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HEALTH TECHNOLOGY BRIEFING
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Pegzilarginase for Arginase-1 deficiency

NIHRIO ID	22745	**NICE ID**	10695
Developer/Company	Immedica Pharma	**UKPS ID**	662017

Licensing and market availability plans	Currently in phase III/II clinical trials.

SUMMARY

Pegzilarginase is in clinical development for the treatment of patients suffering from arginase-1 (ARG1) deficiency. ARG1 deficiency is a rare inherited disease in which the body is unable to process arginine (a building block of protein) due to the lack of the enzyme arginase in the liver and red blood cells. Arginase breaks down and removes nitrogen from the body. The lack of arginase results in excessive accumulation of nitrogen in the form of ammonia in the blood, and arginine in the blood and cerebrospinal fluid. Arginase deficiency presents in early childhood and usually progresses to severe reflexes (spasticity), loss of ambulation, complete loss of bowel and bladder control, and severe intellectual disability. Treatment is focused on lowering arginine levels and preventing buildup of ammonia in the blood.

Pegzilarginase is a novel modified form of the human enzyme ARG1 designed as an intravenous infusion or subcutaneous injection to rapidly and sustainably lower blood arginine levels. If licensed, pegzilarginase will offer an additional treatment option for patients suffering from arginase-1 deficiency who currently have few effective therapies available.

PROPOSED INDICATION

For patients suffering from arginase-1 deficiency.[1]

TECHNOLOGY

DESCRIPTION

Pegzilarginase (AEB1102; Co-ArgI-PEG; Loargys) is a recombinant modified form of the human enzyme arginase 1 (ARG1), in which cobalt is substituted for manganese as a cofactor, covalently attached to polyethylene glycol (PEG), with potential arginine degrading activities. Upon intravenous administration or subcutaneous injection of pegzilarginase, ARG1 metabolizes the amino acid arginine to ornithine and urea, thereby lowering blood arginine levels. This normalizes blood arginine levels in patients with ARG1 deficiency and prevents hyperargininemia. Pegylation improves blood circulation times and cobalt substitution increases the catalytic activity of ARG1.[2]

In the phase III (NCT03921541) clinical trial, pegzilarginase will be administered weekly via intravenous (IV) infusion plus individualised disease management for 24 weeks. After completion of the 24-week double-blind treatment period, each subject will enter the long term, open-label extension, the first 8 weeks of which are blinded. During the long-term extension (LTE), all subjects receive pegzilarginase plus individualised disease management. After 8 weeks of the LTE study, patients have the option to receive treatment by subcutaneous administration (SC).[1]

INNOVATION AND/OR ADVANTAGES

Data from the studies on the clinical effect and safety profile of pegzilarginase in patients with ARG1 deficiency (NCT02488044 and NCT03378531) demonstrated that pegzilarginase is highly effective in lowering plasma arginine (pArg) levels with demonstrated evidence of improvements in important disease-related manifestations. pArg reductions were seen in all patients and 79% of patients with ARG1 deficiency were defined as responders based on clinically meaningful improvements in one or more of the three key mobility assessments. Notably, the observed clinical improvements with pegzilarginase occurred in patients who had experienced persistent and/or progressive disease manifestations while receiving standard current treatment approaches. This suggests that pegzilarginase has the potential to improve disease outcomes over existing disease management.[3]

Current treatment for ARG1-D includes severe dietary protein restriction, EAA and ammonia scavengers.[4] However, reducing plasma arginine to the guideline-recommended level of <200 µM is difficult to achieve via dietary restriction, and may only be achieved in milder cases.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pegzilarginase does not currently have Marketing Authorisation in the EU/UK for any indication.

Pegzilarginase was granted orphan drug designation in the EU in July 2016 for the treatment of hyperargininaemia.[6]

PATIENT GROUP

DISEASE BACKGROUND

Arginase-1 deficiency is a rare inherited disorder characterized by complete or partial lack of the enzyme arginase in the liver and red blood cells. 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. The lack of the arginase enzyme results in excessive accumulation of nitrogen, in the form of ammonia (hyperammonaemia), in the blood and arginine (hyperarginemia) in the blood and cerebrospinal fluid.[7] ARG1 deficiency is caused by mutations in the ARG1 gene and is inherited in an autosomal recessive manner.[8]

ARG1 deficiency in untreated individuals is characterized by episodic hyperammonaemia of variable degree that is infrequently severe enough to be life threatening or to cause death. Most commonly, birth and early childhood are asymptomatic. Untreated individuals have slowing of linear growth at age one to three years, followed by development of spasticity, plateauing of cognitive development, and subsequent loss of developmental milestones. If untreated, arginase deficiency usually progresses to severe spasticity, loss of ambulation, complete loss of bowel and bladder control, and severe intellectual disability.[9]

CLINICAL NEED AND BURDEN OF DISEASE

ARG1 deficiency has been estimated to occur in approximately 1 in 300,000-1,000,000 births.[7] However, the sensitivity of newborn screening for ARG1 deficiency is unknown, since in this disease arginine levels may be within the normal range in the first days of life.[4]

ARG1 deficiency represents 2-3% of all urea cycle disorders (UCDs).[10] The estimated frequency of urea cycle disorders collectively is 1 in 30,000. However, because urea cycle disorders like ARG1 deficiency often go unrecognized, these disorders are under-diagnosed, making it difficult to determine the true frequency of urea cycle disorders in the general population.[7]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main goals in the treatment of ARG1 deficiency are to lower arginine levels and to prevent buildup of ammonia in the blood (hyperammonaemia). People with ARG1 deficiency must be closely supervised by a medical team with experience treating metabolic disorders. They may need frequent blood tests to check arginine levels.[8]

Routine outpatient management includes restriction of dietary protein and consideration of oral nitrogen-scavenging drugs (in those who have chronic or recurrent hyperammonaemia).[9]

Treatment of an acutely ill (comatose and encephalopathic) individual requires:[9]

- rapid reduction of plasma ammonia concentration;
- use of pharmacologic agents (sodium benzoate and/or sodium phenylbutyrate/phenylacetate) to promote excretion of excess nitrogen through alternative pathways; and
- introduction of calories supplied by carbohydrates and fat to reduce catabolism and the amount of excess nitrogen in the diet while avoiding overhydration and resulting cerebral oedema.
- Standard treatment for seizures, spasticity, developmental delay / intellectual disability, and joint contractures.
- In those with persistent hepatic synthetic function abnormalities, fresh-frozen plasma should be considered prior to surgical procedures.
- In the rare instance of progression to hepatic fibrosis and cirrhosis, liver

transplantation can be considered.

CURRENT TREATMENT OPTIONS

Glycerol phenylbutyrate.[8] It is indicated for use as adjunctive therapy for chronic management of patients with urea cycle disorders (UCDs) including ARG1 deficiency. It must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).[11]

PLACE OF TECHNOLOGY

If licensed, pegzilarginase will offer an addition to current individualised disease management for patients suffering from ARG1 deficiency.

CLINICAL TRIAL INFORMATION

Trial	NCT02488044; A Phase 1/2 Open-label Study in Patients With Arginase I Deficiency to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous AEB1102 **Phase I/II –** Completed **Location(s):** One EU country, UK and USA **Study Completion Date:** February 2019	NCT03378531; An 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 **Phase II** - Active, not recruiting **Location(s):** One EU country, UK, USA and Canada **Primary completion date:** June 2022
Trial design	Single group assignment, open label, multicentre	
Population	N=16; Subjects with documented diagnosis of ARG1 deficiency; aged 2 years and older	N=14; Subjects with ARG1 deficiency who previously received treatment in Study CAEB1102-101A; aged 2 years and older
Intervention(s)	Pegzilarginase (IV). Part 1 Each patient may receive up to 7 doses given up to every other week over a maximum of 14 weeks. Part 2 Each patient will receive up to 8 weeks of repeat-dose therapy.	Pegzilarginase (IV) for up to approximately 4 years.
Comparator(s)	No comparator	
Outcome(s)	Primary outcome measure : Number of subjects with adverse events [time frame: weekly throughout the study, up to 14 weeks] See trial record for full list of other outcomes	Primary outcome measure : Incidence of treatment-related adverse events [time frame: up to 4 years] See trial record for full list of other outcomes.

Results (efficacy)	Substantial disease burden at baseline included lower-limb spasticity, developmental delay, and previous hyperammonemic episodes in 75%, 56%, and 44% of patients, respectively. Baseline plasma arginine (pArg) was elevated (median 389 µM, range 238-566) on standard disease management. Once weekly repeat dosing resulted in a median decrease of pArg of 277 µM after 20 cumulative doses (n = 14) with pArg in the normal range (40 to 115 µM) in 50% of patients at 168 hours post dose (mean pegzilarginase dose 0.10 mg/kg). Lowering pArg was accompanied by improvements in one or more key mobility assessments (6MWT, GMFM-D & E) in 79% of patients.[3]	
Results (safety)	Seven hypersensitivity reactions occurred in four patients (out of 162 infusions administered). Other common treatment-related adverse events (AEs) included vomiting, hyperammonaemia, pruritus, and abdominal pain. Treatment-related serious AEs that occurred in five patients were all observed in this study.[3]	-

Trial	**PEACE; NCT03921541, EudraCT - 2018-004837-34;** Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints: A Randomised, Double-blind, Placebo-controlled Phase 3 Study of the Efficacy and Safety of Pegzilarginase in Children and Adults With Arginase 1 Deficiency **Phase III** – Active, not recruiting **Location(s):** Four EU countries, UK, USA and Canada **Primary completion date:** September 2022
Trial design	Randomised, parallel assignment, quadruple-blind, placebo-controlled
Population	N=32; Subjects with ARG1 deficiency; aged 2 years and older
Intervention(s)	Pegzilarginase (IV) plus individualised disease management weekly for 24 weeks. After completion of the 24-week double-blind treatment period, each subject will enter the long term, open-label extension, the first 8 weeks of which are blinded. During the long-term extension, all subjects receive pegzilarginase plus IDM. After 8 weeks of the LTE study, patients have the option to receive treatment by SC administration.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: Change from baseline in plasma arginine concentration after 24 weeks of treatment [time frame: baseline through week 24] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Cost of pegzilarginase was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant NICE guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- National Organization for Rare Disorders (NORD). Urea Cycle Disorders. 2021.[12]
- All Wales Medicines Strategy Group (AWMSG) Decisions. Glycerol phenylbutyrate (Ravicti®) as adjunctive therapy for chronic management of patients with urea cycle disorders. (AWMSG No.2127). December 2019.[13]
- Häberle, J, Burlina, A, Chakrapani, A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. April 2019.[4]
- Healthcare Improvement Scotland. Glycerol phenylbutyrate (Ravicti). 2018.[14]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *Efficacy and Safety of Pegzilarginase in Patients With Arginase 1 Deficiency.* Available from: https://clinicaltrials.gov/ct2/show/NCT03921541?term=NCT03921541&draw=2&rank=1 [Accessed 17 September 2021].

2 National Cancer Institute. *Pegzilarginase.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/pegzilarginase [Accessed 17 September 2021].

3 Diaz GA, Schulze A, McNutt MC, Leão-Teles E, Merritt JL, 2nd, Enns GM, et al. Clinical effect and safety profile of pegzilarginase in patients with arginase 1 deficiency. *Journal of inherited metabolic disease*. 2021;44(4):847-56. Available from: https://doi.org/10.1002/jimd.12343.

4 Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. *Journal of inherited metabolic disease*. 2019;42(6):1192-230. Available from: https://doi.org/10.1002/jimd.12100.

5 Schlune A, vom Dahl S, Häussinger D, Ensenauer R, Mayatepek E. Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature. *Amino Acids*. 2015 2015/09/01;47(9):1751-62. Available from: https://doi.org/10.1007/s00726-015-2032-z.

6 European Medicines Agency (EMA). *Orphan Designation - EU/3/20/2288. 2020.* Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3202288 [Accessed

7 National Organization for Rare Disorders (NORD). *Arginase-1 Deficiency.* Available from: https://rarediseases.org/rare-diseases/arginase-deficiency/ [Accessed 17 September 2021].
8 Genetic and Rare Diseases Information Center. *Arginase deficiency.* 2017. Available from: https://rarediseases.info.nih.gov/diseases/5840/arginase-deficiency [Accessed 17 September 2021].
9 Sun A, Crombez EA, Wong D. Arginase Deficiency. *GeneReviews(®).* 1993. Available from: https://pubmed.ncbi.nlm.nih.gov/20301338/.
10 Summar ML, Koelker S, Freedenberg D, Le Mons C, Haberle J, Lee H-S, et al. The incidence of urea cycle disorders. *Molecular Genetics and Metabolism.* 2013 2013/09/01/;110(1):179-80. Available from: https://doi.org/10.1016/j.ymgme.2013.07.008.
11 EMC. Ravicti 1.1 g/ml oral liquid. 2021. Available from: https://www.medicines.org.uk/emc/product/10984.
12 National Organization for Rare Disorders (NORD). *Urea Cycle Disorders (UCD).* 2021. Available from: https://rarediseases.org/physician-guide/urea-cycle-disorders/ [Accessed 17 September 2021].
13 All Wales Medicines Strategy Group (AWMSG). *glycerol phenylbutyrate (Ravicti®).* 2019. Available from: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/glycerol-phenylbutyrate-ravicti/ [Accessed 17 September 2021].
14 Healthcare Improvement Scotland. *Glycerol phenylbutyrate (Ravicti).* 2018. Available from: https://www.scottishmedicines.org.uk/medicines-advice/glycerol-phenylbutyrate-ravicti-fullsubmission-134218/ [Accessed 19 October 2021].

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