National Institute for Health and Care Excellence

Health Technology Evaluation

Pegzilarginase for treating arginase-1 deficiency [ID4029]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	British Inherited Metabolic Disorders Group (BIMDG)	This should be evaluated as a highly specialised technology (HST) because: 1. Rarity of the condition –22 patients in England&Wales have been identified with the condition treated within a small number of specialist metabolic centres 2. Chronic progressive neurodebilitating condition causing significantly shortened life expectancy 3. Existing treatments are of limited efficacy in altering the disease course and are therefore unsatisfactory	Thank you for your comment. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.
	Genetic Alliance UK	We believe Pegzilarginase is eligible for HST routing and therefore we would like some clarity as to why it has been routed via an STA. Arginase-1 deficiency is a very rare, severe condition with an unmet need and therefore would be disadvantaged going through an STA pathway. See our comments below for more details.	Thank you for your comment. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's

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		It would be useful to understand whether the treatment's status as an 'add on' has contributed to the routing decision result, as we discuss below this label appears to be applied inconsistently.	Highly Specialised Technology program.
	Immedica Pharma	Pegzilarginase, for the treatment of arginase-1 deficiency (ARG1-D), clearly meets all four highly specialised technology criteria as set out in the response to the HST criteria checklist. ARG1-D is a rare and debilitating condition, with limited treatment options. An approved treatment option for patients with ARG1-D is long-awaited for those living with the condition, and their families. Arginine is an amino acid that plays an important part in NH3 removal from the body and is a precursor of nitric oxide (NO), which is responsible for maintaining vascular homeostasis and other physiological functions (1). All patients with ARG1-D have a defective arginase 1 (ARG1) enzyme, with low or absent activity levels. In the absence of functional ARG1 enzyme, arginine, and arginine-related metabolites, guanidino compounds (GCs), accumulate in patients with ARG1-D (2,3) The specific genetic defect in the ARG1 enzyme leads to increased arginine in the liver. Increased arginine is the primary causal component that drives elevations in those downstream contributors to disease pathogenesis, such as GCs, and NO which have been implicated in CNS neuromotor changes associated with spasticity and seizures. Pegzilarginase represents the first potential enzyme therapy for patients with ARG1-D by substituting for the deficient human ARG1 enzyme activity in these patients. Pegzilarginase has been shown to rapidly and sustainably	Thank you for your comment. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.

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		reduce plasma arginine and convert it to urea and ornithine. This cannot be achieved with current treatment options.	
	Metabolic Support UK	We strongly feel that the Highly Specialised Technology appraisal route would be the most appropriate routing for this topic. We feel that Arginase deficiency fits this criteria required for this routing. There are less than 40 cases in the UK* which means the number of patients falls well under the threshold set for this routing option. Current treatment for the condition remains symptomatic and supportive, alongside dietary management and ammonia scavangers. Spasticity is problematic and develops into severe mobility problems leaving patients reliant on wheelchairs and illnesses can leave patients bedbound for many weeks. Arginase deficiency severely impacts quality of life and is associated with a shortened life span due to complications of the condition and hyperammonaemia. *Arginase 1 Deficiency: using genetic databases as a tool to establish global prevalence | Orphanet Journal of Rare Diseases | Full Text (biomedcentral.com)	Thank you for your comment. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program..
Wording	British Inherited Metabolic Disorders Group (BIMDG)	The scope needs to take into account the cost of standard therapy in terms of health and social care resource 1. Prescription diet requires lifelong specialist dietitian oversight, prescription foods and specially formulated feeds, in some cases via gastrostomy tube; also to consider the burden of standard therapy and its impact on patients' and carers' quality of life 2. Standard treatment is not fully effective in preventing recurrent hospital admissions for acute metabolic decompensation 3. Standard treatment is not effective in preventing progressive neurological and cognitive deterioration necessitating multiple specialist appointments (neurology, metabolic, neurophysiology, epilepsy). Additional measures to	Thank you for your comment. No action required.

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		manage spasticity may include baclofen pump and regular botox injections. 4. Patients are dependent on others for many or all aspects of daily living because of progressive physical and intellectual disability	
	Genetic Alliance UK	Further detail on the choice to label this treatment as an 'add-on' would be helpful. The scope refers to the Market Authorisation as the source, which is not yet secured. The clinical trials use 'individual disease management' as a further aspect of treatment for all participants including in the placebo arm. The draft scope did not appear to clearly state to what this medicine is additional. We are concerned that the term 'add-on' appears to imply that the medicine is used alongside another specific branded medicine. If this medicine is used additionally to individual disease management, rather than a separate branded medicine, then the 'add on' label might portray this medicine in a weaker light than deserved. It is our understanding that most medicines for metabolic conditions are provided in the context of individual disease management, though we have not seen these medicines labelled as 'add ons' in the past.	Thank you for your comment. The wording has been updated to reflect to reflect the feedback heard at the scoping workshop and from consultation. *'Add on'* has been removed and the wording has been replaced with *'Pegzilarginase for treating arginase-1 deficiency'.*
	Immedica Pharma	Immedica considers that the proposed wording of the draft remit does not fully reflect the proposed indication. The proposed indication is for the treatment of Arginase 1 Deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older. The inclusion of the phrase "as an add-on treatment" does not clarify the base offering (which is assumed to be standard of care). Immedica	Thank you for your comment. The wording has been updated to reflect to reflect the feedback heard at the scoping workshop and

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		proposes that the wording be changed to state that pegzilarginase is used in conjunction with individualised disease management such as dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers.	from consultation. *'Add on'* has been removed and the wording has been replaced with *'Pegzilarginase for treating arginase-1 deficiency'.*
	Metabolic Support UK	N/A	No action needed.
Timing Issues	British Inherited Metabolic Disorders Group (BIMDG)	There is a significant unmet need in these patients who generally do not meet treatment targets with current standard therapy and would therefore benefit from additional treatment when available. The new therapy may in many cases reduce morbidity and mortality.	Thank you for your comment. No action required.
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	As outlined, current treatment options do not address the underlying increased arginine levels associated with ARG1-D, and patients continue to deteriorate in their disease progression. Manifestations of ARG1-D are both severely debilitating and progressive, with patients at increased risk of early death and seizures. ARG1-D usually progresses to severe spasticity with complete loss of ambulation, complete loss of bowel and bladder control, and severe intellectual disability (4). Patients with ARG1-D may die early (5–7), and as such, the timely introduction of an effective treatment option to halt disease progression and to improve clinical outcomes is crucial for patients.	Thank you for your comment. In any appraisal NICE aims to publish guidance as close as possible to the granting of a marketing authorisation. No action needed.

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	Metabolic Support UK	N/A	No action needed.
Additional comments on the draft remit	British Inherited Metabolic Disorders Group (BIMDG)	N/A	No action needed.
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	N/A	No action needed.
	Metabolic Support UK	N/A	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Inherited Metabolic Disorders Group (BIMDG)	Section 'background' paragraph 1 – we do not generally refer to nitrogen being 'stored in the body in the form of ammonia'. Suggest rewording to 'the lack of arginase leads to an excess of arginine in blood and CSF, and can impair urea cycle function leading to hyperammonaemia'. Newborn screening is not currently a relevant consideration for the UK (we are not currently screening for this condition)	Thank you for your comment. The text in the background information section has been amended as suggested following feedback from the consultation and that heard at the scoping workshop.

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		The treatment involves a protein-restricted diet but in practice it is extremely difficult to achieve target plasma arginine levels (<200 umol/L) with this diet alone. The degree of protein restriction required is often severe and the diet is very challenging. Dietary management includes the use of amino acid supplements and medically prescribed low protein foods. There is also the potential for acute metabolic decompensation, particularly post-adolescence. Therefore treatment also involves the use of a glucose-polymer based emergency regimen and ammonia scavenging medication at times of illness. Liver transplantation is a potential therapeutic option for selected individuals but there are risks associated with surgery and with long term immunosuppression High blood and CSF arginine level is toxic to the neurological system causing progressive impaired motor and intellectual function. The background information does not touch on the burden of the illness and its treatment for patients and carers or the limitations of existing standard treatment ie. 1. Leg weakness and spasticity causes reduced mobility and patients are usually wheelchair-bound. Intellectual and physical disability results in a lifelong dependence on others for many or all aspects of daily living. 2. High blood arginine is toxic to the liver causing progressive liver dysfunction and hyperammonaemia. High ammonia can lead to acute decompensation with encephalopathy and is potentially life-threatening. Standard treatment is not fully effective in preventing recurrent hospital admissions for metabolic decompensation associated with hyperammonaemia. 3. Existing treatment to lower arginine involves a following a prescription diet which requires lifelong oversight from a specialist dietitian, prescription foods and specially formulated feeds, in some cases via gastrostomy tube;	

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		also to consider the burden of following the diet and its impact on patients' and carers' quality of life 4. Standard treatment for spasticity may include physiotherapy, splints and adapted footwear, baclofen pump and/or botox injections 5. Standard care involves multiple appointments with medical and allied healthcare professionals	
	Genetic Alliance UK	The severity of the condition hasn't been fully captured in the scope. We have been informed by our member organisation Metabolic Support UK that this condition has been shown to significantly shorten life and significantly impair quality of life. They have experience of families where the condition has led to severe disability, multiple hospital stays, transplants and has been fatal for at least one of their affected families. We believe this would satisfy the third criteria for HST routing. We also understand that affected individuals often receive misdiagnoses before being diagnosed with arginase deficiency as it has overlapping symptoms with other urea cycle disorders, therefore effective treatment as soon as a correct diagnosis is found is imperative.	Thank you for your comment. The background information has been amended to reflect the feedback from the consultation and that heard at the scoping workshop.
	Immedica Pharma	The information presented in the background section of the draft scope generally appears accurate, although there are some key points that Immedica feels should be adjusted to properly represent the disease background. 1. Toxicity of arginine: it is important to note that excess arginine in the blood and cerebrospinal fluid (as acknowledged in the scope) plays an important role in ARG1-D, as patients with elevated plasma arginine experience progressive disease and multiple disease manifestations (6,8–10). In addition, cumulative arginine exposure is correlated with deterioration in select neuropsychological outcomes in patients with ARG1-D (11)	Thank you for your comment. The background information has been amended to reflect the feedback from the consultation and that heard at the scoping workshop.

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		2. Screening for ARG1-D is not part of the NHS newborn screening programme. The sensitivity of newborn screening for ARG1-D is unknown with a risk of false negative values as arginine levels may be within the normal range the first days of life (12) 3. Current treatment options only address the symptoms of ARG1-D. In addition to the treatment options in the draft scope, patients with ARG1-D may also be treated with antiepileptics for seizures, undergo surgery or receive botulinum toxin for spasticity (4).	
	Metabolic Support UK	Hyperammonaemia is only mentioned in the first paragraph. We are keen to ensure that there is a clear emphasis on the impact of hyperammonaemia and it's symptoms. Symptoms of hyperammonaemia include: vomiting, irritability, poor feeding, failure to thrive, and weak muscle tone (appearing floppy). In those older, symptoms are more neurological in presentation with behaviour changes, lethargy, and encephalopathy. Symptoms for any age if untreated can progress to seizures, coma and can quickly become life-threatening. We are keen to ensure hyperammonaemia is not overlooked in this review. This is a complex condition. It needs to be clear in the text that the treatments listed do not resolve symptoms of Arginase deficiency, they aim to slow progression and manage ammonia levels reducing crises. Despite maintaining a low protein diet with supplementation and ammonia scavenger treatments those patients we support have still progressed to develop spasticity and severe mobility problems with long periods of complete immobility following illness or falls. Patients have an emergency regimen to follow if they become unwell or are unable to tolerate food, this is in the form of a glucose polymer. If symptoms	Thank you for your comment. The background information has been amended to reflect the feedback from the consultation and that heard at the scoping workshop.

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		persist, worsen, or if the patient is unable to tolerate this then immediate medical intervention must be sought and IV treatment started.	
Population	British Inherited Metabolic Disorders Group (BIMDG)	Yes	Thank you for your comment. No action required.
	Genetic Alliance UK	The population numbers stated in the scope - estimated UK population prevalence of 0.58 cases per million which would equate to approximately 40 people in the UK – demonstrate the rarity of this condition and the numbers are small enough to meet the first two criteria for HST routing.	Thank you for your comment. No action required.
	Immedica Pharma	Based on the available trial data to date, and anticipated regulatory indication (stated below), the population should be amended to acknowledge that pegzilarginase will only be used in patients suffering from ARG1-D who are 2 years and older. Proposed indication: Pegzilarginase is indicated for the treatment of Arginase 1 Deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older.	Thank you for your comment. The final scope has been updated to include 'aged 2 years and older' in line with the marketing authorisation for pegzilarginase.
	Metabolic Support UK	N/A	No action needed.
Subgroups	British Inherited Metabolic Disorders Group (BIMDG)	Suggest considering children and adults/adolescents separately. Clinical experience of looking after sibships with arginase deficiency shows that initiating treatment very early in life (as seen in prospectively treated	Thank you for your comment. After discussion at the scoping workshop, the subgroups were

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		younger siblings) leads to improved intellectual development and motor function. Initiating treatment in adolescence or adulthood (after brain development is complete) may not improve cognitive / intellectual outcomes. Initiating treatment in adolescence or adulthood may still prevent progressive loss of mobility with its associated implications for dependence on carers. Clinical experience suggests hyperammonaemic decompensation is more common in adults and adolescents than in younger children. Therefore initiating treatment in adulthood may help to reduce recurrent hospital admissions with hyperammonaemia.	removed from the scope.
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	Immedica does not believe subgrouping by age is appropriate due to the rarity of the disease with only 20 known patients in England and lack of sufficient data to support further subgrouping.	Thank you for your comment. After discussion at the scoping workshop, the subgroups were removed from the scope.
	Metabolic Support UK	N/A	No action needed.

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Comparators	British Inherited Metabolic Disorders Group (BIMDG)	Comparators are the standard treatment as listed. Liver transplantation is not a standard treatment but there are increasing numbers of case reports of utility in arginase I deficiency.	Thank you for your comment. No action required.
	Genetic Alliance UK	The comparators stated in the draft scope demonstrate the lack of condition specific treatments available for this condition. Current treatments consist of a restrictive diet, amino acid supplements and ammonia scavenger medicines, therefore pegzilarginase is a novel treatment as it is the only one that looks to treat the lack of arginase enzyme. This indicates that there is an unmet need for people living with arginase deficiency and therefore would meet the fourth and final criteria for HST routing.	Thank you for your comment. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.
	Immedica Pharma	Immedica does not consider the treatments listed in the draft scope to be comparators. There are currently no available treatments that address the high arginine levels. Pegzilarginase is the first treatment to target the underlying cause of the disease. Current standard of care (including dietary protein restrictions, essential amino acid supplementation and/or the use of ammonia scavengers) only treats symptoms of ARG1-D.	Thank you for your comment. No action required.
	Metabolic Support UK	N/A	No action needed.
Outcomes	British Inherited Metabolic Disorders Group (BIMDG)	For a subgroup of patients we see morbidity from hyperammonaemia. Outcomes such as ammonia levels, frequency/length of hospitalisation, ICU admission frequency, will be relevant. Arginine and ornithine concentrations are biochemical markers relevant to the chronic neurological manifestations (seizures, progressive spasticity, learning	Thank you for your comment. No action required.

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		difficulties). Normalisation of arginine and ornithine would be expected stabilise these neurological features. Measurement of guanidino compounds (though theoretically relevant) is not routinely available on the NHS and interpretation of results problematic and poorly understood. A potential benefit of pegzilarginase is to enable relaxation of the low protein diet ie. to allow increased dietary protein intake which would also be expected to improve muscle strength, mobility and quality of life. Functional assessments of mobility and impact on quality of life and adaptive behaviour will be more clinically relevant markers of treatment efficacy than surrogate biochemical markers (arginine, ornithine).	
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	Yes, the outcomes listed are appropriate. In addition, we highlight the below: As ARG1-D is a disease affecting children from a young age, and the clinical symptoms result in functional disability and impairment of activities of daily living, placing a significant burden on caregivers and family that should be considered in addition to the patient burden. [redacted] (13). There is limited data on caregiver burden in ARG1-D, but studies in other metabolic diseases report that the quality of life for both parents and caregivers is affected by dietary restrictions, even to a higher extent than taking medications (14–16). Neurocognition is another outcome measure to be considered.	Thank you for your comment. The list of outcomes is not exhaustive. Caregiver burden is captured under 'health-related quality of life' outcome. The final scope has been updated to include 'Neurocognitive function'.

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	Metabolic Support UK	For the families of the patients we have spoken to, there are recurrent experiences of hyperammonaemia and we would support it as an outcome measure, however we would welcome clinical opinion on this matter.	Thank you for your comment. No action required.
Equality	British Inherited Metabolic Disorders Group (BIMDG)	The scope should take into account the ethnicity of the UK patient population with arginase deficiency and the economic and quality of life impact of being a patient or carer of a patient with intellectual and physical disabilities	Thank you for your comment. The appraisal committee will consider the impact of its recommendations on protected characteristics as stated in equality legislation during the appraisal. No action required.
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	Immedica is not aware of any relevant equality issues relating to this remit and scope.	Thank you for your comment. No action required.
	Metabolic Support UK	N/A	No action needed.
Other considerations	British Inherited Metabolic Disorders Group (BIMDG)	N/A	No action needed.
	Genetic Alliance UK	N/A	No action needed.

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	Immedica Pharma	N/A	No action needed.
	Metabolic Support UK	N/A	No action needed.
Questions for consultation	British Inherited Metabolic Disorders Group (BIMDG)	Confirmation of molecular diagnosis by genetic testing is routine. Where will pegzilarginase fit in to existing care pathway? In our experience the majority of patients do not achieve target arginine levels with standard therapy and it could be considered a potential first-line therapy. If used as an adjunct for patients already on standard therapy, we would seek to liberalise dietary restrictions and ammonia scavenging medication. Managed access agreement: potentially suitable – neurological outcomes are anticipated to be a major benefit of treatment but may take many years to become evident if at all. Neurological outcomes should be monitored part of a MAA; it'd be important to understand the natural course of the condition in a population not treated with pegzilarginase for comparison because we don't yet know if pegzilarginase would halt neurological decline completely or slow its progression. Alternatively if the time course is too long for a MAA there could be defined stop criteria if neurological decline progresses despite pegzilarginase. Not all patients develop hyperammonaemia but for those who do have a history of decompensations, a change in the frequency/severity of these would be relevant.	Thank you for your comment. No action required.

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		Other health-related benefits might potentially include: liberalisation / normalisation of diet; reduced need for specialist dietetic support and prescription products (lifelong); reduced hospital admissions / ICU beds with decompensations; reduced need for physiotherapy/OT/home adaptations for mobility issues; ability to remain in mainstream education and/or employment	
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	**What is the prevalence of arginase-1 deficiency in England?** ARG1-D is a condition with different country specific estimates of prevalence. However, it is most accurate to use country level data as consanguinity rates are higher in the UK than in some other EU countries. (13) ARG1-D is rare and debilitating, and is estimated to occur in 0.58 cases per million (0.03 per 50,000) in the UK, in accordance with most recent literature (17). As stated in the draft scope, the anticipated label for pegzilarginase is for patients 2 years and older with ARG1-D. Immedica is aware from market research with key centres of a total of 20 known patients in England. (13) The estimated prevalence from Catsburg et al. (2022) noted above and used to support HST criteria 1 would equate to a total of 33 patients eligible to receive pegzilarginase in England, which could be understood to represent a maximum number of potential patients in England above the 20 known to Immedica. **Is it routine to perform a genetic test in the NHS to confirm diagnosis of arginase-1 deficiency?** ARG1-D can be confirmed using ARG1 enzyme activity assays in red blood cells, by molecular genetic testing, or by use of a multi-gene panel that includes ARG1 (8,18).	Thank you for your comment. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program. No action needed.

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		Genetic testing is routinely used to confirm diagnosis of ARG1-D in England, as supported by structured clinical interviews conducted by Immedica (13). **Where do you consider pegzilarginase will fit into the existing care pathway for arginase-1 deficiency?** Pegzilarginase is expected to be indicated for the treatment of Arginase 1 Deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older. **Would pegzilarginase be a candidate for managed access? Would hyperammonemic episodes/crises be considered a key outcome measure?** Yes, Immedica considers Pegzilarginase a candidate for managed access. Immedica does not consider hyperammonaemic episodes to be a key outcome measure. Severe hyperammonaemia observed in other urea cycle defects is rarely observed in patients with ARG1-D. Although ARG1-D has overlapping features with other urea cycle disorders, it has distinct characteristics and manifestations – severe hyperammonaemia is rare (triggered by physiological stress e.g. injections, food refusal). (7,9,12) **Do you consider that the use of pegzilarginase can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** N/A **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** N/A	

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		Other As noted above, pegzilarginase for the treatment of ARG1-D in patients 2 years or older should be assessed under the NICE HST programme rather than the STA process. This topic meets all the HST criteria (according to HST methods process and guide). Specifically: **1. The condition is very rare defined by 1:50,000 in England** Immedica believes that pegzilarginase meets all four highly specialised technology criteria for the treatment of arginase-1 deficiency (ARG1-D). As highlighted in both the HST criteria checklist and the draft scope, ARG1-D is a rare and debilitating condition, estimated to occur in 0.58 cases per million (0.03 per 50,000) in the UK, in accordance with most recent literature (17). **2. Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications** The prevalence rate (0.06 in 10,000 people) stated in the NICE HST criteria checklist is based on information submitted for the EMA orphan designation, and would result in a calculated number of 320 eligible patients in England. At the time of application, following extensive literature searches, no articles specific to ARG-1 D prevalence were identified. Searches therefore focused on UCDs and inborn errors of metabolism, using numbers diagnosed with ARG1-D from these subsets where data was available to calculate prevalence. Prevalence per 10,000 was estimated in 5 countries (Spain, Finland, Italy, UK, Portugal) as 0.002-0.06 per 10,000, the highest of which was used for this estimate, as it still fell below the orphan designation threshold of 5/10,000.	

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		The actual prevalence and incidence of ARG1-D is much lower in reality. ARG1-D accounts for a small proportion of urea cycle disorders (UCDs). Applying the US incidence rate (1:35,000 births) to live births in England and Wales (based on 624 ,828 live births recorded in 2021 (19)) results in 18 patients born with UCDs each year. Estimates for the incidence of UCDs in Europe (Spain, Germany, Austria and Switzerland) would result in an even smaller number of patients if applied to England. ARG1-D represents only 2-3% of all UCDs, which would equate to less than a single patient being born per year (20–22) Since the original application for orphan designation, Catsburg et al. (2022) has published the prevalence of ARG1-D as 0.58 cases per million (17), which will also be used to support the orphan maintenance report. As stated in Catsburg et al. (2022), it is also more accurate to use country level data for country estimates, as consanguinity rates are higher in the UK than in some other EU countries (17). With regards to the incidence of ARG1-D, the draft scope states an incidence of 1 in 300,000 to 1,000,000 live births, which would equate to a maximum of 2 new patients a year in England and Wales (based on 624 ,828 live births recorded in 2021 (19)). As stated in the draft scope, the anticipated label for pegzilarginase is for patients over 2 years and older with ARG1-D. Immedica is aware from market research with key centres of a total of 20 known patients in England. (13) The estimated prevalence from Catsburg et al. (2022) noted above and used to support HST criteria 1 would equate to a total of 33 patients eligible to receive pegzilarginase in England, which could be understood to represent a maximum number of potential patients in England above the 20 known to Immedica.	

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		Even with some patients remaining undiagnosed, this data would suggest that pegzilarginase clearly meets HST criteria #2, i.e. that “no more than 300 people in England are eligible for the technology in its licensed indication..”. **3. The very rare condition significantly shortens life or severely impairs its quality** ARG1-D is a rare, debilitating, progressive, inherited, neurotoxic, metabolic disease associated with increased arginine and its metabolites, with significant reductions in quality of life, increased morbidity, and premature mortality (7,11,18,22). Neuromotor complications of the disease are a hallmark feature of ARG1-D. The clinical picture is characterized by spasticity, gait disorders, difficulties in walking and climbing stairs, and developmental and cognitive disability, with some patients having seizures, although variation in timeframe and progression of symptoms has been observed between patients (2,11,23). Approximately 60% to 75% of the patients typically present with some form of lower limb spasticity at initial presentation which increases with extended follow-up (6,9). This progressive spastic diplegia results in increasing immobility, inability to perform activities of daily living, and increased caregiver burden. Patients with ARG1-D may experience issues such as growth impairment, progressive stiffness and lack of control of voluntary movements of the legs, as well as slowed cognitive development, severe spasticity, an inability to walk, loss of bowel and bladder control, and severe intellectual disability. Many patients also experience seizures. As discussed in section 4 of this document, there are no pharmacological agents known to effectively reduce arginine level in patients with ARG1-D, and no agents have been approved that specifically target the enzyme deficiency.(24)	

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		Patients with ARG1-D therefore show persistent hyperargininaemia with continued disease progression despite the use of individualised disease management (IDM).(24) A systematic literature review reported the proportion of patients with various manifestations of disease, suggesting that of patients receiving best supportive care, 84.8% had intellectual disability, 81.3% had spasticity, 70.7% had motor deficits, 60.3% experienced seizures, 49.3% had developmental delays, 13.2% had adaptive behaviour issues, and 6.5% had impaired balance or ataxia. These studies indicate a large impact on patients' lives despite the availability of current treatments.(25) A case study review showed that some patients on comparable treatments to those described in the draft scope continued to decline on treatment, with 30.6% of patients hospitalised, and 10.2% (16 patients) dying of various causes.(26) Similarly, an analysis of baseline data from the phase I/II data for pegzilarginase (27), showed that even with current individualised disease management (IDM; severe protein restriction, essential amino acid supplementation, and the use of nitrogen scavengers), mean plasma arginine and clinically relevant disease-related abnormalities were observed at baseline in all enrolled subjects. The analysis further demonstrated that a majority of patients had detectable deficits in neuromotor, neurocognitive, and/or adaptive behaviour at baseline in spite of IDM treatment. As an example of these deficits at baseline, 14 of the 16 patients evaluated (87.5%) had a deficit at baseline in the 6-minute walk test (6MWT). Spasticity is a common manifestation that impacts mobility and balance. The average baseline value for the 2-minute walk test (2MWT) in PEACE is 106	

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		meters. Comparing baseline 2MWT for individual patients with what has been reported for healthy children of the same sex and age show that patients in PEACE in average can walk 63% of the distance compared to healthy children (varying between 13% and 104%).(28) It is also important to note that patients with ARG1-D may die early (5–7). In a literature review, including 140 patient cases, 20 patients had died at the time of the report (median age at time of death was 17.0 years) (10) In another systematic review of case reports by Bin Sawad et al (2022), at time of publication, 10% (16 patients) of reported patients in this sample were deceased (median age 5.7 years). The reported causes of death included cardiac arrest, cerebral oedema, pneumonia/respiratory complications, and/or sepsis (26). In a UK-based retrospective review of medical records from a single centre, two of six patients included died following severe metabolic decompensation in adolescence (24) The oldest patient in the phase III PEACE trial was 29 years old (included patients were 2 years or older), supporting the point that there are few patients surviving into adulthood with ARG1-D (28). **4. There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.** There are no licensed treatment options for ARG1-D known to effectively reduce arginine levels in patients with ARG-1, and no agents have been approved that specifically target the enzyme deficiency (24).	

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		Current management for ARG1-D only includes blood testing and severe dietary protein restrictions for dealing with high arginine levels, with oral nitrogen scavenging therapies targeting the high ammonia levels that are less commonly associated with ARG1-D than other UCDs (25). The goal of treatment for patients with ARG1-D is to lower plasma arginine levels below 200 µmol/l or as low as possible (12). However, even with strict dietary restriction, reducing and maintaining plasma arginine levels below treatment recommendations is rarely successfully achieved, and may only be achieved in milder cases (6–8,18,27,29), due to difficulty with adherence as well as its failure to address endogenous arginine production. With continued disease progression, an increasing variety of supportive pharmacological therapies are required to mitigate some of the effects of the disease, including control of seizures, reduction of spasticity, and improvement in nutritional status. In addition, these patients may require surgical procedures to address complications including contractures related to long term spasticity. [redacted] Patients continue to experience disease progression, and there is scope for preventing cognitive decline and mobility decline. In addition, there are manifestations of disease that do not have treatment options associated (e.g., spasticity) Pegzilarginase represents the first potential enzyme therapy for patients with ARG1-D by substituting for the deficient human ARG1 enzyme activity in these patients. Pegzilarginase has been shown to rapidly and sustainably	

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		reduce plasma arginine and convert it to urea and ornithine, which is something that cannot be achieved with current treatment options as no other pharmacological treatment option exists to lower arginine levels. In the PEACE trial, pegzilarginase demonstrated early, clinically meaningful, consistent, and sustained statistically significant reduction in plasma arginine to both therapeutic guidelines and normal levels, corresponding decreases in plasma guanidino compound (GC) levels, increases in ornithine levels, and clinically meaningful improvements in mobility as assessed by neuromotor function through 48 weeks of treatment in PEACE and 120 weeks of treatment in Study 102A. Subjects treated with pegzilarginase had a rapid and sustained decrease in mean plasma arginine, with declines seen at week 1 and by week 12 were within normal limits, which was sustained through week 24. The reduction in plasma arginine levels observed for patients in the pegzilarginase group after 24 weeks of double-blind treatment in PEACE was sustained as subjects continued to maintain normal plasma arginine levels through an additional 24 weeks of treatment in the LTE period. In addition, mean (SD) plasma arginine levels in subjects who transitioned from placebo to pegzilarginase for the LTE period decreased from a baseline value of more than twice the guideline recommendations to within the normal range after 12 weeks of pegzilarginase treatment, and normalisation was sustained after 24 weeks of pegzilarginase. The long-term benefit of pegzilarginase treatment is supported by early, consistent, and sustained reductions in plasma arginine through 120 weeks of treatment in study 102A. At 168 hours after the first administration of IV pegzilarginase in study 102A, the mean plasma arginine level was within the	

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		treatment guidelines, close to the normal range (121.8 µM [range: 68.3 to 222 µM]), and generally remained within the normal range through the data cutoff date. At week 24 and week 48, almost all subjects achieved a plasma arginine level that met the guideline recommendations (<200 µM) (13/14 [92.9%] and 13/13 [100.0%], respectively) and the majority of subjects achieved a plasma arginine level within the normal range (9/14 [64.3%] and 9/13 [69.2%], respectively) The reductions in plasma arginine in PEACE were associated with clinically meaningful improvements in mobility. Pegzilarginase demonstrated positive trends in GMFM-E and GMFM-D compared to placebo and numerical improvements in the 2MWT compared to placebo. The magnitude and extent of improvement in plasma arginine, GMFM-E and GMFM-D scores, and timed walk test demonstrated in PEACE was supported by consistent findings in Study 102A. Ornithine and urea are products of the hydrolysis of arginine by the enzyme ARG1 in the final step of the urea cycle. Ornithine levels are generally low in patients with ARG1-D due to the lack of ARGI available to convert it from arginine. Pegzilarginase demonstrated early, consistent, and sustained increases in ornithine levels that corresponded with reductions in plasma arginine through 24 weeks of double-blind treatment in PEACE. At Week 24, subjects in the pegzilarginase group had a clinically relevant and statistically significant 106.9% increase in mean ornithine (70.2 µM, 15/21 subjects) compared to the placebo group (31.9 µM, 10/11 subjects) (p<0.0001). The long term benefit of pegzilarginase treatment is supported by the early, consistent, and sustained increases in ornithine levels that were associated	

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		with reductions in plasma arginine through 120 weeks of treatment in study 102A In summary, pegzilarginase represents a novel targeted treatment option to address the unmet medical need for patients affected by ARG1-D, with the totality of the efficacy data ranging from 24 to over 120 weeks in duration. Pegzilarginase demonstrated positive and consistent benefit profile for patients affected by this rare progressive and debilitating disease. As acknowledged in the draft scope, current pharmacological treatments are limited to oral nitrogen scavenging medicines to address other clinical symptoms, i.e. chronic or recurrent hyperammonaemia	
	Metabolic Support UK	N/A	No action needed.
Additional comments on the draft scope	British Inherited Metabolic Disorders Group (BIMDG)	N/A	No action needed.
	Genetic Alliance UK	N/A	No action needed.
	Immedica Pharma	There are errors in the HST criteria checklist that have been previously flagged by Immedica during horizon scanning that may affect the interpretation and judgement of the applicability of this criterion to pegzilarginase. The first is the statement that “most affected infants are now identified at birth through newborn screening”, which is incorrect, as there is currently no newborn screening for ARG1-D in England (30). Furthermore,	Comment noted. No action required.

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		patients typically don't present with high arginine levels in the first few days of life, and therefore this type of newborn testing would be at risk of false negatives.	
	Metabolic Support UK	N/A	No action needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Neonatal and Paediatric Pharmacists Group (NPPG)