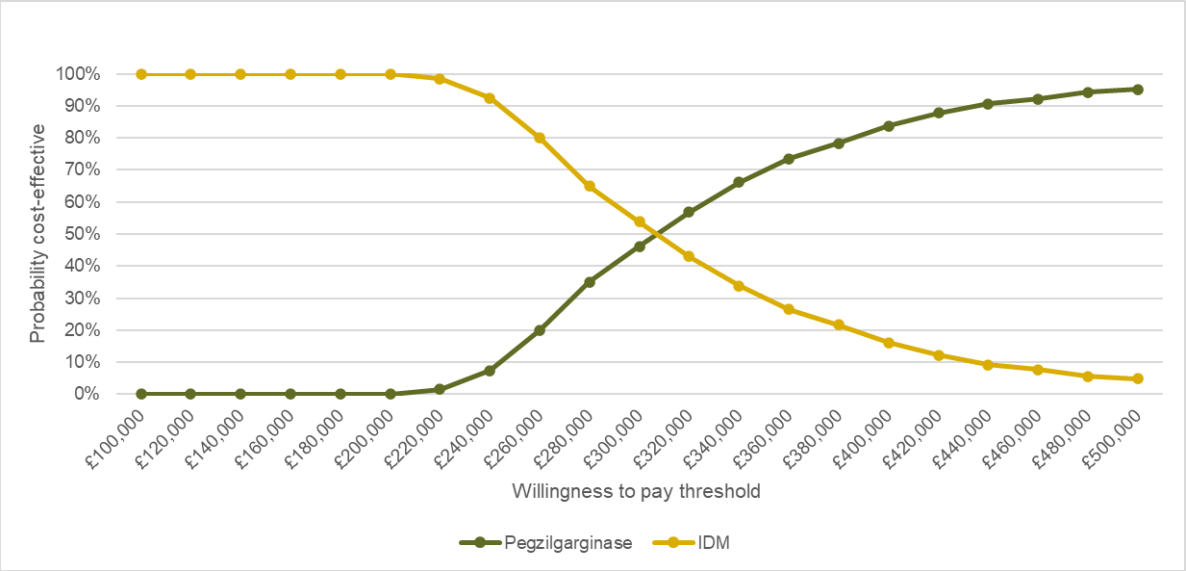


Figure 12: Cost-effectiveness acceptability curve (generated by the EAG having amended an error)



4.5 Critique of company's submitted economic evaluation by the EAG

The EAG adopted several approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- Checking that key scenario analyses could be reproduced.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.5.1 *Adherence to the NICE Reference Case*

The company's economic analysis is generally in line with the NICE Reference Case[45] (see Table 26). Each element is discussed in further detail within the EAG report.

Table 26: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	This is aligned with the NICE Reference Case
Comparators	As listed in the scope developed by NICE	This is aligned with the NICE Reference Case, although is called IDM.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Direct health effects for patients and caregivers were used.
Perspective on costs	NHS and PSS	The perspective used was that of the NHS and PSS.
Type of economic evaluation	Cost-utility analysis with full incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts an [redacted]-year time horizon which was assumed to equate to a patient's maximum lifetime.
Synthesis of evidence on health effects	Based on systematic review	The company estimated short-term transition probabilities (3 years for pegzilarginase and 0.5 years for IDM) from the PEACE study. Longer-term transition probabilities were assumed for pegzilarginase, and for IDM, were calculated based on GMFM DE scores from the PEACE and Phase 1/2 clinical studies. The rate ratio for HAC between pegzilarginase and IDM was estimated from the long-term extension of PEACE and the number of HACs in the IDM arm of PEACE. The distribution of peak ammonia level in HACs were estimated from Bin Sawad *et al*.,[24] the UCDC registry,[41] and the PEACE study. The effect on pegzilarginase on cognitive impairment was assumed.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	This is aligned with the NICE Reference Case. Health gains are valued in terms of QALYs. The EQ-5D-3L was used.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	This is aligned with the NICE Reference Case with utilities from the European BOI survey,[25] with responses from [redacted] patients and [redacted] carers. The company stated that caregiver disutility was taken from HST 18.[35]
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	This is aligned with the NICE Reference Case.

Element	Reference case	EAG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances.	This is aligned with the NICE Reference Case with respect to HSTs (see Sections 6.2.23 – 6.2.25 of the NICE manual).[22]
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs relate to NHS and PSS. Unit costs from 2020/21 were used to calculate administration costs, and the location of administration was assumed. The health states costs extracted from HST 18[35] were valued at 2018/19 prices.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	This is aligned with the NICE Reference Case.

EAG: external assessment group; EQ-5D: Euroqol 5-Dimensions; IDM: individualised disease management; NICE: national institute for health and care excellence; PSS: personal social Services; SmPC: Summary of Product Characteristic; QALY: quality-adjusted life year

4.5.2 The main issues identified by the critical appraisal

In general, the EAG believes that the revised model structure and the parameter values used are largely appropriate for the decision problem. However, uncertainties in parameter values caused by sparse data can make notable changes to the ICER. Box 1 summarises these main issues which are discussed in further detail in the subsequent sections. Uncertainties identified by the EAG that were thought to change the ICER only marginally are not discussed. The first three issues in Box 1 are included in the EAG's base case; the remaining issues are explored in scenario analyses. It is anticipated that the Appraisal Committee would determine which scenarios exploring uncertainty presented by the EAG are most plausible.

Box 1: Main issues identified within the critical appraisal undertaken by the EAG

(1) Identification of an error in calculating the transition probabilities for IDM
(2) Uncertainty around the likely starting GMFM DE score for patients in GMFCS-I
(3) Uncertainty around the decrease in GMFM DE score as patients age
(4) Uncertainty around the appropriateness of assuming that patients on pegzilarginase treatment remain in the same GMFCS state after 3 years of treatment
(5) Uncertainty around the cognitive improvement associated with pegzilarginase treatment
(6) Uncertainty around the utility gain associated with an improved diet due to pegzilarginase treatment
(7) Uncertainty around pegzilarginase drug wastage assumed within the company's model
(8) Uncertainty around the starting distribution of patients across GMFCS states
(9) Uncertainty around the assumption that almost all patients die by 35 years of age
(10) Uncertainty around transition probabilities for IDM as not all patients start at the upper GMFM DE score associated with each GMFCS state
(11) Uncertainty around the distribution of peak ammonia levels during a HAC
(12) Uncertainty around the assumed discontinuation rate
(13) Uncertainty around the disutility for carers
(14) Uncertainty around life expectancy for patients receiving pegzilarginase treatment
(15) Uncertainty around whether QALY losses attributed to carers should be included in the incremental QALY gains when calculating the weights for QALYs
(16) Identification of an error in the execution of the PSA
(17) Responders and non-responders not considered in the model

4.5.2.1 Identification of an error in calculating the transition probabilities for IDM

For patients receiving IDM, the company estimated the time spent in a GMFCS state by calculating the time to move from one GMFM DE threshold value to the next threshold value. Transition probabilities were then generated using the inverse of the time in each state. However, the EAG believes that the inverse of the time spent in a GMFCS state is a rate which needs to be converted to a probability. The EAG has calculated corrected transition probabilities between GMFCS states, given the company's assumptions.

4.5.2.2 Uncertainty around the likely starting GMFM DE score for patients in GMFCS-I

In calculating the transition probabilities for progressing from GMFCS-I to GMFCS-II, the company assumed that patients in GMFCS-I would have a combined GMFM DE score of [redacted]; however, based on the observations within PEACE and Study 101A/102A, the 95% CI around the GMFM DE score was [redacted] The company's assumption appears to suggest that patients can be identified as having ARG1-D without deterioration on the GMFM DE score, which the EAG considers to be unlikely. Therefore, the EAG prefers to use a GMFM DE score of [redacted] for patients starting in GMFCS-I which is the mean of the PEACE and Study 101A/102A data.

4.5.2.3 Uncertainty around the decrease in GMFM DE score as patients age

In calculating transition probabilities, the company assumed that patients' GMFM DE score declines by 1.45 per year; however, there is considerable uncertainty around this value (95% CI 0.23 to 2.66) and importantly the time estimated to move from GMFCS-I to GMFCS-V (approximately [redacted] years) was significantly higher than that predicted by the clinicians whose estimates ranged from 5-6 years to decades. The EAG has used the lower limit of the 95% CI associated with this coefficient (2.66) which reduced the estimated mean time of moving from GMFCS-I to GMFCS-V to approximately [redacted] years, which whilst still likely higher than the estimates provided by the clinician are more aligned with their values.

4.5.2.4 Uncertainty around the appropriateness of assuming that patients on pegzilarginase treatment remain in the same GMFCS state after 3 years of treatment

The company's model assumes that people receiving pegzilarginase treatment will remain in the same state after 3 years of treatment. Whilst the clinical experts consulted by the EAG believe that this is plausible, there is also a large degree of uncertainty related to this assumption. The PEACE study only reported data on mobility outcomes for a relatively short period and therefore the company's assumption hinges on expert opinion alone. The EAG presents analyses relating to four scenarios: (i) that after 3 years of treatment, the risk of transition to the next worse GMFCS state is 10% of that associated with IDM; (ii) that after 3 years of treatment, the risk of transition to the next worse GMFCS state is 20% of that associated with IDM; (iii) that patients on pegzilarginase treatment remain in the same GMFCS

state after 2 years of treatment; and (iv) that patients on pegzilarginase treatment remain in the same GMFCS state after 4 years of treatment.

4.5.2.5 Uncertainty around the cognitive improvement associated with pegzilarginase treatment

The company's model assumes arbitrary improvements in cognitive ability associated with pegzilarginase treatment over IDM for patients in the same GMFCS state for GMFCS-I to GMFCS-III. Whilst the clinical experts consulted by the EAG believe that this is plausible, there is also a large degree of uncertainty related to this benefit provided by pegzilarginase treatment. The EAG has provided an exploratory analysis where it is assumed that cognitive impairment by GMFCS state is independent of treatment.

4.5.2.6 Uncertainty around the utility gain associated with an improved diet due to pegzilarginase treatment

The company has estimated that patients will accrue a utility gain of 0.010 across the cohort due to the additional proportion of patients eating more protein on pegzilarginase treatment (see Section 4.2.4.9.4). The clinical experts consulted by the EAG supported an increase in HRQoL for patients eating more protein; however, as the gain is uncertain, the EAG has explored the impact on the ICER by setting this gain to zero.

4.5.2.7 Uncertainty around pegzilarginase drug wastage assumed within the company's model

As detailed in Section 4.2.4.10.1, the company assumed a 10% margin when estimating the number of vials required for patients. The company also assumed a single value for weight at each age that was assumed to be applicable for all patients, although used a more appropriate method of using a weight distribution for the sensitivity analyses which assumed either full drug wastage or no drug wastage. The clinical experts contacted by the EAG indicated that there would be concerted efforts to reduce drug wastage, which could include having an additional vial every two weeks should the optimal dose indicate half a vial a week. From the options available within the model (10% margin with all patients with the same weight at each age, no drug wastage using a distribution for weight at each age, and full drug wastage using a distribution for weight at each age) the clinical advice to the EAG was that the company's chosen approach was most appropriate, although there is uncertainty around the true level of drug wastage. The EAG has provided scenario analyses assuming full drug wastage and no drug wastage.

4.5.2.8 Uncertainty around the starting distribution of patients across GMFCS states

Clinical advice to the EAG suggested that the distribution of patients across GMFCS states may be more representative in the European BOI survey than in clinical studies where more severe patients

may be underrepresented. As such, the EAG has conducted scenario analyses setting the initial distribution equal to that observed in the BOI survey.

4.5.2.9 Uncertainty around the assumption that almost all patients die by 35 years of age

Clinical advice provided to the EAG suggested that it was unlikely that nearly all patients would die by 35 years of age (and the EAG notes that one patient was aged [redacted] years in the BOI survey). The EAG ran a scenario analysis whereby the age at which nearly all people were dead was 50 years. Additionally, the EAG ran another scenario analysis whereby the assumption that nearly all patients were dead at 35 years was maintained but calibrated the model using the assumed start age of patients in the model ([redacted] years) rather than assuming patients were aged 4 years.

4.5.2.10 Uncertainty around the transition probabilities for IDM as not all patients start at the upper GMFM DE score associated with each GMFCS state

The method used by the company to calculate the transition probabilities for IDM (which was suggested by the EAG at the clarification stage) has the limitation that at the start of the model patients are not at the GMFM DE score threshold for the relevant GMFCS state, but instead are nearer the midpoint GMFM DE score for that GMFCS state. A sensitivity analysis has been conducted where the transition probabilities have been calculated based on a time in GMFCS state assuming a decline in GMFM DE score per year of 2.66 points and assuming the total decrease in GMFM DE score required to change state was the difference in the GMFM DE score midpoints between the current GMFCS state and the more severe GMFCS state (and assuming a midpoint GMFM DE score of [redacted] in GMFCS-V. This resulted in declines in GFMF DE scores of: [redacted] when moving from GMFCS-I to GMFCS-II; [redacted] when moving from GMFCS-II to GMFCS-III; [redacted] when moving from GMFCS-III to GMFCS-IV; and [redacted] when moving from GMFCS-IV to GMFCS-V. Expressed in the number of years to move health states these values are: [redacted] and [redacted] respectively. The transition probabilities used in the EAG's scenarios are presented in Table 27.

Table 27: Transition probabilities for patients receiving IDM

Transitioning from	Time from previous cut off to next cut-off in years			Transition probability per cycle		
	Company's base-case	EAG's base-case	EAG scenario	Company's base-case	EAG's base-case	EAG scenario
GMFCS-I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-I II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-I V	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

4.5.2.11 Uncertainty around the distribution of peak ammonia levels during a HAC

There is considerable uncertainty around the peak ammonia levels during a HAC when on pegzilarginase treatment as this has been informed by only [redacted] data points and [redacted]. To explore the impact of sparse data, the EAG has 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 adds 0.25 to all observed values.

4.5.2.12 Uncertainty around the assumed discontinuation rate

Clinical advice provided to the EAG indicated that patients were unlikely to discontinue pegzilarginase treatment. As such, the EAG has explored a sensitivity analysis whereby no patients discontinue treatment.

4.5.2.13 Uncertainty around the disutility for carers

The EAG could not identify the value used in the model within HST 18[35] but it was found in a MLD study by the Institute for Clinical and Economic Review.[42] In the ERG report for HST 18, it was stated that *"Based on the responses of all 21 participants, a disutility of -0.108 was applied to caregivers. The company assumed that there would be zero caregivers required until patients reached GMFC Stage 5, at which point two caregivers were required, both of whom incurred the caregiver disutility of -0.108 (total -0.216)."* According to the HST 18, it is also written that *"The company assumed that no carers were needed until GMFC-MLD 5, when 2 carers were needed. The ERG considered that carers would be needed from GMFC-MLD 1 (0.5 carers) to GMFC-MLD 6 (2 carers)."*

The EAG notes that Sevin *et al.*,[46] which appears to be the same work as outlined in the Pang *et al.* abstract,[47] reported a median EQ-5D utility for caregivers of MLD patients (0.794; n=5) and the population norm EQ-5D in the UK as 0.856, suggesting a disutility of 0.062. The EAG has explored using this disutility value for caregivers, assuming that this value is applicable in patients with a GMFCS score III or greater and with no disutility for carers assumed for patients in GMFCS-I or GMFCS-II.

4.5.2.14 Uncertainty around life expectancy for patients receiving pegzilarginase treatment

There is uncertainty around the SMRs associated with pegzilarginase treatment used in the company's model. It is assumed that data from an age- and sex-matched population with MLD, with the impact of toxicity removed, were generalisable to patients with ARG1-D receiving pegzilarginase treatment. The EAG has explored the impact of assuming that the SMRs associated with pegzilarginase treatment were double those assumed in the company's base case analysis.

4.5.2.15 Uncertainty around whether QALY losses attributed to carers should be included in the incremental QALY gains when calculating the weights for QALYs

It is unclear whether the calculation of incremental QALYs that are used to produce the weight for QALYs should include the QALY implications for carers. The EAG has run an analysis where the QALYs associated with carers are removed for the purposes of calculating the QALY weight.

4.5.2.16 Identification of an error in the execution of the PSA.

The EAG identified that there was a cell referencing error in conducting the PSA which meant that the intended distribution of patients across GMFCS health states was not being used. The EAG corrected this error as detailed in Section 4.4 and the probabilistic results became more similar to the deterministic ones.

4.5.2.17 Responders and non-responders not considered in the model.

The EAG comments that the model does not appear to have the functionality to incorporate responders to pegzilarginase treatment and non-responders, where treatment may be discontinued. The EAG has not been able to generate any ICERs incorporating this but posits that the cost-effectiveness of pegzilarginase would likely improve if there were non-responders with only the patients that benefit most remaining on treatment.

4.6 Exploratory analyses undertaken by the EAG

This section presents the methods and results of the EAG's exploratory analyses undertaken using the company's model.

4.6.1 Overview of the EAG's exploratory analyses

The EAG undertook exploratory analyses to address the key points identified within the critical appraisal. Most issues raised are related to the use of alternative plausible assumptions rather than being points that the EAG disagrees with the company's assumptions. In this instance, the EAG has kept these as scenario analyses and has only made changes to the company's base case when it believes there is a strong justification to change the company's assumption or value. Because of this approach, the EAG's base case differs from the company's base case in only three aspects: the first being an error identified by the EAG relating to the longer-term transition probabilities for IDM; the second being the likely starting GMFM DE score for patients in GMFCS-I; and the third being the assumed decrease in GMFM score each year. The error identified in the execution of the PSA has been corrected in both the company's and EAG's probabilistic analyses. All other exploratory analyses have been presented as exploratory sensitivity analyses using the EAG's base case model for the NICE Appraisal Committee to consider. For some of these scenarios, the EAG does not believe that the exploratory analysis is plausible but has chosen an extreme value, rather than an arbitrary one, to inform the Committee; an

example of this is the scenario analysis where full vial wastage is assumed. All scenario analyses were undertaken using the deterministic version of the model although probabilistic ICERs were also generated for the EAG's base case. All analyses were undertaken by one modeller and checked by a second modeller. All analyses presented in this section reflect the PAS price of pegzilarginase and include QALY weighting. The methods of the analyses are provided in Section 4.6.2 and the results are presented in Section 4.6.3.

4.6.2 EAG's exploratory analyses – methods

The following changes were made to the company's base case to form the EAG's base case. Appendix 2 details how these can be implemented in the company's model. In generating PSA results for the EAG base case, the EAG amended the model by

- sampling a single SMR for IDM which was applied to the pegzilarginase SMRs for all health states.
- Sampling an SMR for GMFCS-I for pegzilarginase treatment and then applying the ratios for the deterministic analysis between each GMFCS state and GMFCS-I to estimate SMRs for the remaining GMFCS health state.
- Sampling a probability of HACs that was applied to all GMFCS states.

EA1 Correction of an error in the way the transition probabilities were calculated for IDM

The EAG made the amendment of formulas in the sheet 'Progression estimates' in G37:G40, detailed in Section 4.5.2.1. The transition probabilities which were used for EA1, EA2, EA3 and SA7 are summarised in Table 28.

Table 28: Transition probabilities for patients receiving IDM

Transitioning from	Company's model	EA1 Correction of formulae	EA2 Changing the starting GMFM DE score for GMFCS-I	EA3 Changing the decline in GMFM DE score by age	EAG's base-case (EAG1-EAG3 combined)	SA7 Using the midpoint of GMFM DE scores
GMFCS-I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-I II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFCS-I V	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

EA2 The assumed starting GMFM DE score for patients in GMFCS-I

The EAG set the GMFM DE score for patients in GMFCS-I at the start of the model to [redacted] instead of [redacted].

EA3 The assumed decrement of GMFM DE score per age

The EAG set the decline in GMFM DE score to be 2.66 per year instead of 1.45.

The following EAG's additional sensitivity analyses (SA) were undertaken using the EAG's base case. Appendix 2 details how these can be implemented in the company's model

SA1 Uncertainty around the appropriateness of assuming that patients on pegzilarginase treatment remain in the same GMFCS state after 3 years of treatment

The EAG presents analyses relating to four 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; c) that patients on pegzilarginase treatment remain in the same GMFCS state after 2 years of treatment; and d) that patients on pegzilarginase treatment remain in the same GMFCS state after 4 years of treatment.

SA2 Uncertainty around the cognitive improvement associated with pegzilarginase treatment

In this scenario, the distribution of cognitive impairment was independent of treatment. That is, the distributions of cognitive impairment for pegzilarginase were the same as for IDM.

SA3 Uncertainty around the utility gain associated with an improved diet due to pegzilarginase treatment

The EAG set the utility gain associated with an improvement of diet to zero.

SA4 Uncertainty around pegzilarginase drug wastage assumed within the company's model

The EAG ran analyses assuming a) full drug wastage, where the 10% margin was removed and b) no drug wastage, where it was assumed that any drug left in a vial would be used on a subsequent patient.

SA5 Uncertainty around the starting distribution of patients across GMFCS states

The EAG changed the starting distribution of GMFCS to that associated with the BOI survey. This distribution, and that used in the company's base case are shown in

Table 29.

Table 29: 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])
Scenario analysis - EAG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	BOI survey (n=[redacted])

SA6 Uncertainty around the assumption that almost all patients are dead by 35 years of age

The EAG ran sensitivity analyses where it was assumed that nearly all patients died before 50 years of age when receiving IDM assuming for calibration purposes that all patients were 4 years of age. This resulted in an SMR of 200, which leads to 0.0007% of patients being alive at age 50. A second analysis was run assuming a calibration where the starting age of patients was [redacted] years which resulted in an SMR of [redacted], which was greater than that in the company's base case. In this second analysis, 0.0033% of patients were alive at 35 years of age.

SA7 Uncertainty around transition probabilities for IDM as not all patients start at the upper GMFM DE score associated with each GMFCS state.

The EAG ran an analysis where the transition probabilities between GMFCS states for patients receiving IDM, were changed from the EAG base case to those associated with the time in a GMFCS state calculated using the midpoint GMFM DE score values for each GMFCS state. These values are presented in Table 28.

SA8 Uncertainty around the distribution of peak ammonia levels during a HAC

The EAG used a continuity correction that divided an additional data point across the four peak ammonia levels. This changed the distribution in the company's base case as shown in Table 30.

Table 30: Alternative distribution for peak ammonia levels

Peak ammonia levels	Company's base-case		EAG sensitivity analysis	
	Pegzilarginase	IDM	Pegzilarginase	IDM
≤200 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
>200-500 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
>500-1000 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
>1000 µmol/L	[redacted]	[redacted]	[redacted]	[redacted]

IDM: Individualised disease management.

SA9 Uncertainty around the assumed discontinuation rate

The EAG ran a scenario analysis where it was assumed that no patient would discontinue pegzilarginase treatment whilst they were alive.

EAG SA10 Uncertainty around calculating the disutility for carers

The EAG explored the impact on the ICER of alternative assumptions related to carer disutility. This disutility was set to 0.062 based on the difference between caregivers and the population norm in the UK reported by Sevin et al.[46] but only applied to the carers of patients in GMFCS-III and above. No caregiver disutility was assumed for patients in GMFCS-I or GMFCS-II. GMFCS-III and over was chosen as the threshold at which to apply carer disutility as mobility in terms of the patient has deteriorated and patients may not be able to climb stairs (see Figure 2) and there may be the possibility that patients recruited in the Sevin et al.[46] study were patients with relatively severe disease. The assumption that patients aged under 16.5 years needed 2 carers and older patients needed 1 carer was maintained. The values used by the EAG are shown in Table 31.

The EAG also explored the impact on the ICER when carer disutility values from the BOI survey was used, and when values for GMFCS-IV and GMFCS-V were pooled. These values are shown in Table 31.

Table 31: Alternative carer disutility values

Health State	Company's base case	EAG alternative assumption 1 (values from MLD)	EAG alternative assumption 2 (values from BOI survey)
GMFCS-I	0.01	0	0.018
GMFCS-II	0.03	0	0.149
GMFCS-III	0.07	0.062	0.106
GMFCS-IV	0.11	0.062	0.063
GMFCS-V	0.16	0.062	0.063

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

EAG SA11 Uncertainty around the SMR associated with pegzilarginase treatment

The EAG explored the impact on the ICER of assuming that the SMR associated with pegzilarginase treatment was twice that assumed in the company's base case. This resulted in an SMR for IDM compared with pegzilarginase treatment of 500. The values used in the sensitivity analyses are shown in Table 32.

Table 32: Alternative SMRs applied in the model

Health State	Mortality		SMR	
	Pegzilarginase	IDM	Pegzilarginase	IDM
Mortality by GMFCS				
GMFCS-I	Age- and sex-matched general population mortality[34]		2.32	1160.00
GMFCS-II			2.64	1320.00
GMFCS-III			3.60	1800.00
GMFCS-IV			3.60	1800.00
GMFCS-V			16.27	8136.00

GMFCS: Gross Motor Function Classification System; IDM: individualised disease management; SMR: standardised mortality ratio.

EAG SA12 Uncertainty around life expectancy for patients receiving pegzilarginase treatment

In the EAG base case the QALY loss associated with carers for patients receiving pegzilarginase treatment was [redacted] and was [redacted] for patients receiving IDM. The undiscounted incremental QALYs were [redacted], resulting in a QALY weighting of [redacted]. When the QALY losses associated with carers were removed the undiscounted incremental QALYs became [redacted], resulting in a QALY weighting of [redacted].

4.6.3 Results of the EAG's exploratory analyses

The results of the EAG's exploratory analyses are provided in

Table 33, reporting both unweighted and weighted QALYs. This reports an EAG base case although the EAG cautions that there is considerable uncertainty around the estimate of the ICER and that the sensitivity analyses provided in Table 34 should be fully considered by the Appraisal Committee to determine the assumptions that it believes are most plausible. The EAG notes that the majority of these sensitivity analyses increase the ICER, and some by a considerable amount.

Table 33 also shows the probabilistic ICER. The cost-effectiveness plane and cost-acceptability curve generated by the EAG's probabilistic analyses do not look material different to the company's (Figure 11 and Figure 12) and have not been presented. As in the company's analyses, the probabilistic ICER was larger than the deterministic ICER.

The EAG's deterministic base case weighed ICER is lower than the company's deterministic weighted base case ICER (£299,636 compared with £308,375) which was also shown in the probabilistic base cases (£297,516 (after correction of an error) compared with £311,119). However, the conclusion that the EAG has a more favourable ICER for pegzilarginase than the company can be misleading as many plausible sensitivity analyses increase the ICER above that in the company's base case.

Table 33: EAG exploratory analysis results

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)	
							Unweighted	Weighted
The company's base case								
Pegzilarginase	48.14	[redacted]	[redacted]	43.54	[redacted]	[redacted]	884,777	308,375
IDM	4.59	[redacted]	[redacted]					
EA1 (Correction of error in IDM transition probabilities)								
Pegzilarginase	48.14	[redacted]	[redacted]	43.54	[redacted]	[redacted]	885,550	308,782
IDM	4.60	[redacted]	[redacted]					
EA2 (Assumed starting GMFM DE score for patients in GMFCS-I)								
Pegzilarginase	48.13	[redacted]	[redacted]	43.56	[redacted]	[redacted]	881,226	306,515
IDM	4.58	[redacted]	[redacted]					
EA3 (Using lower 95% CI for decrease in GMFM DE score when ageing one year)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	870,141	300,737
IDM	4.46	[redacted]	[redacted]					
EAG base case (EA1, EA2, and EA3 combined), deterministic								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	868,004	299,636
IDM	4.46	[redacted]	[redacted]					
EAG base case (EA1, EA2, and EA3 combined), probabilistic								
Pegzilarginase	48.38	[redacted]	[redacted]	42.78	[redacted]	[redacted]	843,567	297,516
IDM	5.60	[redacted]	[redacted]					

*Undiscounted

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 34: EAG sensitivity analyses

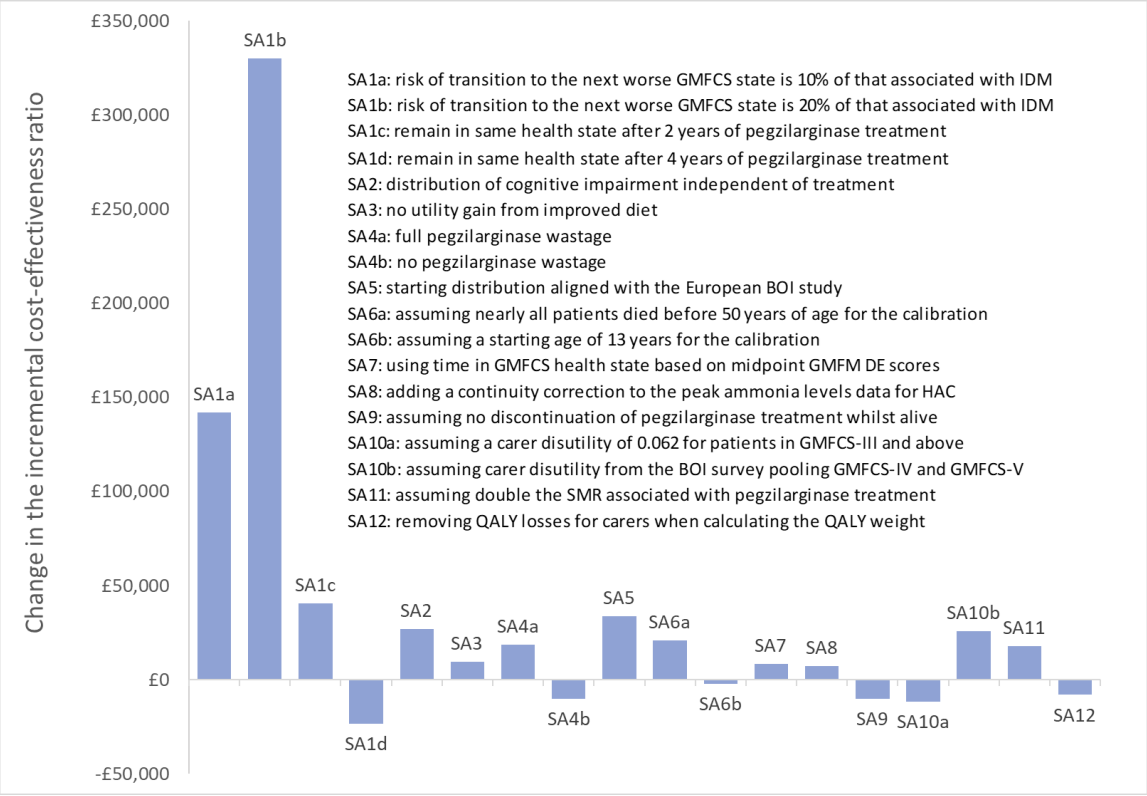
Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)	
							Unweighted	Weighted
EAG's base case								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	868,004	299,636
IDM	4.46	[redacted]	[redacted]					
SA1a (risk of transition to the next worse GMFCS state is 10% of that associated with IDM)								
Pegzilarginase	47.39	[redacted]	[redacted]	42.93	[redacted]	[redacted]	1,005,541	441,714
IDM	4.46	[redacted]	[redacted]					
SA1b (risk of transition to the next worse GMFCS state is 20% of that associated with IDM)								
Pegzilarginase	46.62	[redacted]	[redacted]	42.16	[redacted]	[redacted]	1,150,425	629,638
IDM	4.46	[redacted]	[redacted]					
SA1c (remain in same health state after 2 years of pegzilarginase treatment)								
Pegzilarginase	48.01	[redacted]	[redacted]	43.55	[redacted]	[redacted]	925,293	340,294
IDM	4.46	[redacted]	[redacted]					
SA1d (remain in same health state after 4 years of pegzilarginase treatment)								
Pegzilarginase	48.22	[redacted]	[redacted]	43.76	[redacted]	[redacted]	829,160	276,387
IDM	4.46	[redacted]	[redacted]					
SA2 (distribution of cognitive impairment independent of treatment)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	907,234	326,613
IDM	4.46	[redacted]	[redacted]					
SA3 (no utility gain from improved diet)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	£881,927	309,247
IDM	4.46	[redacted]	[redacted]					
SA4a (full pegzilarginase wastage)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	922,089	318,306
IDM	4.46	[redacted]	[redacted]					
SA4b (no pegzilarginase wastage)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	838,931	289,600
IDM	4.46	[redacted]	[redacted]					
SA5 (starting distribution aligned with the European BOI study)								
Pegzilarginase	47.82	[redacted]	[redacted]	43.48	[redacted]	[redacted]	918,936	333,486
IDM	4.34	[redacted]	[redacted]					
SA6a (assuming nearly all patients died before 50 years of age for the calibration)								
Pegzilarginase	49.17	[redacted]	[redacted]	39.52	[redacted]	[redacted]	905,104	320,392
IDM	9.65	[redacted]	[redacted]					
SA6b (assuming a starting age of [redacted] years for the calibration)								
Pegzilarginase	48.07	[redacted]	[redacted]	43.92	[redacted]	[redacted]	864,149	297,581
IDM	4.15	[redacted]	[redacted]	0				
SA7 (using time in GMFCS health state based on midpoint GMFM DE scores)								
Pegzilarginase	48.13	[redacted]	[redacted]	43.68	[redacted]	[redacted]	883,897	307,896
IDM	4.45	[redacted]	[redacted]	0				
SA8 (adding a continuity correction to the peak ammonia levels data for HAC)								
Pegzilarginase	47.06	[redacted]	[redacted]	42.60	[redacted]	[redacted]	869,108	306,991
IDM	4.46	[redacted]	[redacted]	0				
SA9 (assuming no discontinuation of pegzilarginase treatment whilst alive)								
Pegzilarginase	65.56	[redacted]	[redacted]	61.10	[redacted]	[redacted]	868,502	289,501
IDM	4.46	[redacted]	[redacted]	0				
SA10a (assuming a carer disutility of 0.062 for patients in GMFCS-III and above)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	851,725	287,990
IDM	4.46	[redacted]	[redacted]	0				

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)	
							Unweighted	Weighted
SA10b (assuming carer disutility from the BOI survey pooling GMFCS-IV and GMFCS-V)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	902,688	325,422
IDM	4.46	[redacted]	[redacted]					
SA11 (assuming double the SMR associated with pegzilarginase treatment)								
Pegzilarginase	44.28	[redacted]	[redacted]	40.38	[redacted]	[redacted]	859,006	317,596
IDM	3.89	[redacted]	[redacted]					
SA12 (removing QALY losses for carers when calculating the QALY weight)								
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	868,004	291,639
IDM	4.46	[redacted]	[redacted]					

*Undiscounted
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

A visual representation of how the EAG's weighted base case ICER changes in each sensitivity analysis is provided in Figure 13. The majority of sensitivity analyses increase the ICER, with SA1a and SA1b having a marked impact. These relate to the possibility that patients on pegzilarginase treatment do not remain in the same GMFCS state after 3 years of treatment and that there can be disease progression (at either 10% or 20% of the IDM progression rate). Many other scenarios can increase the EAG's weighted base case ICER by more than £20,000 per QALY gained.

Figure 13: Change in the incremental cost-effectiveness by EAG's sensitivity analyses



BOI: Burden of illness; GMFCS: Gross Motor Function Measure Classification System; GMFM: Gross Motor Function Measure; IDM: Individualised disease management.

4.7 Discussion

The EAG concludes that pegzilarginase appears to have a robust effect on pArg within the first 24 weeks of treatment, based on results from PEACE (-76.7% from baseline), but that the effects on clinical outcomes in the short-term are less certain since across the mobility outcomes in PEACE (2MWT, GMFM-E, GMFM-D), no between-group differences were both statistically and clinically significant at the end of the double-blind period. The difference in GMFM-D was statistically but not clinically significant (LS mean difference 2.3 (95% CI 0.4, 4.2, MMRM p=0.021, Wilcoxon Rank Sum (WRS) p=[redacted]) whilst the differences in 2MWT (LS mean difference 5.5 metres (95% CI: -15.6%, 26.7%; p=[redacted])) and GMFM-E (LS mean difference 4.6 (95% CI: -1.1, 10.2; [redacted]) were clinically but not statistically significant. There was, however, some uncertainty around the generalisability of the MCIDs used to ARG1-D, underpowering may have been an issue and there was some risk of bias from baseline imbalances. Long-term outcomes generally showed numerical effects were maintained or increased but were uncertain due to the lack of a comparator and small numbers at later time points.

Neurocognitive outcomes were also non-significant but numerically favoured pegzilarginase in one case (VABS-II LS mean change from baseline [redacted], (95% CI: [redacted], [redacted]; p=[redacted])) whereas for the intelligence batteries, results were superior in the placebo arm at 24 weeks. Quality of Life outcomes were not analysed statistically, but generally favoured pegzilarginase in the double-blind period, whilst a post-hoc analysis demonstrated statistically significant changes in total health and psychosocial health, but not physical health. Long term outcomes effects on neurocognition and quality of life were mixed and uncertain.

Adverse events were generally mild to moderate in nature. Results for HACs favoured pegzilarginase numerically but were subject to limitations regarding the analyses performed, and at risk of bias due to imbalances at baseline in age. One clinical advisor to the EAG noted that chronic hyperammonaemia may cause harm without hospitalisations.

The decision problem has considerable uncertainty due to sparse data and a relatively short follow-up for patients receiving pegzilarginase. The company estimates a deterministic weighted ICER of £308,375 and an EAG-corrected probabilistic weighted ICER of £311,119; both values are comfortably above the threshold associated with HSTs of £100,000. The weighted ICERs in the EAG base case are lower than the company's estimates being £299,636 (deterministic) and £297,516 (probabilistic).

However, the EAG's ICERs could be noticeably underestimated given the uncertainty around key parameters and assumptions. If patients treated with pegzilarginase can still progress after 3 years of

treatment, then the ICERs increase substantially, if progression is assumed to be 10% that of patients on IDM the deterministic weighted ICER rises to £441,714 and if progression is 20% that of IDM the weighted ICER is £629,638 per QALY gained. These sensitivity analyses may be particularly pertinent given the lack of long-term data related to pegzilarginase treatment and the company's (and EAG's) base case assumption that patients do not change GMFCS state if remaining on pegzilarginase treatment beyond 3 years.

Many other sensitivity analyses increase the weighted ICER, by values greater than £20,000, whilst some decrease the weighted ICER (see Figure 13). The EAG anticipates that at the Appraisal Committee a set of preferred assumptions will be established that will be used to generate a Committee-preferred ICER, that can be provided by the EAG after the meeting. However, it appears extremely unlikely that weighted ICER is below £100,000.

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6. APPENDICES

Appendix 1: Quality assessment of the systematic review performed by the company

Table 35: Critical appraisal of the company's systematic review using AMSTAR 2[48]

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☐ Population ☐ Intervention ☐ Comparator group ☐ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☑ Ye ☐ s No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial ☑ Yes No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI		☑ Ye ☐ s No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☐ searched at least 2 databases (relevant to research question) ☐ provided key word and/or search strategy ☐ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☑ Yes ☐ Partial ☐ Yes No
5. Did the review authors perform study selection in duplicate?		

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☑ Ye
☐ s
No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☑ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☑ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☑ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☑ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

✓

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☐ Yes
- ☐ Partial Yes
- ☐ No
- ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☑ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

- ☐ Yes
- ☐ No
- ☑ No meta-analysis conducted

For NRSI

For Yes:
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

- ☐ Yes
- ☐ No
- ☑ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:
- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

- ☐ Yes
- ☐ No
- ☑ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:
- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

- ☐ Yes
- ☑ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☑ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☑ No

Appendix 2: Technical appendix – instructions for implementing the EAG's exploratory analyses within the company's model

Scenario		Instructions
EAG exploratory analysis	1	Set H8 (A_ctrl_ea1) to 'TRUE' in the 'EAG' worksheet
	2	Set H9 (A_ctrl_ea2) to 'TRUE' in the 'EAG' worksheet
	3	Set H10 (A_ctrl_ea3) to '3' in the 'EAG' worksheet or select 'lower' from the drop-down box on F10 in the 'EAG' worksheet
EAG sensitivity analysis	1a	Set H18 (A_ctrl_SA1) to '2' in the 'EAG' worksheet
	1b	Set H18 (A_ctrl_SA1) to '3' in the 'EAG' worksheet
	1c	Set H18 (A_ctrl_SA1) to '4' in the 'EAG' worksheet
	1d	Set H18 (A_ctrl_SA1) to '5' in the 'EAG' worksheet
	2	Set H22 (A_ctrl_SA2) to 'TRUE' in the 'EAG' worksheet
	3	Set H23 (A_ctrl_SA3) to 'TRUE' in the 'EAG' worksheet
	4a	Set H24 (A_ctrl_SA4) to '2' in the 'EAG' worksheet
	4b	Set H24 (A_ctrl_SA4) to '3' in the 'EAG' worksheet
	5	Set H27 (A_ctrl_SA5) to 'TRUE' in the 'EAG' worksheet
	6a	Set H29 (A_ctrl_SA6) to '2' in the 'EAG' worksheet
	6b	Set H29 (A_ctrl_SA6) to '3' in the 'EAG' worksheet
	7	Set H32 (A_ctrl_SA7) to 'TRUE' in the 'EAG' worksheet
	8	Set H33 (A_ctrl_SA8) to 'TRUE' in the 'EAG' worksheet
	9	Set H34 (A_ctrl_SA9) to 'TRUE' in the 'EAG' worksheet
	10a	Set H36 (A_ctrl_SA10) to 'TRUE' in the 'EAG' worksheet
	10b	Set H37 (A_ctrl_SA10b) to 'TRUE' in the 'EAG' worksheet
	11	Set H29 (A_ctrl_SA6) to '5' in the 'EAG' worksheet
	12	Set H39 (A_ctrl_SA12) to 'TRUE' in the 'EAG' worksheet

To correct an error in the PSA, the EAG changed the formulae in E21:I25 in the sheet 'Data_baseline_char.' to reference AL21:AP25, rather than AL20:AP24. As an illustration for cell E21, the formula '=IF(ctrl_SA=2,AL20,O21/SUM($O21:$S21))' was amended to '=IF(ctrl_SA=2,AL21,O21/SUM($O21:$S21))'

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Pegzilarginase for treating arginase-1 deficiency [ID4029]

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Insert deadline for response** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as ’[redacted]’ in turquoise, all information submitted as ‘[redacted]’ in yellow, and all information submitted as ‘[redacted]’ in pink.

Issue 1 Estimated number of ARG1-D patients in England

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.1, Page 13: The EAG states 'The company estimates that there are less than 40 patients with the disease in England.'	We propose that the text should be amended to the following: 'The company estimates that there is a maximum of 33 patients with the disease in England.'	Immedica views the current text as inaccurate reporting of maximum number of potential ARG1-D patients in England, given the evidence presented in the company submission.	Whilst the text is not factually incorrect, we have changed the text as requested.

Issue 2 Reporting of sample sizes for outcomes measured in the PEACE LTE and Study 102A

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.3.1, Page 36: The EAG states 'In the LTE, the mean change from baseline in the pegzilarginase arm remained similar to that seen at week 24 [redacted] through to week LTE96 [redacted], though numbers in the analysis were small at this time point (n=[redacted]).'	We propose that the text should be amended to the following: 'In the LTE, the mean change from baseline in the pegzilarginase arm remained similar to that seen at week 24 [redacted], n=21) through to week LTE96 [redacted], though numbers in the analysis were small at this time point (n=[redacted])	Immedica requests clarification that the sample size of patients in PEACE differed at each of the cited study timepoints, with each sample containing different patients who had data available, as this impacts on the interpretation of the longer-term evidence.	This change has been made.

Section 3.3.1, Page 36: The EAG states 'Upon switching after the 24-week double-blind period, the placebo-pegzilarginase patients pArg levels also fell by LTE week 24, though by a numerically higher amount than the pegzilarginase-pegzilarginase group after the same time on treatment (24 weeks) [redacted] compared to [redacted], respectively).'	We propose that the text should be amended to the following: 'Upon switching after the 24-week double-blind period, the placebo-pegzilarginase patients pArg levels also fell by LTE week 24, though by a numerically higher amount than the pegzilarginase-pegzilarginase group after the same time on treatment (24 weeks) [redacted] compared to [redacted], n=21), respectively).'		This change has been made.
Section 3.3.1, Page 37: The EAG states '…but the fall was smaller in absolute numbers in Study 102A [redacted] compared to the two arms of PEACE [redacted] (SD [redacted]) and [redacted].'	We propose that the text should be amended to the following: '…but the fall was smaller in absolute numbers in Study 102A [redacted] compared to the two arms of PEACE [redacted] (SD [redacted], n=21) and [redacted].'		This change has been made.
Section 3.3.2, Page 42: The EAG states 'Upon switching to pegzilarginase, the placebo-pegzilarginase	We propose that the text should be amended to the following: 'Upon switching to pegzilarginase, the placebo-pegzilarginase patients 2MWT		This change has been made.

patients 2MWT had not improved after 24 or 48 weeks on treatment (mean change from baseline [redacted] and [redacted] meters)…'	had not improved after 24 or 48 weeks on treatment (mean change from baseline [redacted] and -7.5 (SD [redacted] meters)…'		
Section 3.3.2, Page 43: The EAG states 'In Study 102A, the company did not note any clinically meaningful improvements, but did note numerical improvement up to week 144 (mean change from baseline [redacted].'	We propose that the text should be amended to the following: ''In Study 102A, the company did not note any clinically meaningful improvements, but did note numerical improvement up to week 144 (mean change from baseline [redacted].'	Immedica requests clarification that the sample size of patients in Study 102A at Week 144 differed to that at study baseline, as this could impact on the interpretation of the available clinical evidence.	This change has been made.
Section 3.3.3.1, Page 54: The EAG states '. In the LTE, mean change from baseline values indicated an initial improvement [redacted] at LTE24 and [redacted] at LTE96) then worsening by the end of study timepoint in the pegzilarginase arm (mean change from baseline at end of study: [redacted]).'	We propose that the text should be amended to the following: 'In the LTE, mean change from baseline values indicated an initial improvement [redacted] at LTE24 and [redacted] at LTE96) then worsening by the end of study timepoint in the pegzilarginase arm (mean change from baseline at end of study: [redacted]).'	Immedica requests clarification that the sample size of patients in PEACE differed at each of the cited study timepoints, with each sample containing different patients who had data available, as this could impact on the interpretation of the available clinical evidence	This change has been made.

Section 3.3.3.1, Page 54: The EAG states 'A similar pattern in the placebo arm was observed when they switched to pegzilarginase (mean change from baseline [redacted] at LTE24, [redacted] at LTE96, and [redacted] at end of study).'	We propose that the text should be amended to the following: 'A similar pattern in the placebo arm was observed when they switched to pegzilarginase (mean change from baseline [redacted] at LTE24, [redacted] at LTE96, and [redacted] at end of study).		This change has been made.

Issue 3 Incorrect data

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.1, Page 8: The EAG cites an incorrect probabilistic weighted ICER of £345,005,	The latest version of the company's model submitted as part of the clarification response produced a probabilistic weighted ICER of £338,263. We suggest that this value is utilised in the report.	The current wording contains inaccurate reporting of probabilistic weighted ICER from company's model which was updated during Clarification stage.	We intended to amend the report as suggested but have found the error which makes the PSA weighted ICER higher than the deterministic value. New text has been added to address this and revised estimates of the company's
Section 1.3, Page 11, Table 2: The EAG cites an incorrect probabilistic			

weighted ICER of £345,005,			PSA results and the EAG's PSA results have been added.
Section 3.3.1, Page 38, Table 8, Column 4, Row 3: The EAG reports the GM (SD) pArg at Week 24 as 86.4 (0.50)* µmol/L.	Data should be aligned with data reported in Table 92, Appendix M of CS: GM 86.4 (1.60)*	The current wording uses inaccurate reporting of pArg data from PEACE.	This change has been made.
Section 3.3.1, Page 38, Table 8, Column 3, Row 4: The EAG reports the GM (SD) pArg at baseline as 471.7 (79.9)* µmol/L.	Data should be aligned with data reported in Table 92, Appendix M of CS: 464.7 (0.2)*	The current wording uses inaccurate reporting of pArg data from PEACE.	This change has been made.
Section 3.3.1, Page 38, Table 8, Column 4, Row 4: The EAG reports the GM (SD) pArg at Week 24 as	Data should be aligned with data reported in Table 92, Appendix M of CS: 426.5 (1.31)*	The current wording uses inaccurate reporting of pArg data from PEACE.	This change has been made.

426.5 (0.27)* µmol/L.			
Section 3.3.1, Page 38, Table 8, Column 7, Row 4: The EAG reports the Mean (SD) pArg at LTE120 as 150 79.1 (-)*** µmol/L.	Data should be aligned with data reported in Table 36 in the PEACE CSR: 79.1 (-)***	The current wording uses inaccurate reporting of pArg data from PEACE.	This change has been made.
Section 3.3.2, Page 44: The EAG states 'Upon switching to pegzilarginase, the pattern of improvement was similar to that seen in GMFM-D, in that improvements were small [redacted]) up to week 120, when a more notable improvement was reported [redacted] though numbers in the analysis were small	Data should be aligned with data reported in Table 41 of PEACE CSR and Table 99, Appendix M of CS. We propose that the text should be amended to: 'Upon switching to pegzilarginase, the pattern of improvement was similar to that seen in GMFM-D, in that improvements were small [redacted]) up to week 120, when a more notable improvement was reported [redacted] though numbers in the analysis were small (n=[redacted]) at this time point.'	The current wording uses inaccurate reporting of GMFM-D data from PEACE.	This change has been made.

(n=[redacted]) at this time point.'			
Section 3.3.2, Page 57, Column 4, Row 5: The EAG cites incorrect values for FSIQ at Week 24 in the pegzilarginase arm.	Data should be aligned with Table 14.2.13.5 in the PEACE CSR: [redacted] [redacted] MCFB: [redacted]	The current wording uses inaccurate reporting of FSIQ data from PEACE. Correction of this would also remove need for definition of * in the table legend.	The EAG does not have access to the CSR table cited (the link in the CSR is disabled) and had taken data from the CS. This change has been made.
Section 3.3.2, Page 57, Column 8, Row 6: The EAG cites incorrect values for FSIQ at EOS in the placebo-pegzilarginase arm.	Data should be aligned with Table 14.2.13.5.1 in the PEACE CSR: [redacted] [redacted] MCFB: [redacted]	The current wording uses inaccurate reporting of FSIQ data from PEACE	This change has been made.

Section 3.3.4.4, Page 61, Column 9, Row 3: The EAG incorrectly describes no change in the mean change from baseline in the Physical Functioning domain in placebo-pegzilarginase patients. Incorrect values are also provided form the mean change from baseline in the Social Functioning and School Functioning domains.	Data should be aligned with Table 14.2.11.1 in the PEACE CSR: n=2 Physical MCFB: [redacted] Emotional MCFB: [redacted] Social MCFB: [redacted] School MCFB: [redacted]	The current wording uses inaccurate reporting of PedsQL data from PEACE	The EAG does not have access to the CSR table cited (the link in the CSR is disabled). The changes have been made. We note that the text on p190 of the CSR does not match the information given by the company in that for physical functioning MCFB it states “no change” for the placebo-pegzilarginase group.
Section 3.3.4.4, Page 61, Column 6, Row 3: The EAG incorrectly reports the mean changes from baseline in the Social Functioning	Data should be aligned with Table 14.2.11.1 in the PEACE CSR: Social MCFB: [redacted]School MCFB:_[redacted]		The EAG does not have access to this table. The change has been made.

and School Functioning domains at LTE48.			
Section 3.3.4.4, Page 61, Table 11, Column 3, Row 2: The EAG incorrectly cites the sample size at baseline for PedsQL in the pegzilarginase arm as 'NR'.	Data should be aligned with Table 14.2.11 in the PEACE CSR: [redacted]		The EAG does not have access to this table. The change has been made.
Section 3.3.4.4, Page 61, Table 11, Column 7, Row 2: The EAG incorrectly cites the MCFB at LTE96 for PedsQL in the pegzilarginase arm as [redacted]. Mean value is incorrectly rounded down, and SD is incorrect.	Data should be aligned with Table 14.2.11 in the PEACE CSR: MCFB: [redacted]		The EAG does not have access to this table. The change has been made.

Section 3.3.4.4, Page 61, Table 11, Column 3, Row 3: The EAG incorrectly cites the sample size at baseline for PedsQL in the placebo-pegzilarginase arm as 'NR'	Data should be aligned with Table 14.2.11 in the PEACE CSR: [redacted]		The EAG does not have access to this table. The change has been made.
Section 3.3.4.4, Page 62, Column 3, Row 8: The EAG provides the incorrect sample size at baseline for ZBI-12 for the pegzilarginase arm.	Data should be aligned with Table 14.2.12 in the PEACE CSR: [redacted]	The current wording uses inaccurate reporting of ZBI-12 data from PEACE	The EAG does not have access to this table. The change has been made.
Section 3.3.4.4, Page 62, Column 5, Row 8: The EAG provides the incorrect sample size at LTE24 for ZBI-12 for the pegzilarginase arm.	Data should be aligned with Table 14.2.12 in the PEACE CSR: [redacted]		The EAG does not have access to this table. The change has been made.

<table>
<tr>
<td>Section 3.3.4.4, Page 62, Column 9, Row 9: The EAG provides the incorrect sample size at EOS for ZBI-12 for the pegzilarginase arm.</td>
<td>Data should be aligned with Table 14.2.12 in the PEACE CSR:
[redacted]</td>
<td></td>
<td>The EAG does not have access to this table. The change has been made.</td>
</tr>
<tr>
<td>Section 4.2.4.1, Page 77, Table 14: The EAG provides incorrect values for each GMFCS level at model entry.</td>
<td>The CS presented values rounded to one decimal place. Given that Table 14 in the EAG report presents values to two decimal places, the values are incorrectly rounded. We suggest amending the values in the table, as presented below:
<table>
<tr><th></th><th colspan="5">Proportion of patients, started in health states by GMFCS</th><th>Source</th></tr>
<tr><th></th><th>I</th><th>II</th><th>III</th><th>IV</th><th>V</th><th></th></tr>
<tr><td>Base-case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Pooled data from the PEACE study, study 101A/102A, and BOI survey (n=[redacted])</td></tr>
</table>
</td>
<td>The current wording reflects inaccurate rounding of GMFCS levels at model entry</td>
<td>This change has been made.</td>
</tr>
<tr>
<td>Section 4.2.4.2, Page 77, Table 15, Column 8: The EAG has provided incorrect patient</td>
<td>The correct numbers can be found in sheet ‘GMFCS patient counts’ cells AN17:AN20 for the pegzilarginase arm, and cells BC17:BC20 for the IDM intervention arm.
The number of patients with data for the IDM arm (from GMFCS Level I to GMFCS Level V) was [redacted] For the</td>
<td>The current wording reflects incorrect reporting of transition probabilities</td>
<td>This change has been made.</td>
</tr>
</table>

numbers across both treatment arms for each GMFCS health state. Patient counts for IDM have been used for pegzilarginase, and those for pegzilarginase have been used for IDM.	pegzilarginase arm, the number of patients with data was [redacted].	according to intervention arm and GMFCS health state	
Section 4.4, Page 89: The EAG states 'In the company's base case the undiscounted QALY gain associated with pegzilarginase treatment was [redacted], resulting in a QALY weighting of [redacted].'	The EAG reports the results provided in the CS, however the base-case results have since been updated in the model as part of the response to the clarification questions. The QALY gain and QALY weighting here should be [redacted] and [redacted], respectively.	The current wording uses inaccurate reporting of QALYs	This change has been made, but QALY weighting is [redacted]
Section 4.4, Page 91, Table 25: The EAG cites an incorrect probabilistic	The latest version of the company's model submitted as part of the clarification response produced a probabilistic weighted ICER of £338,263. We suggest that this value is utilised in the report.	The current wording reflects inaccurate reporting of probabilistic	We intended to amend the report as suggested but have found the error which makes

weighted ICER of £345,005,		weighted ICER from company's model	the PSA weighted ICER higher than the deterministic value. New text has been added to address this and revised estimates of the company's PSA results and the EAG's PSA results have been added.
Section 4.7, Pages 105 – 106: The EAG cites an incorrect probabilistic weighted ICER of £345,005,	The latest version of the company's model submitted as part of the clarification response produced a probabilistic weighted ICER of £338,263. We suggest that this value is utilised in the report.		
Section 4.7, Page 109: The EAG cites an incorrect probabilistic weighted ICER of £345,005,	The latest version of the company's model submitted as part of the clarification response produced a probabilistic weighted ICER of £338,263. We suggest that this value is utilised in the report.		

Issue 4 Calculation error

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.3.2, Page 45: The EAG states 'Amongst the GMFCS level 1-3 patients, [redacted] in Study 102A and the	The calculation concerning the pegzilarginase arm does not account for Study 102A. We propose that the text	The current wording appears to contain a calculating error which should be updated to reflect	This has been edited as suggested, along with some additional edits for wording and to correct the data for the placebo-pegzilarginase group as follows:

pegzilarginase arm of PEACE [redacted],	should be amended to reflect the correct calculation: 'Amongst the GMFCS level 1-3 patients, [redacted] in Study 102A and the pegzilarginase arm of PEACE [redacted]	the correct calculation.	Amongst the GMFCS level 1-3 patients, proportionately [redacted] in Study 102A and the pegzilarginase arm of PEACE [redacted]

Issue 5 Missing data

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.3.2, Page 47, Table 9, Column 2, Row 14: Baseline 6MWT results for patients in Study 102A are not reported.	Immedica suggests completing this cell in Table 9 with the following data: n=[redacted] Mean: [redacted]	Immedica requests insertion of baseline 6MWT data as was previously presented in Table 15, page 67 of the CS.	This change has been made.

Section 3.3.3.2, Page 57, Table 10: Table header incorrectly states that Table 11 presents clinical efficacy results for neurocognitive outcomes from PEACE and Study 102A. Only results from PEACE are presented.	Immedica suggests to amend the table header to reflect that Table 11 presents data for PEACE only, or add in the neurocognitive outcomes from Study 102A into Table 11.	Table 11 does not report outcomes data for VABS-II and FSIQ for Study 102A, despite this being specified in the table heading. Immedica requests an amendment to the table heading or the insertion of Study 102A FSIQ and VABS-II outcomes into Table 11.	The Header for table 10 has been changed. The header for Table 11 was correct.
Section 3.3.4.4, Page 62, Table 11, Column 5, Row 9: ZBI-12 results at LTE48 in the placebo-pegzilarginase arm are not reported in the cell.	Immedica suggests completing this cell in Table 11 with the following data: n=[redacted] MCFB: [redacted]	Immedica requests insertion of ZBI-12 data as presented in Table 14.2.12.1 in the PEACE CSR.	The change has been made.
Section 3.3.4.4, Page 62, Table 11, Column 4, Row 4: The EAG does not disclose the sample size for the Physical Health and Psychosocial Health Summary Scores Week 24 (this differs from the sample size for the remaining domains).	Immedica suggests providing the sample size alongside the Physical Health and Psychosocial Summary Scores at Week 24: 'Physical: [redacted]' 'Psychosocial: [redacted]'	Immedica requests insertion of sample size for Physical Health and Psychosocial Health Summary Scores, as described in Table 14.2.16.7 and Table 14.2.16.9 in the PEACE CSR.	The EAG did not have access to this table (the link was disabled in the CSR). The data has been added.

Issue 6 Formatting of Table 9, Pages 46-48

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.3.2, Page 47, Table 9: The column headings refer to timepoints in PEACE only, without providing the corresponding timepoint in Study 102A (as presented in Table 8).	Immedica requests that the EAG provides study week number alongside LTE timepoint in column headings, as provided inn Table 8: Baseline, Week 24, LTE24/Week 48, LTE96/Week 120, and LTE120/Week144.	Immedica requests that the EAG add clarification that Study 102A did not have an LTE period.	This change has been made.
Section 3.3.2, Page 47, Table 9, Column 2, Row 14: Baseline 6MWT results for patients in Study 102A are not reported.	Immedica suggests completing this cell in Table 9 with the following data: n=[redacted] Mean: [redacted]	Immedica requests insertion of baseline 6MWT data presented in Table 15, page 67 of the CS.	This data already appears in the table in the row below the table divider “Study 102A results”. We have assumed the company were referring to the cell in column 2, row 15 (counting the header row and the divider rows, i.e. the final row), which was blank and should have contained the word “pegzilarginase”.

Section 3.3.2, Page 48, Table 9: A single asterisk (*) in Table 9 has not been defined in the table legend.	Immedica are unable to respond to the accuracy of this asterisks without an explanation of what the * in Table 9 means in the table legend. If there is a footnote missing, Immedica requests the opportunity to review this.	The current table legend is incomplete.	The single asterisk has been removed from these data, it was historical. However, a new single asterisk has been added to explain the meaning of the headers with respect to the weeks for PEACE and 102A.

Issue 7 Model time horizon

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 4.2.1, Page 72: The EAG states 'The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over an [redacted]-year (lifetime) horizon.'	Immedica suggests to correct the current wording to 'The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over an [redacted]-year (lifetime) horizon (calculated as 100 minus the baseline age).'	The proposed wording provides clarification that the time horizon was calculated using the mean baseline age from the pegzilarginase clinical studies	This change has been made.

Issue 8 Model assumptions

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 4.2.3, Page 75: The EAG states 'Patients with ARG1-D are assumed to weigh less than an age- and sex-matched population.'	Immedica requests clarification that this assumption was informed by comparing the age and sex-matched weight characteristics from PEACE and Phase 1/2 studies of pegzilarginase to the weight characteristics expected in the general population, sourced from NHS digital.	Immedica requests that the wording be adjusted to provide clarification that the assumption was informed by clinical data and UK data sources	The text has been amended to add this extra detail
Section 4.2.3, Page 75: The EAG states 'For patients under 16 years of age, the reduction is assumed to be [redacted]; for patients aged 16 years or over, the reduction is assumed to be [redacted].'	Immedica requests clarification that this assumption was calculated based on the ratio of actual weight in pooled PEACE and Phase 1/2 patients versus the expected weight given the same age and gender distribution. Percentage reductions can be obtained from those weight ratios by taking [1 – weight ratio].	Immedica requests that the wording be adjusted to provide clarification that the assumption was informed by clinical data and UK data sources	The text has been amended to add this extra detail
Section 4.2.4.1, Page 77: The EAG states 'Patients with ARG1-D are assumed to weigh less than an age- and sex-matched population.'	Immedica requests clarification that this assumption was informed by comparing the age and sex-matched weight characteristics from PEACE and Phase 1/2 studies of pegzilarginase to the weight	Immedica requests that the wording be adjusted to provide clarification that the assumption was informed by clinical data and UK data sources	The text has been amended to add this extra detail

	characteristics expected in the general population, sourced from NHS digital.		
Section 4.2.4.1, Page 77: The EAG states 'For patients under 16 years of age, the reduction is assumed to be [redacted]; for patients aged 16 years or over, the reduction is assumed to be [redacted].'	Immedica requests clarification that this assumption was calculated based on the ratio of actual weight in pooled PEACE and Phase ½ patients versus the expected weight given the same age and gender distribution. Percentage reductions can be obtained from those weight ratios by taking [1 – weight ratio].	Immedica requests that the wording be adjusted to provide clarification that the assumption was informed by clinical data and UK data sources	The text has been amended to add this extra detail
Section 4.2.4.6, Page 80: The EAG states 'However, the company had to assume a distribution amongst cognitive states for those in GMFCS-I.'	Immedica requests clarification that the assumption of the distribution amongst cognitive health states for those in GMFCS-I in the IDM arm was informed by the fact that [redacted] in the BoI study was in a severe state, and it was therefore likely that some may be in the moderate state given a larger sample size (see CS, Section B.3.3.2).	Immedica requests that the wording be adjusted to provide clarification that this assumption was informed by the European BoI study	This has been added.
Section 4.2.4.6, Page 80: The EAG states 'For a cohort of patients receiving pegzilarginase treatment, the company assumed that after 52 weeks cognitive abilities would be improved	Immedica requests clarification that the assumption of small benefit from treatment with pegzilarginase was based on the small improvement on VABS-II scores observed in the clinical studies (See CS, Section B.3.3.2)	Immedica requests that the wording be adjusted to provide clarification that this assumption was informed by clinical data from the pegzilarginase clinical studies	This has been added.

and used a different distribution for those with GMFCS-I to GMFCS-III.'			
Section 4.5.1, Page 92, Table 26: The EAG states 'Longer-term transition probabilities were assumed for pegzilarginase, and for IDM, were calculated based on GMFM DE scores.'	Immedica suggests adding further detail and reword to: 'Longer-term transition probabilities for pegzilarginase and IDM were calculated based on pooled GMFM DE scores from the PEACE and Phase 1/2 clinical studies.'	Immedica requests that the wording be adjusted to provide clarification that this calculation was based on GMFM DE scores from pooled PEACE and Phase 1/2 data	The data source was added for IDM, we maintain that this is an assumption for pegzilarginase rather than a calculation.

Issue 9 Methodology for HAC rate ratio calculation

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 4.2.4.5, Page 80: The EAG have referenced outdated methodology for calculating the rate ratio in the model.	The method for calculating the rate ratio has been updated in the model as part of the clarification response. The treatment effect on HAC rate is now stratified between the first 6 months and follow-on months in the model, based on the results of a Poisson regression model. The new approach derives the rate ratio using both the double-blind period and the LTE, and yields separate rate	The current wording reflects outdated methodology for calculating the HAC rate ratio reported, which was updated at clarification stage.	The EAG has amended the text (and highlights that the numbers marked CIC were not marked as such in the clarification response)

	ratios for each period (of [redacted] and [redacted], respectively). See response to Clarification Question B18 in the clarification response.		
Section 4.2.4.5, Page 80: The EAG states 'The derived probability of HACs per cycle was 0.63% for pegzilarginase and 8.10% for IDM.'	As the method for calculating the rate ratio has been updated to stratify between the double-blind and LTE period, the derived probabilities of HACs per cycle are now also stratified by period. This yields a probability of HACs per cycle of approximately [redacted] for pegzilarginase in the first 24 weeks, and a probability of HACs per cycle of [redacted] for pegzilarginase post-24 weeks. The probability of HACs per cycle for IDM remains unchanged.	The current wording reflects outdated methodology for calculating the HAC rate ratio reported, which was updated at clarification stage.	The text has been amended
Section 4.5.1, Table 26, Page 93: The EAG states 'The rate ratio for HAC between pegzilarginase and IDM was estimated from the long-term extension of PEACE and the number of HACs in the IDM arm of PEACE.'	The method for calculating the rate ratio in the model has been updated following the clarification response. The rate ratio for HACs between pegzilarginase and IDM is now estimated for both the double-blind period and LTE of PEACE using a Poisson regression model.	The current wording reflects outdated methodology for calculating the HAC rate ratio reported, which was updated at clarification stage.	The text has been amended

Issue 10 EAG's description of uncertainty in parameters

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 4.4, Page 90: The EAG states 'It may be the case that the uncertainty in parameters is mis-specified in the PSA, for example, using Gamma distributions to determine the starting GMFCS states rather than a Dirichlet distribution.'	Immedica does not believe that the uncertainty in GMFCS starting state parameters were mis-specified in the way described by the EAG. A Dirichlet distribution to determine the starting GMFCS health state was added to the model as part of the clarification response. The Gamma distributions by baseline GMFCS category, observable in the 'Data_baseline char' sheet of the model, are simply used to parameterise the Dirichlet distribution. Each Dirichlet iteration is obtained by taking the ratio of the Gamma random variates to the sum of the random Gamma variates for each baseline GMFCS category. We believe this change to be the source of the higher PSA value, as it was only observed following the addition of the Dirichlet distribution to the model. The impact is likely due to the high sensitivity of the model to the utility	Immedica believes that clarification that the uncertainty in parameters is not mis-specified in the PSA as described by the EAG should be clarified.	We have identified an error in the PSA (related to starting GMFCS states, but not to the Gamma distributions used in the sampling). New text has been added to address this and revised estimates of the company's PSA results and the EAG's PSA results have been added.

	value of GMFCS Level I, as any decrease in proportions in GMFCS Level I at baseline during sampling reduces QALY gain.		

Issue 11 Clarification on reporting of undiscounted LYGs

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 4.6.3, Pages 106 - 107 The EAG reports the results from their exploratory analyses and sensitivity analyses in Table 33 and Table 34, respectively. However, it is unclear from the tables as to whether the discounted or undiscounted LYGs are presented	The undiscounted LYG are used to estimate the QALY weighting, so the EAG should indicate in the where undiscounted LYs are presented in the EAG report, particularly with reference to Table 33 and Table 34.	Immedica believes that the EAG should provide clarification as to when discounted vs. undiscounted LYGs are used throughout the report.	All LYG presented in Table 33 and Table 34 are undiscounted. A footnote has been added to state this.

Issue 12 Inaccuracies in Table of Abbreviations

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 6: Table of abbreviations expands GMFC-MLD to 'Gross Motor Function Classification Metachromatic Leukodystrophy'	'Gross Motor Function Classification in Metachromatic Leukodystrophy' is the correct form	The current table of abbreviations includes inaccurate definitions	This change has been made.
Page 6: Table of abbreviations expands GMFM-E to 'Global Motor Function Measure'	'Gross Motor Function Measure, Part E' is the correct form		This change has been made.
Page 7: Table of abbreviations expands VABS-II to 'Vineland Adaptive Behaviour Scale'	'Vineland Adaptive Behaviour Scales, Second Edition' is the correct form, and highlights the edition of VABS used in the study protocol		This change has been made.

Issue 13 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 11, Table 2: The EAG uses the following key in the table legend: CI: confidence	Immedica would like to flag a number of typographical errors that have been made as per the following rows.	Immedica notes instances of typographical errors throughout the report,	This change has been made.

interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Classification System;	The definitions for GMFCS and GMFM are currently reversed. Immedica suggests to correct to 'CI: confidence interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Measure…'	which we request that the EAG update prior to publishing the report.	
Page 12, Table 3: The EAG uses the following key in the table legend: CI: confidence interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Classification System;	As per the above, the definitions for GMFCS and GMFM are the wrong way around. Suggested to correct to 'CI: confidence interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Measure…'		This change has been made.
Page 21: The EAG states 'All studies were multinational (including Europe and North America), but primarily recruited from the United States of American (USA).'	Suggested to correct to 'All studies were multinational (including Europe and North America), but primarily recruited from the United States of America (USA).'		This change has been made.
Page 25: The EAG states 'The EAG therefore focusses on study 102A from hereon in, except where necessary to provide details of relevance to 102A.'	Incorrect study cited, suggested to correct to 'The EAG therefore focusses on study 102A from hereon in, except where necessary to provide details of relevance to Study 101A'.		The EAG has made an alternative change as follows: "The EAG therefore focusses on study 102A from hereon in, except where it is

			necessary to refer to Study 101A to provide details of relevance to 102A.
Page 29: The EAG states 'The primary endpoint was plasma arginase (pArg), with key secondary outcomes of (2MWT (a measure of distance walked in 2 minutes) and Global Motor Function Measure (GMFM-E) (a measure of ability to walk, run, and jump).'	Suggested to correct to 'The primary endpoint was plasma arginine (pArg), with key secondary outcomes of (2MWT (a measure of distance walked in 2 minutes) and Global Motor Function Measure, Part E (GMFM-E) (a measure of ability to walk, run, and jump).		This change has been made.
Page 36: The EAG states '…and was numerically higher at week 240 -212.3 (SD 16.55) though numbers in the analysis were small at this time point (n=[redacted]).	Missing brackets; suggested to correct to '…and was numerically higher at week 240 (-212.3 (SD 16.55)) though numbers in the analysis were small at this time point (n=[redacted]).		This change has been made.
Page 64: The EAG states 'Most TEAEs were mild or moderate, [redacted] patients required dosing reductions (all in the LTE)…'	Suggest rewording to 'Most TEAEs were mild or moderate, [redacted] patients required dosing reductions (all in the LTE)…'		This change has been made.

Page 69: The EAG states '…though the difference in GMFM-D was statistically significant (LS mean difference 2.3 (95% CI 0.4, 4.2, MMRM p=0.021, Wilcoxon Rank Sum (WRS) p=[redacted]) and the differences in 2MWT…'	Missing a closed bracket; suggested to correct to '…though the difference in GMFM-D was statistically significant (LS mean difference 2.3 (95% CI 0.4, 4.2, MMRM p=0.021, Wilcoxon Rank Sum (WRS) p=[redacted])) and the differences in 2MWT…;		though the difference in GMFM-D was statistically significant
Page 99: The EAG states 'In ERG report for HST 18, it was stated that "*Based on*…'	Suggest to correct to 'The EAG states 'In the ERG report for HST 18, it was stated that "*Based on*…'		This change has been made.

Issue 14 Grammatical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 23: The EAG states 'The primary outcome was a surrogate outcome (pArg), and clinical advisors to the EAG noted that pArg levels do not have a consistent relationship with clinical severity of the disease but is one marker of disease used to monitor patients and is	Immedica would like to flag a number of grammatical errors that have been made, as per the remainder of this table. We suggest that this statement is corrected to 'The primary outcome was a surrogate outcome (pArg), and clinical advisers to the EAG noted that pArg levels do not have a consistent relationship with clinical	Immedica notes instances of grammatical errors throughout the report, which we request that the EAG update prior to publishing the report.	The EAG has made an alternative change to maintain the source of the information about the relationship to HACs as being from the clinical advisors, not a statement of fact from the EAG.

more closely linked to hyperammonaemic crises (HACs).'	severity of the disease. However, it is one marker of diseased used to monitor patients and is more closely linked to hyperammonaemic crises (HACs).'		"The primary outcome was a surrogate outcome (pArg). Clinical advisors to the EAG noted that pArg levels do not have a consistent relationship with clinical severity of the disease but also noted that it is one marker of disease used to monitor patients and is more closely linked to hyperammonaemic crises (HACs)."
Page 46, Table 9, Column 4, Row 6: Week 24 2MWT MCFB for pegzilarginase arm referred to as 'MCFB: : 4.2 (7.7)'	As above, suggested to correct to 'MCFB: 4.2 (7.7)'		This change has been made.
Page 46, Table 9, Column 4, Row 7: Week 24 GMFM-E MCFB for placebo-pegzilarginase arm referred to as 'MCFB: : -0.4 (6.2)'.	Suggest to correct to 'MCFB: -0.4 (6.2).		This change has been made.
Page 72: The EAG states 'Unit costs are not valued at the same price year. although as the earliest was 2018/2019 the EAG was not	Suggest rewording to 'Unit costs are not valued at the same price year although, as the earliest was 2018/2019, the EAG was not		This change has been made.

concerned by this small inconsistency.'	concerned by this small inconsistency.'		
Page 73: The EAG states 'At model entry, patients are assumed to have a mean age of [redacted] years, with [redacted] of patients are assumed to be female.'	Suggest to correct to 'At model entry, patients are assumed to have a mean age of [redacted] years, with [redacted] of patients assumed to be female.'		This change has been made.
Page 75: The EAG states 'For patients treated with pegzilarginase, it is assumed after 3 years that patients would remain in their current GMFCS state.'	Suggest rewording to 'For patients treated with pegzilarginase, it is assumed after 3 years that they would remain in their current GMFCS state.'		This change has been made.
Page 78: The EAG states '…with all patients remaining in the GMFCS state that they were in after 3 years of treatment provided, they remained on pegzilarginase treatment.'	Suggested to correct to '…with all patients remaining in the GMFCS state that they were in after 3 years of treatment, provided they remained on pegzilarginase treatment.'		The text has been amended.

Issue 15 Formatting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 10: The EAG state '…,the extension of life for patients results in more non-drug costs for patients receiving pegzilarginase treatment.	There are some instances of double spacing or no spacing in the report at present, as highlighted in this table. Immedica suggests to remove double spacing in these locations, correcting to 'state '…,the extension of life for patients results in more non-drug costs for patients receiving pegzilarginase treatment.'	Immedica notes instances of formatting errors throughout the report, which we request that the EAG update prior to publishing the report.	This change has been made
Page 13: The EAG states 'In Section B.1.3 of CS,1 the company provides a good description of arginase 1 deficiency (ARG1-D) which is an ultra-rare disease characterised by markedly elevated plasma arginine (pArg) levels.	As above, suggested to remove double spacing, correcting to: 'In Section B.1.3 of CS,1 the company provides a good description of arginase 1 deficiency (ARG1-D) which is an ultra-rare disease characterised by markedly elevated plasma arginine (pArg) levels.'		This change has been made
Page 20: The EAG states '…such as the impact of baseline imbalances, and the open-label nature of the LTE of PEACE (see section 3.2.1.1) and Study 102A.'	Suggested to correct to '…such as the impact of baseline imbalances, and the open-label nature of the LTE of PEACE (see section 3.2.1.1) and Study 102A.		This change has been made

Page 36: The EAG states '…through to week LTE96 (-270.2 µmol/L (SD138.1), though numbers in the analysis were small at this time point (n=[redacted]).'	Suggested to correct to 'through to week LTE96 [redacted], though numbers in the analysis were small at this time point (n=[redacted]).		The highlighting was already present in the version of the report sent to NICE.
Page 43: The EAG states '…,but greater numerical improvements were seen at week 120 (MCFB: [redacted], though numbers in the analysis were small (n=3) at this time point.'	Suggested to correct to '…,but greater numerical improvements were seen at week 120 (MCFB:[redacted], though numbers in the analysis were small (n=3) at this time point.'		This change has been made.
Page 43: The EAG states 'In Study 102A, the company did not note any clinically meaningful improvements, but did note numerical improvement up to week 144 (mean change from baseline [redacted]'	Suggested to correct to 'In Study 102A, the company did not note any clinically meaningful improvements, but did note numerical improvement up to week 144 (mean change from baseline [redacted].'		This change has been made.
Page 44: The EAG states 'An improvement was maintained at week 96 (mean change from baseline ([redacted] points, n=[redacted]),…'	Suggested to correct to 'An improvement was maintained at week 96 (mean change from baseline [redacted] points, n=[redacted]),…'		This change has been made.

Page 46, Table 9, Columns 5-9, Row 7: Double-spacing occurs in all MCFB results.	Suggest to correct each cell as follows: LTE24 – 'MCFB[redacted]', LTE48 – 'MCFB: [redacted])', LTE96 – 'MCFB: [redacted])', LTE120 – 'MCFB[redacted]', and EOS – 'MCFB: [redacted]'.		This change has been made.
Page 51: The EAG states '…mean GMFM-D [redacted] at baseline compared to 28.2 (SD 13.28) at week 24).'	Suggested to correct to 'mean GMFM-D [redacted] at baseline compared to 28.2 (SD 13.28) at week 24).'		This change has been made.
Page 54: The EAG states 'In the LTE, mean change from baseline values indicated an initial improvement ([redacted] at LTE24 and [redacted] at LTE96)…'	Suggested to correct to 'In the LTE, mean change from baseline values indicated an initial improvement ([redacted] at LTE24 and [redacted] at LTE96)…'		This change has been made, and SD added to ([redacted]
Page 57, Table 10, Column 4, Row 2: Week 24 MCFB contains a double space**.**	Suggest to correct to 'MCFB: [redacted]'		This change has been made.
Page 61, Table 11, Column 5, Row 2: LTE24 Emotional MCFB contains a double space	Suggest to correct to 'MCFB: [redacted]'		This change has been made.
Page 61, Table 11, Column 6, Row 2: LTE48 Emotional MCFB contains a double space	Suggest to correct to 'MCFB: [redacted]'		This change has been made.

Page 61, Table 11, Column 6, Row 3: LTE48 Emotional MCFB contains a double space	Suggest to correct to 'MCFB: [redacted]'		This change has been made.
Page 63: The EAG states '…(PEACE CSR,33 p.112) and in the [redacted] (PEACE CSR, p.170)…'	Suggest rewording to …(PEACE CSR,33 p.112) and in the [redacted] (PEACE CSR, p.170)…'		This change has been made.
Page 76, Table 13: The EAG states 'The model assumes that there is no change in GMFCS state in the pegzilarginase group. For IDM, assumptions were made relating to the GMFM DE score at which GMFCS state changes and the decline in GMFM DE score per year to derive transition probabilities.'	Suggest to correct to 'The model assumes that there is no change in GMFCS state in the pegzilarginase group. For IDM, assumptions were made relating to the GMFM DE score at which GMFCS state changes and the decline in GMFM DE score per year to derive transition probabilities'		The space was removed.
Page 77: The EAG states 'The company states that: "This approach was chosen, firstly, because the larger data pool is likely to be more representative of clinical practice and more likely to	Suggest to correct to 'The company states that: "This approach was chosen, firstly, because the larger data pool is likely to be more representative of clinical practice and more likely to include all GMFCS health states at baseline" (CS,1 page 129).'		The space was removed.

include all GMFCS health states at baseline" (CS,1 page 129).'			
Page 79: The EAG states 'Once the thresholds were established, the average times taken to move through the GMFCS states were calculated based upon a linear regression of GMFM DE score and patient age,…'	Suggest to correct to 'Once the thresholds were established, the average times taken to move through the GMFCS states were calculated based upon a linear regression of GMFM DE score and patient age,…'		The space was removed.
Page 99: The EAG states 'In ERG report for HST 18, it was stated that "*Based on*…'	Suggest to correct to 'The EAG states 'In the ERG report for HST 18, it was stated that "*Based on*…'		This change had been made.
Page 102: The EAG states 'The EAG ran analyses assuming a) full drug wastage, where the 10% margin was removed and b) no drug wastage, where it was assumed that any drug left in a vial would be used on a subsequent patient.'	Suggest to correct to 'The EAG ran analyses assuming a) full drug wastage, where the 10% margin was removed and b) no drug wastage, where it was assumed that any drug left in a vial would be used on a subsequent patient.'		The space was removed.

Issue 16 Inaccurate definitions

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 29: The EAG states 'Other secondary outcomes were changes in ornithine and guanidino compounds (GC), GMFM-D (a measure of ability to stand) and Vineland Adaptive Behaviour Scale (VABS-II) (a measure of adaptive behaviour).'	Immedica notes that there are some instances whereby the EAG have provided the incorrect definition when providing an abbreviation. Immedica suggests to correct to 'Other secondary outcomes were changes in ornithine and guanidino compounds (GC), GMFM-D (a measure of ability to stand) and Vineland Adaptive Behaviour Scale, Second Edition (VABS-II) (a measure of adaptive behaviour).'	Immedica requests that the EAG updates the definitions prior to publishing the report.	This change has been made.
Page 83: The EAG states '…the company assumed that: the average of gross motor function classification metachromatic leukodystrophy (GMFC-MLD) scores 0 to 1 was generalisable to GMFCS-I;…'	As above, suggest to correct to '…the company assumed that: the average of Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD) scores 0 to 1 was generalisable to GMFCS-I;…'		This change has been made.
Page 86, Table 22: The EAG uses the following key in the table legend: GMFCS: Gross	Suggest to correct to 'GMFCS: Gross Motor Function Classification System; GMFC-MLD: Gross Motor		This change has been made.

Motor Function Classification System; GMFC-MLD: Gross Motor Function Classification Metachromatic Leukodystrophy	Function Classification in Metachromatic Leukodystrophy		
Page 108, Figure 13: The key provided by the EAG provides an incorrect definition for GMFCS	Suggest to correct to 'GMFCS: Gross Motor Function Measure Classification System.'		This change has been made.

Issue 17 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Throughout	Throughout the EAG report, there are a number of locations where commercial-in-confidence information has not been correctly marked up.	Immedica requests that confidentiality markup be added as per the suggestions in this column.	
Page 29	Studies 101A and 102A had similar baseline characteristics (see CS, Table 15). Of note, Study 102A had a higher mean age (15.7 years (SD 9.2)) compared to PEACE and lower pArg levels (309.2µM (SD 97.60)). Otherwise, baseline characteristics were similar.	Studies 101A and 102A had similar baseline characteristics (see CS, Table 15). Of note, Study 102A had a higher mean age ([redacted] years (SD [redacted])) compared to PEACE and lower pArg levels (309.2µM (SD	This change has been made.

		97.60)). Otherwise, baseline characteristics were similar.	
Page 31	The EAG notes that the 15% change to protein intake rule was not adhered to in all cases (34.4% broke protein intake restrictions in the pegzilarginase group, and 18.2% in the placebo group) during the double-blind period, and that this would be more likely to disadvantage treatment with pegzilarginase; the company noted that pArg level reductions were maintained despite the additional protein intake (roughly equivalent to a handful of nuts per day), and cited this as evidence of the efficacy of the treatment.	The EAG notes that the 15% change to protein intake rule was not adhered to in all cases (34.4% broke protein intake restrictions in the pegzilarginase group, and 18.2% in the placebo group) during the double-blind period, and that this would be more likely to disadvantage treatment with pegzilarginase; the company noted that pArg level reductions were maintained despite the additional protein intake (roughly equivalent to [redacted]), and cited this as evidence of the efficacy of the treatment.	This change has been made.
Page 36	In the LTE, the mean change from baseline in the pegzilarginase arm remained similar to that seen at week 24 [redacted] through to week LTE96 [redacted],	In the LTE, the mean change from baseline in the pegzilarginase arm remained similar to that seen at week 24 [redacted] through to week LTE96 [redacted], though	This change has been made.

	though numbers in the analysis were small at this time point (n=7).	numbers in the analysis were small at this time point (n=[redacted]).	
Page 36	This fall was maintained through to week 96 of the LTE, though numbers in the analysis were small at this time point (n=4). Only one patient remained on treatment at week 120.	This fall was maintained through to week 96 of the LTE, though numbers in the analysis were small at this time point (n=[redacted]). [redacted] remained on treatment at week 120.	This change has been made.
Page 36	The fall was maintained at week 144, with a mean change from baseline of [redacted], indicating that the reduction in pArg was maintained, and was numerically higher at week 240 [redacted] though numbers in the analysis were small at this time point (n=2).	The fall was maintained at week 144, with a mean change from baseline of [redacted], indicating that the reduction in pArg was maintained, and was numerically higher at week 240 [redacted] though numbers in the analysis were small at this time point (n=[redacted]).	This change has been made.
Page 37	The pooled (PEACE and Study 102A) mean change from baseline compared to placebo was -77.9%, which was consistent with -76.7% in PEACE.	The pooled (PEACE and Study 102A) mean change from baseline compared to placebo was [redacted], which was consistent with -76.7% in PEACE.	This change has been made.

Page 38, Table 8, Column 5, Row 4	n=8 Mean: [redacted]*** MCFB: [redacted] [redacted] ***	[redacted] Mean: [redacted]*** MCFB: [redacted] [redacted] ***	This change has been made.
Page 38, Table 8, Column 6, Row 4	n=4 Mean[redacted]*** MCFB: [redacted] ***	[redacted] Mean[redacted]*** MCFB: [redacted] ***	This change has been made.
Page 38, Table 8, Column 7, Row 4	n=1 Mean: [redacted]***	[redacted] Mean: [redacted]***	This change has been made.

Page 42	An improvement was maintained at week 96 (mean change from baseline [redacted] meters, n=10), through to week 120 of the LTE (mean change from baseline [redacted] meters) though numbers in the analysis were small (n=2) at this time point.	An improvement was maintained at week 96 (mean change from baseline [redacted] meters, n=[redacted]), through to week 120 of the LTE (mean change from baseline [redacted] meters) though numbers in the analysis were small (n=[redacted]) at this time point.	This change has been made.
Page 42	Upon switching to pegzilarginase, the placebo-pegzilarginase patients 2MWT had not improved after 24 or 48 weeks on treatment (mean change from baseline [redacted] and [redacted] meters), but had improved by LTE96 [redacted], and this was maintained/increased through to LTE120 (mean change from baseline [redacted] meters), though numbers in the analysis were small (n=2) at this time point.	Upon switching to pegzilarginase, the placebo-pegzilarginase patients 2MWT had not improved after 24 or 48 weeks on treatment (mean change from baseline [redacted] and [redacted] meters), but had improved by LTE96 [redacted], and this was maintained/increased through to LTE120 (mean change from baseline [redacted] meters), though numbers in the analysis were small (n=[redacted]) at this time point.	This change has been made.
Page 43	An improvement was maintained at week 96 (mean change from baseline [redacted] points, n=10), through to	An improvement was maintained at week 96 (mean change from baseline	This change has been made.

	week 120 of the LTE (mean change from baseline [redacted] points) though numbers in the analysis were small (n=3) at this time point.	[redacted] points, n=[redacted]), through to week 120 of the LTE (mean change from baseline [redacted] points) though numbers in the analysis were small (n=[redacted]) at this time point.	
Page 43	Upon switching to pegzilarginase, the placebo-pegzilarginase patients had very small improvements up to week 96 (MCFB range [redacted]), but greater numerical improvements were seen at week 120 (MCFB: [redacted]), though numbers in the analysis were small (n=3) at this time point.	Upon switching to pegzilarginase, the placebo-pegzilarginase patients had very small improvements up to week 96 (MCFB range [redacted]), but greater numerical improvements were seen at week 120 (MCFB: [redacted]), though numbers in the analysis were small (n=[redacted]) at this time point.	This change has been made.
Page 44	An improvement was maintained at week 96 (mean change from baseline ([redacted])) points, n=10), though was small at week 120 of the LTE (mean change from baseline [redacted] points) though numbers in the analysis were small (n=3) at this time point.	An improvement was maintained at week 96 (mean change from baseline ([redacted])) points, n=[redacted]), though was small at week 120 of the LTE (mean change from baseline [redacted] points) though numbers in the analysis were small (n=[redacted]) at this time point.	This change has been made.

Page 44	Upon switching to pegzilarginase, the pattern of improvement was similar to that seen in GMFM-D, in that improvements were small [redacted] up to week 120, when a more notable improvement was reported ([redacted]) though numbers in the analysis were small (n=3) at this time point.	Upon switching to pegzilarginase, the pattern of improvement was similar to that seen in GMFM-D, in that improvements were small [redacted] up to week 120, when a more notable improvement was reported ([redacted]) though numbers in the analysis were small (n=[redacted]) at this time point.	This change has been made.
Page 44	In the analysis pooling PEACE and Study 102A, reported in the company's response to clarification question A21, the LS mean difference at 24 weeks between the treatment groups was [redacted] with a p-value of [redacted] (p-value worsened compared to PEACE result [p=0.021]).	In the analysis pooling PEACE and Study 102A, reported in the company's response to clarification question A21, the LS mean difference at 24 weeks between the treatment groups was [redacted] with a p-value of [redacted] (p-value worsened compared to PEACE result [p=[redacted]]).	This change has been made.
Page 44	In PEACE, MAS was introduced as an outcome in a protocol amendment and was only measured for 12/32 (37.5%) patients.	In PEACE, MAS was introduced as an outcome in a protocol amendment and was only measured for [redacted]/32 ([redacted]) patients.	This change has been made.

Page 45	Amongst pegzilarginase GMFCS IV patients [redacted], values at week 24 are [redacted] compared to pegzilarginase GMFCS I-III patients in all outcomes but appear to be [redacted] over time in the LTE period.	Amongst pegzilarginase GMFCS IV patients (n=3), values at week 24 are [redacted] compared to pegzilarginase GMFCS I-III patients in all outcomes but appear to be [redacted] over time in the LTE period.	This change has been made.
Page 46, Table 9, Column 4, Row 6	n= 19 Mean [redacted] MCFB: [redacted]	[redacted] Mean [redacted] MCFB: [redacted]	This change has been made.
Page 46, Table 9, Column 5, Row 6	n= 18 Mean [redacted] MCFB: [redacted]	[redacted] Mean [redacted] MCFB: 8.3 (10.3)	This change has been made.

Page 46, Table 9, Column 6, Row 6	n= 10 Mean [redacted] MCFB: [redacted]	[redacted] Mean [redacted] MCFB: [redacted]	This change has been made.
Page 46, Table 9, Column 7, Row 6	n= 3 Mean [redacted] MCFB: [redacted]	[redacted] Mean [redacted] MCFB: [redacted]	This change has been made.
Page 46, Table 9, Column 8, Row 6	n= 6 Mean [redacted] MCFB: [redacted]	[redacted] Mean [redacted] MCFB: [redacted]	This change has been made.
Page 47, Table 9, Column 3, Row 10	n=[redacted] Mean [redacted] [redacted]	n=11 Mean [redacted] [redacted]	This change has been made.
Page 51	The EAG notes that, based on baseline and week 24 values, this is true on average for GMFM-D and -E, but not for	The EAG notes that, based on baseline and week 24 values, this is true on average for	This change has been made.

	the 2MWT, and where there was a deterioration, this was quite small (mean GMFM-E 46.5 (SD 24.6) at baseline compared to 46.1 (SD 25.7) at week 24; mean GMFM-D [redacted] at baseline compared to 28.2 (SD 13.28) at week 24).	GMFM-D and -E, but not for the 2MWT, and where there was a deterioration, this was quite small (mean GMFM-E 46.5 (SD 24.6) at baseline compared to 46.1 (SD 25.7) at week 24; mean GMFM-D 29.5 (SD12.42) at baseline compared to 28.2 (SD 13.28) at week 24).	
Page 52	However, clinical advisors were also of the opinion that patients with the most severe disease were unlikely to see their symptoms resolve completely, and this is reflected in patient [redacted] (see Figure 9).	However, clinical advisors were also of the opinion that patients with the most severe disease were unlikely to see their symptoms resolve completely, and this is reflected in patient [redacted] (see Figure 9).	This change has been made.
Page 53	The introduction of MAS as a protocol amendment means the group of patients was small (n=12 total). Results in the CS and in the CSR appear to only relate to 7 subjects in total (sum of n=5 and n=2 noted in the text relating to “improved scores”), making it difficult to draw any meaningful conclusions about the effect of pegzilarginase on spasticity from these results	The introduction of MAS as a protocol amendment means the group of patients was small (n=[redacted] total). Results in the CS and in the CSR appear to only relate to [redacted] subjects in total (sum of n=[redacted] and n=[redacted] noted in the text relating to “improved scores”), making it difficult to draw any meaningful conclusions about	This change has been made.

		the effect of pegzilarginase on spasticity from these results.	
Page 53	Since an MCID was not reported for this outcome, it is unclear whether the results, which appear numerically small (-0.16 on a scale ranging from 0 to 4) are clinically meaningful.	Since an MCID was not reported for this outcome, it is unclear whether the results, which appear numerically small ([redacted] on a scale ranging from 0 to 4) are clinically meaningful.	This change has been made.
Page 53, Table 11, Column 3, Row 4	[redacted] Total MCFB: [redacted] Physical: [redacted] Psychosocial: [redacted]	[redacted] Total MCFB: [redacted] Physical: [redacted] Psychosocial: [redacted]	This change has been made.
Page 64	Most patients reported at least one treatment-emergent adverse event (TEAE) (90.6%) in the double-blind period, and [redacted] did in the LTE period where patients were on treatment for longer.	Most patients reported at least one treatment-emergent adverse event (TEAE) (90.6%) in the double-blind period, and all (100%) did in the LTE period where patients were on treatment for longer.	This change has been made.

Pegzilarginase for treating arginase-1 deficiency. [Review of ID4029]

A Highly Specialised Technology evaluation

Appendix following an increase in the patient access scheme discount for pegzilarginase

Produced by	School of Health and Related Research (SCHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK Sunhong Kwon, Research Associate, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
Date completed	25/07/2024

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1 INTRODUCTION

This document (Sections 2, 3 and 4) replicates Tables 2, 3, 25, 33 and 34 in the EAG's report after the Factual Accuracy Check having incorporated the increase in Patient Access Scheme (PAS) discount for pegzilarginase after submission of the EAG report. The PAS, which is a simple discount, has been increased from [redacted] to [redacted]. The EAG also presents additional sensitivity analyses in Section 4, which could be considered by the Appraisal Committee, that resulted from discussions with NICE at the pre-meeting briefing (PMB). The first increases the average age of patients to 18 years and the second uses a different source for estimating utility.

Additionally, the EAG identified errors in Table 21 of the EAG's report,[1] which provided the values before the company updated its utility mapping to use Hernandez-Alava *et al*.[2] rather than Van Hout *et al*.[3] A corrected version is presented in Table 1. Table 20 in the EAG report also needed to be amended due to the change to the Hernandez-Alava *et al*.[2] mapping. The corrected version is provided in Table 2.

Table 1: Summary of the starting utility values for patients used in the company's base case excluding age-adjustments and decrements due to HACs

	GMFCS-I	GMFCS-II	GMFCS-III	GMFCS-IV	GMFCS-V
IDM					
Mild/no cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegzilarginase + IDM					
Mild/no cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe cognitive impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GMFCS: Gross Motor Function Classification System; IDM: Individualised Disease Management.

Table 2: Cognitive deficit by GMFCS health state

	Disutility Associated with		
Health State	**Moderate impairment**	**Severe impairment**	**Source**
GMFCS-I	0.24	0.53	Calculated from an Institute for Clinical and Economic Review report[4] on MLD
GMFCS-II	0.28	0.57	
GMFCS-III	0.28	0.49	
GMFCS-IV	0.16	0.17[2]	
GMFCS-V	0.12[1]	0.12[3]	

1 Original value 0.17; 0.12 used as the company assumes utility cannot be below -0.250
2 Original value 0.33; 0.17 used as the company assumes utility cannot be below -0.250
3 Original value 0.33; 0.12 used as the company assumes utility cannot be below -0.250
GMFCS: Gross Motor Function Classification System; MLD: metachromatic leukodystrophy.

2 The company's base case results

Table 3 updates Table 25 in the EAG's report. The company's base case with the updated PAS is above the £100,000 per QALY gained. In the PSA, no results produced a weighted ICER below £100,000 per QALY gained.

Table 3: The company's base case results

Treatment	**Total costs (£)**	**Total QALYs (patient; carers)**	**Inc Costs (£)**	**Inc QALYs**	**ICER (£)**	**Weighted ICER (£)**	**QALY weights**
Deterministic model, updated PAS							
Pegzilarginase	[redacted]	[redacted]	[redacted]	[redacted]	581,036	202,511	[redacted]
IDM	[redacted]	[redacted]					
Probabilistic model, updated PAS							
Pegzilarginase	[redacted]	[redacted]	[redacted]	[redacted]	568,635	202,647	[redacted]
IDM	[redacted]	[redacted]					

1 [redacted]
IDM: individualised disease management; Inc.: incremental; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

3 EAG exploratory analyses results

The results of the EAG's exploratory analyses are provided in Table 4 with QALY weights. The sensitivity analyses previously run are provided in Table 5.

Table 4: EAG exploratory analysis results (updated PAS)

Option	LYGs[1]	QALYs	Costs (£)	Inc. LYGs[1]	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£)		QALY weights
							Unweighted	Weighted	
The company's base case									
Pegzilarginase	48.14	[redacted]	[redacted]	43.54	[redacted]	[redacted]	581,036	202,511	[redacted]
IDM	4.59	[redacted]	[redacted]						
EA1 (Correction of error in IDM transition probabilities)									
Pegzilarginase	48.14	[redacted]	[redacted]	43.54	[redacted]	[redacted]	581,541	202,777	[redacted]
IDM	4.60	[redacted]	[redacted]						
EA2 (Assumed starting GMFM DE score for patients in GMFCS-I)									
Pegzilarginase	48.13	[redacted]	[redacted]	43.56	[redacted]	[redacted]	578,715	201,293	[redacted]
IDM	4.58	[redacted]	[redacted]						
EA3 (Using lower 95% CI for decrease in GMFM DE score when ageing one year)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	571,449	197,503	[redacted]
IDM	4.46	[redacted]	[redacted]						
EAG base case (EA1, EA2, and EA3 combined), deterministic									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	570,050	196,782	[redacted]
IDM	4.46	[redacted]	[redacted]						
EAG base case (EA1, EA2, and EA3 combined), probabilistic									
Pegzilarginase	48.41	[redacted]	[redacted]	42.64	[redacted]	[redacted]	558,411	197,659	[redacted]
IDM	5.77	[redacted]	[redacted]						

1 Undiscounted
2 [redacted]
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 5: EAG sensitivity analyses (updated PAS)

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£), unweighted	Incremental cost per QALY gained (£), weighted	QALY weights
EAG's base case									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	570,050	196,782	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA1a (risk of transition to the next worse GMFCS state is 10% of that associated with IDM)									
Pegzilarginase	47.39	[redacted]	[redacted]	42.93	[redacted]	[redacted]	660,361	290,084	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA1b (risk of transition to the next worse GMFCS state is 20% of that associated with IDM)									
Pegzilarginase	46.62	[redacted]	[redacted]	42.16	[redacted]	[redacted]	756,108	413,825	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA1c (remain in same health state after 2 years of pegzilarginase treatment)									
Pegzilarginase	48.01	[redacted]	[redacted]	43.55	[redacted]	[redacted]	607,880	223,560	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA1d (remain in same health state after 4 years of pegzilarginase treatment)									
Pegzilarginase	48.22	[redacted]	[redacted]	43.76	[redacted]	[redacted]	544,422	181,474	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA2 (distribution of cognitive impairment independent of treatment)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	595,814	214,499	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA3 (no utility gain from improved diet)									

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£), unweighted	Incremental cost per QALY gained (£), weighted	QALY weights
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	579,193	203,093	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA4a (full pegzilarginase wastage)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	604,664	208,731	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA4b (no pegzilarginase wastage)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	551,443	190,359	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA5 (starting distribution aligned with the European BOI study)									
Pegzilarginase	47.82	[redacted]	[redacted]	43.48	[redacted]	[redacted]	604,747	219,465	[redacted]
IDM	4.34	[redacted]	[redacted]						
SA6a (assuming nearly all patients died before 50 years of age for the calibration)									
Pegzilarginase	49.17	[redacted]	[redacted]	39.52	[redacted]	[redacted]	590,812	209,138	[redacted]
IDM	9.65	[redacted]	[redacted]						
SA6b (assuming a starting age of [redacted] years for the calibration)									
Pegzilarginase	48.07	[redacted]	[redacted]	43.92	[redacted]	[redacted]	567,728	195,504	[redacted]
IDM	4.15	[redacted]	[redacted]	0					
SA7 (using time in GMFCS health state based on midpoint GMFM DE scores)									
Pegzilarginase	48.13	[redacted]	[redacted]	43.68	[redacted]	[redacted]	580,493	202,208	[redacted]
IDM	4.45	[redacted]	[redacted]	0					
SA8 (adding a continuity correction to the peak ammonia levels data for HAC)									
Pegzilarginase	47.06	[redacted]	[redacted]	42.60	[redacted]	[redacted]	570,730	201,596	[redacted]
IDM	4.46	[redacted]	[redacted]	0					
SA9 (assuming no discontinuation of pegzilarginase treatment whilst alive)									

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£), unweighted	Incremental cost per QALY gained (£), weighted	QALY weights
Pegzilarginase	65.56	[redacted]	[redacted]	61.10	[redacted]	[redacted]	570,668	190,223	[redacted]
IDM	4.46	[redacted]	[redacted]	0					
SA10a (assuming a carer disutility of 0.062 for patients in GMFCS-III and above)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	559,359	189,134	[redacted]
IDM	4.46	[redacted]	[redacted]	0					
SA10b (assuming carer disutility from the BOI survey pooling GMFCS-IV and GMFCS-V)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	592,828	213,717	[redacted]
IDM	4.46	[redacted]	[redacted]						
SA11 (assuming double the SMR associated with pegzilarginase treatment)									
Pegzilarginase	44.28	[redacted]	[redacted]	40.38	[redacted]	[redacted]	564,433	208,685	[redacted]
IDM	3.89	[redacted]	[redacted]						
SA12 (removing QALY losses for carers when calculating the QALY weight)									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	570,050	191,530	[redacted]
IDM	4.46	[redacted]	[redacted]						

*Undiscounted

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

4 Summary of EAG's preferred assumptions and resulting ICER

Table 6 and Table 7 are replicates of Tables 2 and 3 in the summary section in the EAG's main report updated given the new PAS.

Table 6: The EAG's base case including QALY weighting (updated PAS)

Scenario	Incremental cost (£)	Incremental QALYs gained	QALY weights	Weighted cost per QALY gained (£)	Change from company's base case (£)
Deterministic model					
Company's base case	[redacted]	[redacted]	[redacted]	202,511	-
EA1 (Correction of error in IDM transition probabilities)	[redacted]	[redacted]	[redacted]	202,777	266
EA2 (Assumed starting GMFM DE score for patients in GMFCS-I)	[redacted]	[redacted]	[redacted]	201,293	-1218
EA3 (Using lower 95% CI for decrease in GMFM DE score when ageing one year)	[redacted]	[redacted]	[redacted]	197,503	-5008
EAG base case (EA1, EA2 and EA3 combined)	[redacted]	[redacted]	[redacted]	196,782	-5729
Probabilistic model					
Company's base case	[redacted]	[redacted]	[redacted]	202,647	-
EAG base case	[redacted]	[redacted]	[redacted]	197,659	-4988

1
2 [redacted]

CI: confidence interval; GMFCS: Gross Motor Function Measure; GMFM: Gross Motor Function Measure; IDM: individualised disease management; LYG: life year gained; QALY: quality-adjusted life year

Table 7: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results (updated PAS)

Scenario	Incremental cost (£)	Incremental QALYs	QALY weights	Weighted cost per QALY (£)	Change from EAG's base case (£)
EAG's base case	[redacted]	[redacted]	[redacted]	196,782	-
SA1a (risk of transition to the next worse GMFCS state is 10% of that associated with IDM)	[redacted]	[redacted]	[redacted]	290,084	93,302
SA1b (risk of transition to the next worse GMFCS state is 20% of that associated with IDM)	[redacted]	[redacted]	[redacted]	413,825	217,043
SA1c (remain in same health state after 2 years of pegzilarginase treatment)	[redacted]	[redacted]	[redacted]	223,560	26,778
SA1d (remain in same health state after 4 years of pegzilarginase treatment)	[redacted]	[redacted]	[redacted]	181,474	-15,308
SA2 (distribution of cognitive impairment independent of treatment)	[redacted]	[redacted]	[redacted]	214,499	17,717
SA3 (no utility gain from improved diet)	[redacted]	[redacted]	[redacted]	203,093	6,312
SA4a (full pegzilarginase wastage)	[redacted]	[redacted]	[redacted]	208,731	11,949
SA4b (no pegzilarginase wastage)	[redacted]	[redacted]	[redacted]	190,359	-6,423
SA5 (starting distribution aligned with the European BOI study)	[redacted]	[redacted]	[redacted]	219,465	22,684
SA6a (assuming nearly all patients died before 50 years of age for the calibration)	[redacted]	[redacted]	[redacted]	209,138	12,356
SA6b (assuming a starting age of 13 years for the calibration)	[redacted]	[redacted]	[redacted]	195,504	-1,277
SA7 (using time in GMFCS health state based on midpoint GMFM DE scores)	[redacted]	[redacted]	[redacted]	202,208	5,427
SA8 (adding a continuity correction to the peak ammonia levels data for HAC)	[redacted]	[redacted]	[redacted]	201,596	4,815

Scenario	Incremental cost (£)	Incremental QALYs	QALY weights	Weighted cost per QALY (£)	Change from EAG's base case (£)
SA9 (assuming no discontinuation of pegzilarginase treatment whilst alive)	[redacted]	[redacted]	[redacted]	190,223	-6,559
SA10a (assuming a carer disutility of 0.062 for patients in GMFCS-III and above)	[redacted]	[redacted]	[redacted]	189,134	-7,648
SA10b (assuming carer disutility from the BOI survey pooling GMFCS-IV and GMFCS-V)	[redacted]	[redacted]	[redacted]	213,717	6,935
SA11 (assuming double the SMR associated with pegzilarginase treatment)	[redacted]	[redacted]	[redacted]	208,685	11,903
SA12 (removing QALY losses for carers when calculating the QALY weight)	[redacted]	[redacted]	[redacted]	191,530	-5,252

5 EAG's additional analyses after the Pre-Meeting Briefing

During the PMB meeting, NICE commented that the age of the patients in the company's and EAG's base case could be too low and additionally that the absolute values of EQ-5D used in more severe health states were lower than typically seen by NICE. The EAG therefore ran two additional sensitivity analyses to inform the committee (SA13 and SA14).

5.1 SA13 Uncertainty around the age of the patients

The EAG explored the impact on the ICER of using a starting age of 18 years old rather than 13 years old.

5.2 SA14 Uncertainty around utility from the burden of illness study

The EAG ran a scenario analysis with utility values from Ryan *et al*.[5] This study used the EQ-5D-Y instrument which was completed with patients with cerebral palsy. The values for sensitivity analysis are presented in Table 8 to allow comparison with the base case values.

Table 8: Alternative base utility values

Health State	Base-case	EAG sensitivity analysis (values from Ryan et al. [5])
GMFCS-I	[redacted]	0.82
GMFCS-II	[redacted]	0.75
GMFCS-III	[redacted]	0.39
GMFCS-IV	[redacted]	0.14
GMFCS-V	[redacted]	0.03

The results of these sensitivity analyses are provided in Table 9 and in Table 10.

Table 9: EAG sensitivity analyses (updated PAS)

Option	LYGs*	QALYs	Costs (£)	Inc. LYGs *	Inc. QALYs	Inc. costs (£)	Incremental cost per QALY gained (£), unweighted	Incremental cost per QALY gained (£), weighted	QALY weights
SA13 (Using a starting age of 18 years)									
Pegzilarginase	45.37	[redacted]	[redacted]	42.64	[redacted]	[redacted]	557,132	201,354	[redacted]
IDM	2.73	[redacted]	[redacted]						
SA14 (Utility from Ryan *et al.*[5])									
Pegzilarginase	48.12	[redacted]	[redacted]	43.66	[redacted]	[redacted]	566,727	193,127	[redacted]
IDM	4.46	[redacted]	[redacted]						

*Undiscounted

IDM: Individualised disease management. LYG: life year gained; SA: sensitivity analysis; QALY: quality-adjusted life year

Table 10: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results (updated PAS)

Scenario	Incremental cost (£)	Incremental QALYs	QALY weights	Weighted cost per QALY (£)	Change from EAG's base case (£)
EAG's base case	[redacted]	[redacted]	[redacted]	196,782	-
SA13	[redacted]	[redacted]	[redacted]	201,354	4572
SA14	[redacted]	[redacted]	[redacted]	193,127	-3654

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