EU Risk Management Plan for Loargys (pegzilarginase)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 14 Oct 2021

Date of final sign-off: 11 Oct 2023

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

Table of content

List of Abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibodies
ARG1-D	Arginase 1 Deficiency
DLP	Data Lock Point
DNA	Deoxyribonucleic acid
HCP	Health Care Professional
IV	Intravenous
µM	Micromolar
MTD	Maximum Tolerated Dose
NOAEL	No Observable Adverse Effect Level
PEG	Polyethylene Glycol
QW	Every Week
SC	Subcutaneous
UCD	Urea Cycle Disorder

Part I: Product(s) Overview

Table Part I.1: - Product(s) Overview

Active substance(s) (INN or common name)	Pegzilarginase
Pharmacotherapeutic group(s) (ATC Code)	A16AB24
Marketing Authorisation Applicant	Immedica Pharma AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Loargys
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Biological (recombinant protein)
	Summary of mode 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.
	Important information about its composition: produced from *E.coli* cells by recombinant DNA technology
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current: Treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: Loargys should be administered by intravenous infusion or subcutaneous injection, using the same dose. In clinical trials, treatment was initiated as intravenous administration with subsequent transition to subcutaneous administration after 8 weeks, at the earliest. The recommended initial dose of Loargys is 0.1 mg/kg per week. The dose may be increased or decreased in 0.05 mg/kg increments to achieve therapeutic goals. Doses above 0.2 mg/kg per week have not been studied in clinical trials in ARG1 D. For dose adjustments see SmPC section 4.2.
	Proposed (if applicable): not applicable
	Current (if applicable): 5 mg/ml solution for injection/infusion

Pharmaceutical form(s) and strengths	Proposed (if applicable): not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Introduction

Pegzilarginase is indicated for the treatment of Arginase 1 deficiency (ARG1-D) also known as hyperargininaemia.

ARG1-D is a urea cycle disorder (UCD) and caused by the complete lack or partial lack of the arginase-1 enzyme which plays a critical role in the breakdown and removal of nitrogen in the urea cycle. ARG1-D has a distinct clinical phenotype characterized by spastic diplegia and variable presence of intermittently elevated plasma ammonia, which is present to a much greater extent in other UCDs [Huemer *et al*, 2016] The principal defect in ARG1-D leads to high levels of plasma arginine (3-4 times the upper limit of normal), which occurs in all patients with this disorder. Therefore, the accumulation of arginine and its direct metabolites are expected to play a key role in the clinical manifestations of ARG1-D [Panza *et al*, 2019].

Incidence

The incidence of ARG1-D has been reported to range between approximately 1:300,000−1:2,000,000 live births [Sin *et al.*, 2015]. An estimate based on newborn screening of other UCDs suggested an incidence of 1:950,000 [Summar *et al, 2013*; Schlune *et al*, 2015].

Prevalence

ARG1-D is one of the least common UCDs, currently estimated to account for approximately 3.5% of all cases [Burrage *et al*, 2015]. Findings of a genetic analysis based on mathematical modelling estimated global birth prevalence for ARG1-D to be 2.8 cases per million live births (1/357,000 live births) and population prevalence to be 1.4 cases per million people (approximately 1/726,000 people) [Catsburg *et al*, 2022]. Affected infants can be identified through screening, however ARG1-D is not included in the screening panels in many countries based on various limitations (e.g., materials and equipment unavailable or lack of appropriate analytical cut off value for disease indicator). Depending on the severity of the disease, diagnosis can be delayed by on average 4 years after manifestations of initial symptoms [Diaz *et al*, 2021; Huemer *et al*, 2016].

Risk Factors

As an autosomal recessive genetic disease, the risk for 2 carriers to both pass the altered gene to a child is 25% in each pregnancy. [Uchino *et al*, 1995]. Consanguinity increases the risk of recessive genetic disorders in children.

Demographics

The condition has the same risk to males and females. The gene expression is pan ethnic although an early study indicated it was more common in French Canadians due to a pathogenic variant [Uchino *et al*, 1995].

Treatments

Current international treatment guidelines recommend reduction of plasma arginine to levels of <200 µM [Häberle *et al*, 2019], and ideally within the normal range (defined as 40 to 115 µM in the clinical trials). Current treatments include dietary restriction aiming at limiting the amount of arginine containing protein with supplemental essential amino acids. Nitrogen scavengers may be used to remove the excess nitrogen. Although rarely considered, selected patients may undergo liver transplantation to address the underlying metabolic abnormalities. Other treatments for management of the symptoms including control of seizures and spasticity [Sun *et al*, 2020] are also administered.

Nitrogen scavenging treatments with sodium phenylbutyrate, glycerol phenylbutyrate, or sodium benzoate can be used to reduce elevated ammonia levels and manage the episodes of hyperammonaemia. However, none of these agents directly affect excess arginine, the primary metabolic abnormality in these patients [Sun *et al*, 2020].

Disease management with dietary protein restrictions and amino acid supplementation can be insufficient to provide adequate nutrition as highly restrictive diets make compliance difficult given that medical foods have poor palatability and are costly. Furthermore only 20% of the arginine is derived from diet and does not address the issue of the endogenous arginine production and protein turnover. Data from a natural history study conducted by the Urea Cycle Disorders Consortium has shown that despite dietary protein restriction, nearly all plasma arginine levels collected at routine study visits in ARG1-D patients were above the normal range [Burrage *et al*, 2015].

Treatment of seizures is offered in the form of anti-convulsants, such as carbamazepine and phenobarbital, but not valproate as this can increase ammonia levels. Spasticity is managed with rehabilitation devices such as orthotic devices, walkers and wheelchairs alongside physical therapies for joint contractures. Baclofen and botulinum toxin are also administered as anti-spasticity agents in these patients [Bin Sawad et al., 2022; Sun *et al.*, 2020].

Liver transplantation has been reported to be effective to achieve normalisation of arginine levels and a halt in the progression of disease, but despite the successes, this intervention is available to only a small fraction of patients and the procedure carries a significant risk of mortality and morbidity [Häberle e*t al*, 2019].

Currently there are no approved medicinal treatments that target the underlying deficiency in the arginase enzyme activity and there is a lack of evidence for the effectiveness of the current approaches for lifelong maintenance of normal arginine levels. The current therapies still lead to long term exposure to the effects of elevated arginine and its metabolites.

Natural history of disease

Patients with ARG1-D typically present with symptoms between the ages of 1-3 years, some with milder symptoms, others more severe [Sun *et al*, 2020]. Neonatal and early infantile presentation of the disease is rare and in fact only six cases of neonatal representation of ARG1-D were reported in literature in a 25-year period [Jain-Ghai *et al*, 2011]. Progression in mental retardation and spastic diplegia is inexorable in the majority of patients even with dietary protein restriction. Clinically, ARG1-D is characterized by progressive dementia, psychomotor retardation, spastic diplegia, seizures and growth failure. Generally, birth and early infancy are relatively normal, but linear growth slows between 1 and 3 years of age and is followed by the development of spasticity, plateauing of cognitive development and loss of developmental milestones. Progressive spastic paraplegia is the most obvious sign of the disease. Early symptoms of the disease include clumsiness, generalized developmental delays, failure to thrive, irritability, recurrent vomiting, feeding/protein aversion, and anorexia [Sin *et al*, 2015].

Initially, cognitive development in early infancy is normal but slows between the ages of one and three years, leading to some degree of cognitive impairment, with both loss of acquired skills and severe intellectual disability if left untreated. For adults, those mildly affected may be able to hold a job, but for the majority in older age groups, only about half are able to live independently, though they experience significant memory and fine motor deficits [Sun *et al*, 2020; Waisbren *et al,* 2016].

Neuromotor complications are the hallmark of the disease, with lower limb spasticity appearing between ages two and four years in 80-90% of cases. This is often misdiagnosed as cerebral palsy causing delays in diagnosis. In untreated individuals, progressive neurologic signs typically include the development of severe spasticity with loss of ambulation and complete loss of bowel and bladder control [Huemer *et al*, *2016;* Chandra *et al,* 2019].

Seizures commonly develop in early childhood occurring in 60-75% of patients, the majority being generalised tonic clonic seizures that are controlled by anti-convulsant medication [Huemer *et al; 2016*; Chandra *et al,* 2019]. Early diagnosis is key to identify patients with this progressive and debilitating disease to begin management to prevent or reduce the key morbidities.

Co-morbidities

ARG1-D manifests other medically important disease-related abnormalities, including complications due to inadequate nutrition, growth impairment, hyperammonemia and hepatocellular injury. These abnormalities are a result of the disease and/or the severe protein restriction currently required to manage the disease. Elevated plasma ammonia rarely develops in the newborn period but episodic episodes of variable degrees of hyperammonaemia may occur triggered by illness. Although rarely severe enough to be life threatening, death has been reported [Sun *et al*, 2020].

Hepatic dysfunction, if present, is usually mild, manifesting as transaminitis, prolonged coagulation time, and in some cases hepatomegaly. Affected individuals typically do not have bleeding problems. Rarely, neonatal cholestatic jaundice has been reported and cirrhosis can occur. Some adults have developed hepatocellular carcinoma [Braga *et al*, 1997; Gomes Martins *et al*, 2010].

Part II: Module SII - Non-clinical part of the safety specification

Table Part II.1: - Key safety findings from non-clinical studies and relevance to human usage.

Key safety findings from non-clinical studies	Relevance to human usage
Safety Pharmacology	
No safety concerns relevant to human use are identified from these data.	
Toxicity	
Body weight loss	These findings were the result of sustained low arginine levels that occurred when pegzilarginase induced a state of exaggerated pharmacology in normal animals, an occurrence not consistently expected to be replicated in patients with ARG1-D receiving pegzilarginase.
Reproductive/developmental Toxicity	
Adverse event in reproductive organs	These findings were the result of sustained low arginine levels that occurred when pegzilarginase induced a state of exaggerated pharmacology in normal animals, an

Key safety findings from non-clinical studies	Relevance to human usage
	occurrence not consistently expected to be replicated in patients with ARG1-D receiving pegzilarginase.
Decreased embryo-foetal size, skeletal malformations	The effects are considered transient secondary effects which manifested as maternal and foetal toxicities due to the exaggerated pharmacology in normal animals observed at these dose levels during pregnancy, an occurrence not consistently expected to be replicated in patients with ARG1-D receiving pegzilarginase.
Carcinogenicity and Genotoxicity	
Not evaluated	Pegzilarginase is a biological product with no expected safety concerns.

Safety pharmacology

Safety pharmacology determinations for pegzilarginase were incorporated into the 4-week and 13-week cynomolgus monkey toxicology studies using 0.1, 0.3 and 1mg/kg doses (AER-MPI-005 and AEB-002-1014). The animal model, while not representative of the highly elevated plasma arginine state indicative of patients with ARG1-D, represent pharmacologically relevant species that showed dose-related reductions, albeit exaggerated, in circulating levels of arginine, the relevant biomarker for the pharmacologic activity of pegzilarginase.

At doses of 1 mg/kg/dose during the 4-week study there was an increase in heart rate observed compared to the control group, but well within the historical normal range of variability and none of the cardiovascular findings were considered biologically significant or adverse. During the 13-week study at doses of 1 mg/kg/dose there were findings of slower heart rate and longer RR interval in males at the Day 1 post-dose interval. While the difference was observed following the high dose, the absolute mean heart rate and RR interval values did not exhibit a clear dose-related progression in either sex, and the within-group percentage changes from the Day 1 pre-dose values were comparable across dosing levels in both sexes. Further, since the highest mean heart rates at the terminal post-dose interval were observed following the high dose in both sexes, the differences from vehicle observed at the Day 1 post-dose interval these were not considered related to pegzilarginase treatment. In both the 4-week and 13-week studies no safety pharmacology findings were observed for short and long-term dosing up to the NOAEL of 0.3 mg/kg in monkeys, therefore no safety concerns relevant to human use are identified from these data.

Single Dose and Repeated Dose Toxicity

In general, in single- and repeat-administration studies of pegzilarginase across multiple species (mice, monkeys, rats, and rabbits), dose-dependent reductions in arginine with pegzilarginase were associated with reversible inappetence and associated decreases in body weight gain at the highest doses tested. Adverse and non-adverse modulations of hematology, serum chemistry, and decreases in non-reproductive organ weight endpoints were considered secondary to body weight loss or were observed at decreasing dose levels as studies increased in duration. At doses above 1 mg/kg in monkeys, adverse effects of skin abrasions, hair loss, and gastrointestinal effects were observed and the level considered the maximum tolerated dose (MTD). Body weight loss and secondary findings are not considered of relevance to clinical use, the manifestation of toxicology findings was the result of

sustained decreases in arginine levels below the normal range, an occurrence not consistently expected to be replicated in patients with ARG1-D receiving pegzilarginase to normalize arginine levels.

Reproductive/developmental Toxicity

Male reproductive toxicities were noted in only a single species, the juvenile male rat.

Juvenile rats were evaluated following 6 weeks to 6 months of weekly pegzilarginase dosing and yielded adverse findings at high- and mid-dose levels on male reproductive organs that were unique to the species and considered adverse. Male reproductive findings were considered adverse either due to the irreversibility of weight decreases alone or in combination with associated and irreversible histopathology. These findings uniquely manifested even at mid-dose levels with longer dosing durations of pegzilarginase and were due to sustained decreases of arginine, which, along with arginine derived polyamines and nitric oxide, are directly involved in spermatogenesis and sperm motility. Therefore, long term abnormally low levels of arginine (below normal range) could be a potential risk on male reproductive development. These findings were not reversible during the extent of the follow up period, albeit the period was too brief to fully characterize reversibility.

Sustained low arginine is an occurrence not consistently expected to be replicated in patients with ARG1-D receiving pegzilarginase.

In the pregnant animals, rabbits proved to be more sensitive to pegzilarginase than rats as evidenced by toxicities at lower dose levels. However, in both species, if arginine levels were not repeatedly and sustained reduced below the normal range for the animals during the dosing intervals, it did not impact normal foetal development. Overall, the developmental and reproductive toxicologies observed were attributable to repeated depletion of arginine below the normal range for the animals for more than120 hours per week and for a sustained time, which is consistent with the general toxicology mode of action for pegzilarginase. In female rats decreased uterine implantation and increased pre-implantation loss were observed at the dose 1mg/kg. Pregnant female rats and rabbits dosed at 1 and 0.3 mg/kg, respectively, during pregnancy had offspring of decreased size that exhibited skeletal malformations. However, such findings have been reported in the literature to resolve with age and are therefore considered transient secondary effects which manifested as maternal and foetal toxicities due to the exaggerated pharmacology observed at these dose levels during pregnancy [DeSesso and Scialli, 2018]. The NOAEL for embryofoetal development was considered 0.3 mg/kg in female rats and 0.1 mg/kg female rabbits. In pre- and post-natal development, at 1 mg/kg an observed decrease in body weight in first filial generation during lactation for most of the growth period and evidence of an effect on learning and memory was seen. The NOAEL was established for the pre- and post-natal development for male and female rats to be 0.3 mg/kg.

Based on the animal model data pegzilarginase at the human equivalent doses of 0.3 mg/kg is not likely to affect reproduction in females but there is a potential transient risk to foetal development when administered in pregnancy if the pegzilarginase treatment leads to repeated and sustained low arginine levels during dosing intervals.

Carcinogenicity and Genotoxicity

Pegzilarginase is considered too large to diffuse across cell membranes and therefore are not expected to pass through the cellular and nuclear membranes of intact cells and interact with DNA or other chromosomal material. In line with ICH S6 R1 Preclinical Safety evaluation of biotechnology derived pharmaceuticals the carcinogenic and mutagenic potential of pegzilarginase has not been evaluated.

Immunogenicity

Animal studies in the rats and monkeys demonstrated a low incidence of anti-drug antibodies (ADAs) on circulating levels of pegzilarginase. It is recognized that immunogenicity in animals is of limited value to predict immunogenicity in humans, therefore a potential risk to humans cannot be determined based on the nonclinical data.

Part II: Module SIII - Clinical trial exposure

Overall, 187 subjects have been enrolled in interventional trials with pegzilarginase in the clinical development program: 48 subjects in ARG1-D studies and 139 subjects in oncology studies. The oncology study program has been discontinued for other reasons than safety whilst the ARG1-D studies are ongoing. The oncology trials were for a different therapeutic indication involving a different target population with a higher dosing targeting a reduction of arginine below the normal range, whereas the ARG1-D studies targeted normalising arginine levels. Therefore, pooling the data from all studies would not be representative and the clinical trial exposure data is presented as cumulative for exposure specifically for the ARG1-D studies for the proposed indication.

Of the 48 subjects enrolled in ARG1-D studies: 16 in Study 101A (14 of whom completed the study and continued into Study 102A) and 32 in Study 300A (21 randomized to pegzilarginase, 11 randomized to placebo) in the initial 24-week double-blind (DB) period and with 31 subjects receiving pegzilarginase in the open-label long term extension (LTE) study portion up to approximately 150 weeks.

Table SIII.1 Summary of pegzilarginase Clinical Studies in Target ARG1-D Population

Study Number	Phase	Study Design	Study objective	Population	Subjects exposed to pegzilarginase (/ placebo)
CAEB1102-101A (completed)	1/2	Open-label study Part 1: single ascending dose (IV) Part 2: Repeat weekly dose (IV)	Safety PD (plasma arginine) PK	Adults and Paediatric subjects >2 years with ARG1-D	Part 1: 16 subjects Part 2: 15 Subjects
CAEB1102-102A (ongoing)	2	Long-term open-label extension with continued dosing up to 4 years	Safety PD (plasma arginine) PK	Adults and Paediatric subjects >2 years with ARG1-D who had previously been included in 101A	14 subjects
CAEB1102-300A (DB period complete, LTE period ongoing)	3	Randomized double-blind, placebo-controlled study	Efficacy Safety	Adults and Paediatric subjects >2 years with ARG1-D	DB: 21/11 LTE: 31

Table SIII.2 Duration of exposure.

Indication	Subjects			Person time (weeks)		
Duration of Exposure	IV	SC	Total	IV	SC	Total
ARG1-D Treatment						
<4 weeks	3	2	3	3.0	5.0	3.0
4 weeks - <24 weeks	8	7	5	73.0	117.0	50.0
24 weeks - <52 weeks	36	10	12	1262.0	366.0	393.0
52 weeks - <104 weeks	1	7	15	54.0	598.0	1049.0
>=104 weeks	0	8	13	0	960.0	1945.0
Total	48	34	48	1392.0	2046.0	3440.0
Oncology Treatment						
<4 weeks	7	NA	7	14.9	NA	14.9
4 weeks - <24 weeks	120	NA	120	1214.6	NA	1214.6
24 weeks - <52 weeks	9	NA	9	285.6	NA	285.6
52 weeks - <104 weeks	3	NA	3	214.6	NA	214.6
>=104 weeks	0	NA	0	0	NA	0
Total	139	NA	139	1729.6	NA	1729.6

Person time is calculated by summing the total exposure time for subjects within each subgroup.

Note: Subjects who received IV and SC treatments will be counted in both columns.

Note: Durations for each route were combined if subjects participated in multiple studies.

Note: Subjects who received both IV and SC are counted in the appropriate duration category based on their exposure to each route respectively and for the total column their combined exposure is taken into account. Therefore, the total column may not equal the sum of the IV and SC columns.

Table SIII.3: Age group and gender.

Indication	Subjects		Person time (weeks)	
Age Group	Male	Female	Male	Female
ARG1-D Treatment				
Neonates (<28 days)	0	0	0	0
Infants (28 days - 23 months)	0	0	0	0
Children (2 - 11 years)	12	12	651.0	904.0
Adolescents (12 - 17 years)	10	6	552.0	310.0
Adults (18 - 64 years)	2	6	134.0	889.0
Elderly (>=65 years)	0	0	0	0
Total	24	24	1337.0	2103.0
Oncology Treatment				
Neonates (<28 days)	0	0	0	0
Infants (28 days - 23 months)	0	0	0	0
Children (2 - 11 years)	0	0	0	0
Adolescents (12 - 17 years)	0	0	0	0
Adults (18 - 64 years)	29	26	296.9	451.7
Elderly (>=65 years)	41	43	481.7	499.3
Total	70	69	778.6	951.0

Person time is calculated by summing the total exposure time for subjects within each subgroup.

Table SIII.4: Dose.

Indication	Subjects			Person time (weeks)		
Dose of Exposure	IV	SC	Total	IV	SC	Total
ARG1-D Treatment						
<0.05 mg/kg	2	0	2	11.0	0	11.0
0.05 - <0.10 mg/kg	11	9	11	413.0	883.0	1296.0
0.10 - <0.15 mg/kg	12	9	12	359.0	495.0	855.0
0.15 - <0.20 mg/kg	23	16	23	609.0	668.0	1278.0
>=0.20 mg/kg	0	0	0	0	0	0
Total	48	34	48	1392.0	2046.0	3440.0
Oncology Treatment						
<0.25 mg/kg	33	NA	33	315.1	NA	315.1
0.25 - <0.30 mg/kg	40	NA	40	672.0	NA	672.0
0.30 - <0.35 mg/kg	46	NA	46	597.3	NA	597.3
>=0.35 mg/kg	20	NA	20	145.1	NA	145.1
Total	139	NA	139	1729.6	NA	1729.6

Person time is calculated by summing the total exposure time for subjects within each subgroup.

Dose of exposure is calculated as the mean dose over the whole study (pooling IV and SC doses) for each subject.

Note: If subjects participated in multiple studies, one mean dose was calculated by considering all doses.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1: Exclusion criterion 1.

Criterion 1	Hyperammonaemia episode (defined as an event in which a subject has an ammonia level ≥100 µM with one or more symptoms related to hyperammonaemia requiring hospitalization or emergency room management) within the 6 weeks before the first dose of study drug is administered.
Reason for exclusion	Hyperammonaemia may lead to episodes of gastrointestinal and neurological manifestations such as anorexia, vomiting, irritability, movement disorders, and, in severe cases, encephalopathy and coma. Patients with episodes within 6 weeks prior to the first dose of study drug were excluded to ensure patient safety and to not confound the safety profile of pegzilarginase.
Is it considered to be included as missing information?	No
Rationale	Unlike other UCD's, persistent hyperammonaemia is not a common effect although it can occur intermittently. Pegzilarginase targets reduction in arginine leading to conversion to urea and ornithine. Pegzilarginase acts extracellularly and is not anticipated to have a direct effect on the urea cycle.

Table SIV.2: Exclusion criterion 2.

Criterion 2	Subject is being treated with botulinum toxin-containing regimens or plans to initiate such regimens during the double-blind or blinded follow-up portions of the study or received surgical or botulinum-toxin treatment for spasticity-related complications within the 16 weeks prior to the first dose of study treatment in this study
Reason for exclusion	Botulinum toxin was excluded to prevent any confounding effects on spasticity as some of the assessments for neuromotor efficacy were related to reduction in spasticity.
Is it considered to be included as missing information?	No
Rationale	Based on pharmacology there is no negative potential impact on the pegzilarginase efficacy profile. However, there is no exclusion of botulinum toxin to treat spasticity during the long term follow up.

Table SIV.3: Exclusion criterion 3.

Criterion 3	Previous liver or hematopoietic transplant procedure
Reason for exclusion	Patients who undergo liver transplantation would not require treatment with pegzilarginase.
Is it considered to be included as missing information?	No
Rationale	Liver transplantation eliminates hyperargininaemia. It is thereby not anticipated that patients who undergo liver transplantation would require treatment with pegzilarginase.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme in ARG1-D patients may not have detected rare and very rare adverse drug reactions at a frequency of <0.1%, considering the small patient population studied (total number of patients receiving treatment was 48). Pegzilarginase is intended for long term use in an orphan population. Limited data is currently available from clinical trials with regards to the long-term safety. Overall, 13 subjects have been exposed to pegzilarginase for >2 years in the ARG1-D clinical trial programme.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.4: Exposure of special populations included or not in clinical trial development programmes.

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not excluded in the clinical development program. Hepatic impairment is a common feature in patients with UCDs and ARG1-D. Approximately 1/3 of the patients in Study 300A had a history of abnormal liver function tests or abnormal liver function tests at baseline.
• Patients with renal impairment	Although not specifically excluded from the clinical development program due to the rare population available there were no specific cases. Nevertheless, this co-morbidity is not relevant to the specific population.

Type of special population	Exposure
• Patients with cardiovascular impairment	Although not specifically excluded from the clinical development program due to the rare population available there were no specific cases. Nevertheless, this co-morbidity is not relevant to the specific population.
• Immunocompromised patients	Although not specifically excluded from the clinical development program due to the rare population available there were no specific cases. Nevertheless, this co-morbidity is not relevant to the specific population.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable as the severity of disease is all inclusive within the clinical development program
Population with relevant different ethnic origin	Not applicable as the data does not present significant differences across ethnicities.
Subpopulations carrying relevant genetic polymorphisms	No genetic polymorphism identified in this patient population

Part II: Module SV - Post-authorisation experience

Not applicable

SV.1 Post-authorisation exposure

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for this medicinal product misuse for illegal purposes has not been studied. Pharmacological properties, non-clinical and clinical data do not indicate an impact on the nervous system suggesting effects that may lead to dependence. Based on the fact the product is administered subcutaneously or intravenously under the supervision of a healthcare professional the potential for misuse for illegal purposes is unlikely.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks that have minimal clinical impact on patients (in relation to the severity of the indication treated):

Injection Site reactions

Injection site reactions were reported by 8.8% (3/34) of the patients included in the open label extension studies with SC administration. The reactions were generally of mild intensity consisting of swelling, rash and erythema. All were non serious and did not lead to discontinuation of treatment. These reactions occurred with the SC administration, and none were reported with the IV administration. Given the potential for immune response following protein therapeutics the injection site would be subject to monitoring during treatment and advice to HCPs would be provided in the SmPC aligned to standard clinical practice for the management of injection site reactions.

Hypersensitivity

Hypersensitivity occurred in 12.5% (6/48) of the patients in the clinical studies. The hypersensitivity occurred following at least one previous dose of pegzilarginase and soon after initiation of the IV infusion. Observed signs and symptoms included rash, facial swelling, feeling hot and flushed, shivering, cough, dyspnoea and abdominal pain. Hypersensitivity reactions were transient and managed by temporarily stopping or slowing the infusion and administering medication (antihistamines, corticosteroids and in some cases also antipyretics). No subject discontinued treatment or had their dose reduced due to a hypersensitivity reaction. All hypersensitivity TEAEs resolved, enabling completion of pegzilarginase infusion on the same day. The majority of subjects with previous hypersensitivity reactions were premedicated prior to subsequent infusions and in some cases the infusion rate was reduced. Although there is the potential for a severe hypersensitivity reaction which is an important potential risk, milder hypersensitivity reactions are not considered a significant safety concern as these are transient and resolved by temporary suspension of treatment and administration of antihistamines, corticosteroids and/or antipyretics. As a preventative measure a warning is included in the SmPC to monitor for signs and symptoms of hypersensitivity to ensure prompt management of the adverse reactions.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

None

Known risks that do not impact the risk benefit profile:

Immunogenicity

Based on the type of medicinal product as a therapeutic protein there is a potential for production of antibodies to the PEG-bound enzyme which could result in lack of efficacy.

ADAs that result in reduced pegzilarginase exposure would lead to elevated plasma arginine. Without obtaining the adequate control of arginine levels patients would continue to develop the debilitating disease manifestations.

During clinical studies subjects were analysed for anti-pegzilarginase and anti-PEG ADAs. Because a neutralizing effect of ADA on pegzilarginase results in decreased enzymatic activity, which can be monitored by measuring plasma arginine levels, the sponsor was using an integrated pharmacokinetic (PK)-pharmacodynamic (PD)-ADA analysis to evaluate the impact of ADA on efficacy as measured by the magnitude of reduction in plasma arginine levels. As of the DLP of this RMP the ADA incidence across the studies was 25.0% and the prevalence was 37.5%. In general, ADAs were transient and resolved with continued pegzilarginase treatment. For most subjects, ADAs developed early following the first IV administration and resolved from the third dose onward. The presence of ADAs was positively associated with reduction in PK and PD effect. The effect was transient in lowering pegzilarginase concentrations and resolved with repeated dosing and therefore the risks of development of ADAs do not overall impact the benefits of continued treatment considering the nature of the disease.

The safety effect of ADA was evaluated based on the incidence of hypersensitivity reactions and injection site reactions. Five out of the six subjects who experienced hypersensitivity reactions were ADA positive. Although a temporal association for Hypersensitivity and the presence of ADA was observed, not all subjects who were ADA positive experienced Hypersensitivity and a causal relationship was not established. With injection site reactions these occurred in both ADA-positive and ADA-negative subjects. The reactions occurred more than 24 weeks after the last positive ADA suggesting a lack of association and were considered to have minimal clinical impact as discussed above.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk:

None

Important Potential Risk 1: Severe Hypersensitivity Reactions

During clinical studies hypersensitivity reactions were observed. Dyspnoea was reported in limited number of subjects, however none of the hypersensitivity reactions resulted in hemodynamic changes. The reactions observed followed prior pegzilarginase administration and resolved on subsequent dosing. All reactions were immediate and not delayed and responded to treatment with antihistamines, corticosteroids and is some cases also antipyretics. No patient discontinued or required a dose reduction. Although the hypersensitivity reactions observed in clinical studies where mild to moderate in severity it is not known if there is potential for more severe reactions.

Risk-benefit impact

Severe hypersensitivity results in hospitalisation and can be potentially life-threatening. However, given the relatively mild hypersensitivity reactions observed to date which have been managed with

routine medical care and the efficacy observed with pegzilarginase, the overall impact on the benefit risk is expected to be low.

Important Potential Risk 2: Prolonged hypoargininaemia and its clinical sequelae

Prolonged hypoargininaemia with depleted or very low arginine levels was observed in nonclinical studies and considered to be due to exaggerated pharmacology following treatment with pegzilarginase in animals with normal levels of arginine at baseline. Transient excursions in plasma arginine to <40 µM is not unexpected with IV dosing of pegzilarginase and to a lesser extent with SC dosing. The population based PK/PD model (Study 265402) describes that concentrations of arginine are expected to remain in the 40 to 115 µM range for 37% to 100% of the dosing interval for the majority of subjects with 168-hour post-dose arginine concentrations of 100 to 200 µM. Additionally, the time below 40 µM is expected to be below 40% of the time when dosed weekly with IV and less than 3% of the time when dosed SC, calculated based on a 168-hour concentration target of less than 200 µM.

Sustained hypoargininaemia occurred infrequently in the clinical trials where only single subjects in the clinical programme had plasma arginine levels <40 µM on multiple occasions. No TEAEs of hypoargininaemia or events reported as results of hypoargininaemia were reported in the ARG1-D clinical study program. Although hypoargininaemia was defined as arginine <40 µM in the clinical study program, reference levels in clinical laboratories with lower limits down to the 10 µM range are commonly seen. Complete depletion of arginine for prolonged periods of time could cause multiple effects including impaired growth and development in the paediatric population.

Based on the pre-clinical data, arginine depletion could lead to impaired fertility and risk to the foetus during pregnancy in adult patients.

It was determined that the reproductive toxicities were related to the enhanced pharmacological event of sustained reduced arginine below normal levels during the dosing intervals consistently throughout the study period for a duration of up to 27 weeks. The study was not extended to determine if the effect was reversible. Notably the low arginine was induced in animals who began treatment with a normal baseline of arginine and therefore the toxicity occurred with a dose 15 times greater than the maximum dose in the ARG1-D studies related to an exaggerated pharmacological effect in those animals with normal endogenous arginase 1 activity where arginine levels remained consistently below normal levels for an extended period of time.

Embryo-foetal abnormalities were observed in pre-clinical studies when levels of arginine fell below normal levels. The toxicities were associated with the exaggerated pharmacology with decreased body weight, foetal growth retardation, alongside increased preimplantation loss.

Clinical studies on pegzilarginase in pregnant and lactating females have not been conducted and pregnant and lactating females were excluded from clinical studies of pegzilarginase. During pregnancy there are hemodynamic and metabolic changes in the mother to adapt to the increase demand for the foetus and it is not known if this results in a depletion in the arginine compared to the non-pregnant female. As there is variability in the arginase deficiency with limited alternative treatment options the benefit of treatment would need to be evaluated against the risk to the foetus by the physician.

Depletion of arginine to very low levels and for extended periods as studied in the pre-clinical programme is very unlikely to occur in clinical practice due to daily multiple food intake and regular monitoring of arginine levels. The important potential risk is not primarily aimed at capturing potential symptoms of hypoargininaemia but focused on gaining additional understanding and mitigating the risk for prolonged hypoargininaemia to levels close to arginine depletion for extended periods of time as well as its clinical sequelae.

Risk-benefit impact

Prolonged low levels close to arginine depletion for multiple repeated weeks are considered very unlikely to occur in clinical practice. After transitioning from IV to SC dosing fewer, less pronounced, and shorter fluctuations of arginine below the normal range will occur. In addition, the arginine levels should be measured at regular intervals according to the SmPC which will decrease the risk of sustained low levels. Sustained low levels of arginine have caused reproductive toxicity and embryofoetal abnormalities in the non-clinical studies. In summary, the likelihood and overall impact of prolonged hypoargininaemia on the benefit-risk balance is expected to be low.

Important Potential Risk 3: Medication errors during administration by a non-healthcare professional

Subcutaneous administration by a non-healthcare professional may be considered, if considered appropriate by the treating physician, after at least 8 weeks of treatment when a stable maintenance dose has been established and the potential risk for initial hypersensitivity reactions has been reduced.

Subcutaneous administration of pegzilarginase by a non-healthcare professional involves multiple steps, including handling of syringes and vials, measurement and withdrawal of the correct dose as well as administration of the injection, which introduces a potential risk for medication errors.

Risk-benefit impact

All caregivers and patients that are to be administering pegzilarginase in the home setting will be educated to ensure correct subcutaneous administration to minimise the important potential risk for medication errors. With detailed instructions in the product information supplemented by additional risk minimisation measures in form of an educational material, the likelihood and overall impact of medication errors during non-healthcare professional administration on the benefit-risk balance is expected to be low.

SVII.1.3. Presentation of Missing Information

Missing information 1: Safety in pregnancy and lactation

The population subset has not been studied during clinical trials. Data from nonclinical studies indicated a potential for increased sensitivity during pregnancy where increased toxicity was noted at lower dose levels in rabbits. However, the arginine levels remained within normal range.

It is not known whether the metabolic changes during pregnancy could result in inadequate control of arginine levels in the mother or the foetal development.

There is no data of the presence of pegzilarginase or its metabolites in the milk of nursing animals and nursing women were excluded from the clinical studies.

Risk-benefit impact:

The effect of administration of pegzilarginase in pregnant and breastfeeding women and the potential impact on the pregnancy outcome is unknown.

Missing information 2: Long Term Safety

There are limited number of subjects exposed to long term treatment with pegzilarginase. In all ARG1-D studies 28 patients have been treated with pegzilarginase for more than one year, out of which 13 patients have been treated for more than two years. Given the limited number of subjects treated, there is insufficient data to determine the longer-term safety profile.

Risk-benefit impact:

It is anticipated that long term treatment with pegzilarginase would be expected to continue to maintain the arginine levels below target level and within normal range for most patients. Considering the current data, it is not anticipated that longer term treatment will result in additional adverse events with continued treatment.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk 1: Severe Hypersensitivity Reactions

Table SVII.1: Important potential risk 1: Severe hypersensitivity reactions.

Potential Mechanism:	Interaction of IgE with the pegzilarginase as a recombinant biologic and/or PEG could result in eosinophil activation and release of mediators such as histamine.
Evidence source and strength of evidence:	Hypersensitivity reactions can occur with enzyme therapy and this risk is supported by epidemiologic evidence and literature reports which also note significant variation in the frequency and severity across different therapies. Furthermore, hypersensitivity reactions were reported in clinical studies. These were solely following IV dosing and there were no reports following SC dosing.
Characterisation of risk:	Of the subjects exposed in the ARG1-D clinical studies, 6 patients (12.5%) reported mild to moderate hypersensitivity reaction during IV administration. In the events reported, all were considered to be at least possibly related with pegzilarginase treatment. Signs and symptoms of hypersensitivity reaction occurred following at least 1 previous dose of pegzilarginase and occurred between 2 to 8 minutes after initiation of the IV infusion. No subject discontinued treatment or had their dose reduced due to a hypersensitivity reaction. All TEAEs of hypersensitivity resolved, enabling completion of pegzilarginase infusion on the same day. All biologically manufactured medicinal products and products with a polyethylene glycol (PEG) component have the theoretical possibility to cause more severe hypersensitivity reactions which could have an impact on the benefit risk in the treatment of the individual patient. Life threatening and fatal systemic reactions including anaphylactic reactions have not been observed in clinical trials with pegzilarginase, however the possibility for such reactions to occur cannot be excluded.
Risk factors and risk groups:	Patients with known hypersensitivity to PEG or any of the excipients.

Preventability:	Hypersensitivity reactions cannot be prevented but can be adequately managed through medication. Dosing is administered by a healthcare professional which allows for prophylactic measures including monitoring for the signs and symptoms of the reaction and consideration of premedication with antihistamines to minimize the risk of occurrence if required.
Impact of benefit risk balance:	Severe hypersensitivity reactions can be potentially life-threatening and require medical intervention and potentially prolonged hospitalisation.
Public health impact:	There is no indication that the frequency or severity of hypersensitivity reactions will be different in patients receiving pegzilarginase in clinical practice compared to patients receiving pegzilarginase in the clinical development program therefore, significant impact on public health is not anticipated.

Important Potential Risk 2: Prolonged hypoargininaemia and its clinical sequelae

Table SVII.2: Important potential risk 2: Prolonged hypoargininaemia and its clinical sequelae

Potential Mechanism:	Treatment with pegzilarginase reduces plasma arginine levels and transient excursions in plasma arginine to below the normal range is not unexpected.
Evidence source and strength of evidence:	No risks related to hypoargininaemia have been observed in the clinical development program. In the nonclinical general and developmental and reproductive toxicology studies, pegzilarginase was well tolerated, with adverse findings associated with exaggerated pharmacology characterized by marked and sustained arginine depletion below the normal range. These findings were reversible and likely the result of exaggerated pharmacology in normal animals at baseline and, as such, are a low risk to patients with ARG1-D that have elevated basal levels of arginine.
Characterisation of risk:	No risks related to hypoargininaemia has been observed in the clinical development program. Potential consequences of prolonged and repeated periods of arginine depletion could include growth retardation and effects of development in growing children, and impact on spermatogenesis and risks to the foetus during pregnancy. In clinical practice the potential risk for prolonged hypoargininaemia resulting in arginine depletion is considered low and balanced by food intake and monitoring of arginine levels. The characterisation of the risk is focused on understanding the risk for and levels of hypoargininaemia in clinical practice.
Risk factors and risk groups:	Paediatric patients that are still under development and risk to the foetus during pregnancy.
Preventability:	The product labelling adequately addresses this risk. The risk of prolonged hypoargininaemia can be mitigated by adequate

	monitoring of arginine concentration and dose adjustments as required.
Impact on the benefit risk balance:	No impact on the benefit risk balance has been identified.
Public health impact:	This potential risk is managed via product labelling and no impact on public health is identified.

Important Potential Risk 3: Medication errors during administration by a non-healthcare professional

Table SVII.3: Important potential risk 3: Medication errors during administration by a non-healthcare professional

Potential Mechanism:	Accidental mistakes in preparation and administration of pegzilarginase.
Evidence source and strength of evidence:	No evidence of risk available from the clinical study programme. The potential risk is based on the theoretical possibility of medication errors when the product is handled by a non-healthcare professional.
Characterisation of risk:	Not applicable since administration by non-healthcare professional were not utilised in clinical trials. No reports of medication errors have been reported so far.
Risk factors and risk groups:	Patients for whom home administration by the patient or their caregiver will be performed.
Preventability:	The treating physician may allow subcutaneous home administration by the patient or caregiver after at least 8 weeks of treatment, once a stable maintenance dose has been established and the risk for hypersensitivity reactions is assessed as low. Before self-administration is allowed, the patient or caregiver should be adequately trained. Clear instructions for use in the package leaflet supplemented by an educational material directed to patients and caregivers as an additional risk minimisation measure to provide instructions to non-healthcare professionals on proper handling and administration of pegzilarginase.
Impact of benefit risk balance:	No impact on the benefit-risk balance has been identified.
Public health impact:	This potential risk is managed via product labelling and educational materials and no impact on public health is identified.

SVII.3.2. Presentation of the missing information

Missing information 1: Safety in pregnancy and lactation

Table SVII.3: Missing information 1: Safety in pregnancy and lactation.

Evidence source	In nonclinical studies, female pregnant rats and rabbits dosed at 1 and 0.3 mg/kg, respectively, had offspring of decreased size that exhibited skeletal malformations. Such findings have been reported in the literature to resolve with age and are therefore considered

	transient secondary effects which manifested as maternal and foetal toxicities due to the exaggerated pharmacology observed at these dose levels during pregnancy [DeSesso and Scialli, 2018]. The NOAEL for embryofoetal development was considered 0.3 mg/kg in female rats and 0.1 mg/kg in female rabbits. Pregnant and lactating women were not included in clinical trials. Arginase activity is also highly up-regulated in term placenta and increased in the peripheral blood of pregnant women [Kropf *et al*, 2007]. There is no data on the safety profile in pregnant and lactating women.
Population in need of further characterisation	The risk in pregnancy and lactation to the mother and foetus cannot be defined based on the available data and therefore the safety profile will be derived from routine pharmacovigilance activities.

Missing information 2: Long-term safety

Table SVII.4: Missing information 2: Long-term safety.

Evidence source	At the DLP [14 Oct 2021] of the Summary of Clinical Safety, clinical exposure with pegzilarginase has been observed in 28 subjects for >1 year out of which 13 subjects have been exposed for more than 2 years (median 60.5 weeks, range: 5 to 197 weeks).
Population in need of further characterisation	Current data indicates that there are no safety concerns for long term use for >2 years. As the treatment is long-term, the risk of use for prolonged therapy cannot be defined based on the available data. The safety profile will be further established from follow-up in the long-term extension studies and post-marketing experience.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns.

Summary of safety concerns	
Important identified risks	None
Important potential risks	Severe hypersensitivity reactions Prolonged hypoargininaemia and its clinical sequelae Medication errors during administration by a non-healthcare professional
Missing Information	Safety in pregnancy and lactation Long-term safety

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

None

Other forms of routine pharmacovigilance activities for safety concerns:

Active surveillance for pegzilarginase

The active surveillance for pegzilarginase is set up to further characterize the safety profile of pegzilarginase, such as the safety concerns severe hypersensitivity and prolonged hypoargininaemia and its clinical sequelae. A questionnaire is asked to be completed by treating physicians for all patients treated with pegzilarginase.

All physicians prescribing pegzilarginase which have patients not enrolled in the post-authorisation safety study (A European, non-interventional, multicentre, post-authorisation safety study to evaluate the long-term safety of Loargys treatment in arginase 1 deficiency patients in standard clinical care), will be contacted every 6 months by the MAH. The physicians will be asked to complete a safety questionnaire for each patient treated with pegzilarginase. In addition to basic questions on adverse drug reactions (ADRs), the questionnaire will also include targeted questions related to hypersensitivity, prolonged hypoargininaemia and medication errors. Data from all patients treated with pegzilarginase within the EU and other countries where the product is marketed, as applicable, will be eligible.

The data collected in the active surveillance will be presented in the Periodic Safety Update Reports as well as in annual reports to be submitted as part of the product annual re-assessment. The active surveillance questionnaire is included in Annex 4.

III.2 Additional pharmacovigilance activities

Title: A European, non-interventional, multicentre registry based post authorisation safety study to evaluate the long-term safety of Loargys treatment in arginase 1 deficiency patients in standard clinical care (IMM-PEG-002)

Rationale: To further evaluate the safety profile of pegzilarginase, including the safety concerns severe hypersensitivity, occurrences of prolonged hypoargininaemia and its clinical consequences, the effectiveness of educational material to minimise the risk for medication errors and to prevent, identify and manage hypersensitivity reactions, use during pregnancy and lactation and long-term safety data.

Study design: A non-interventional, non-comparative, multi-centre post-authorisation registry based safety study performed in collaboration with the E-IMD designed to collect safety data in patients treated with pegzilarginase.

Population: Adult and paediatric patients aged ≥2 years with a diagnosis of ARG1-D.

Milestones:

Protocol submission to EMA: Draft protocol to be submitted within 3 months after notification of the EC decision.

Start of data collection: Planned for Jun 2024 (of note: start of data collection will depend on the availability of a final protocol, the approval by national health authorities and independent ethics committees, the availability of pegzilarginase in the respective country and the consent of the participating patients)

Interim reports: Annually (with annual re-assessment)

End of data collection: Based on annual re-assessments

Final report: Based on annual re-assessments

Title: An Open-label, Multicenter Study to Evaluate the Long-term Safety, Tolerability, and Efficacy of AEB1102 in Patients with Arginase 1 Deficiency (Study 102A)

Rationale: To characterize the long-term safety and tolerability of pegzilarginase administered for up to 4 years

Study design: An open-label long-term extension study of pegzilarginase planned to be conducted for up to 4 years in 14 paediatric and adult subjects with ARG1-D who had previously completed participation in Study 101A. After the initial 24 weeks of IV treatment, it was recommended to transition to SC administration.

Population: Adult and paediatric patients aged ≥2 years with a diagnosis of ARG1-D

Milestones: Final report 31Mar2024

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A European, non-interventional, multicentre post authorisation safety study to evaluate the long-term safety of Loargys treatment in arginase 1 deficiency patients in standard clinical care (IMM-PEG-002) Planned	Evaluate the safety of Loargys in the post-marketing setting	- Severe hypersensitivity reactions - Prolonged hypoargininaemia and its clinical sequelae - Medication errors during administration by a non-healthcare professional - Long-term safety - Safety in pregnancy and lactation	Protocol submission	Within 3 months of EC decision
			Interim reports	Annually (with annual re-assessment)
Open-label extension study (Study CAEB1102-102A) Ongoing	Evaluate the efficacy and safety of pegzilarginase and characterize the PK and PD of pegzilarginase in patients ≥2 years for up to 4 years	- Severe Hypersensitivity reactions - Prolonged hypoargininaemia and its clinical sequelae - Long term safety	Final Report	31Mar2024
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Analysis of patients with ARG1-D treated with Loargys enrolled in a European, non-interventional, multicentre registry (IMM-PEG-003) Planned	To investigate the effectiveness of Loargys in the treatment of ARG1-D in standard clinical care	Effectiveness of Loargys in the real-world setting, including dosing requirements in relation to e.g. dietary changes	Protocol submission	Within 3 months of EC decision
			Interim reports	Annually (with annual re-assessment)
Randomized double-blind, placebo-controlled study extension study (Study CAEB1102-300A) Ongoing	Evaluate the efficacy and safety of pegzilarginase and characterize the PK and PD of pegzilarginase in patients ≥2 years for 2-4 years	Long-term effects of Loargys	Final Report	31Mar2024

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern.

Safety concern	Routine risk minimisation activities
Important Potential Risks	
Severe Hypersensitivity Reactions	Routine risk communication: SmPC section 4.3, 4.4 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Severe hypersensitivity to pegzilarginase contraindicated (SmPC section 4.3) Information included on management of hypersensitivity reactions and that pre-medication with an antihistamine and/or corticosteroid should be considered in patients who have developed a hypersensitivity reaction (SmPC section 4.4) Hypersensitivity reaction is a listed ADR (SmPC section 4.8) Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Prolonged hypoargininaemia and its clinical sequelae	Routine risk communication: SmPC section 4.2 and 4.4 PL section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Regular monitoring of the plasma arginine levels is recommended and to monitor the levels weekly for 2 weeks after any dose adjustments (SmPC section 4.2). Validated sampling procedures to measure arginine must be used in patients treated with Loargys (SmPC section 4.4) Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Medication errors during administration by a non-healthcare professional	Routine risk communication: SmPC section 4.2 PL section 3 and 7 Routine risk minimisation activities recommending specific clinical measures to address the risk: Administration by a non-healthcare professional may be considered with subcutaneous administration and after at least 8 weeks of treatment, once a stable maintenance dose has been established, and if treating physician consider it appropriate. Before self-administration, the patient or caregiver should be adequately trained (SmPC section 4.2).

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Missing Information	
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Information on the lack of clinical data in pregnant or lactating women is included in Section 4.6 with cross reference to the non-clinical safety findings on male fertility and embryofoetal development. Information that pegzilarginase is not recommended during pregnancy and in women of childbearing potential not using contraception is included in Section 4.6 of the SmPC. Information that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from pegzilarginase therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman is included in Section 4.6 of the SmPC. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Long term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription

V.2. Additional Risk Minimisation Measures

Educational material for non-healthcare professionals

An educational material, in the form of an injection guide directed to patients and caregivers, is to be established as an additional risk minimisation measure.

Objectives

The educational material is aimed to provide instructions to non-healthcare professionals (patients and caregivers) for proper administration techniques of Loargys subcutaneously as well as to minimize the risk of severe hypersensitivity reactions during treatment. The educational material will address the following important potential risks:

- Medication errors during administration by a non-healthcare professional
- Severe hypersensitivity reactions

Rationale for the additional risk minimisation activity

The additional risk minimisation activity is to be established to ensure Loargys is administered correctly when self-administered to prevent medication errors as well as minimising the risk of severe hypersensitivity reactions in this patient group.

Target audience and planned distribution path

The target audience include patients and caregivers for whom subcutaneous self-administration of Loargys in the home-setting has been determined appropriate by their healthcare provider.

The educational material is planned to be distributed to hospital clinics with physicians experienced in the management of patients with inherited metabolic diseases and specifically UCDs. The material and distribution plan will be approved by national competent authorities in each country before commercial launch.

Plans to evaluate the effectiveness of the interventions and criteria for success

The effectiveness of the educational material will be evaluated in the Loargys Post Authorisation Safety Study (PASS) (IMM-PEG-002). Evaluation of effectiveness will be performed via the analyses provided during the annual re-assessments.

V.3 Summary of risk minimisation measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Severe hypersensitivity reactions	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8 PL section 2 and 4 Restricted medical prescription Additional risk minimisation measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pegzilarginase active surveillance Additional pharmacovigilance activities: Pegzilarginase registry-based PASS (IMM-PEG-002) To be reported annually (with annual re-assessment) Open-label extension study (Study CAEB1102-102A) Final report due 31Mar2024
Prolonged hypoargininaemia and its clinical sequelae	Routine risk minimisation measures: SmPC section 4.2 and 4.4 PL section 3 Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pegzilarginase active surveillance Additional pharmacovigilance activities: Pegzilarginase registry-based PASS (IMM-PEG-002) To be reported annually (with annual re-assessment) Open-label extension study (Study CAEB1102-102A) Final report due 31Mar2024
Medication errors during administration by a non-healthcare professional	Routine risk minimisation measures: SmPC section 4.2 PL section 3 and 7 Restricted medical prescription Additional risk minimisation measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pegzilarginase active surveillance Additional pharmacovigilance activities: Pegzilarginase registry based PASS (IMM-PEG-002) To be reported annually (with annual re-assessment)
Missing Information		
Safety in pregnancy and lactation	Routine risk minimisation measures: SmPC section 4.6	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL section 2 Restricted medical prescription Additional risk minimisation measures: None	reactions reporting and signal detection: Pegzilarginase active surveillance Additional pharmacovigilance activities: Pegzilarginase registry-based PASS (IMM-PEG-002) To be reported annually (with annual re-assessment)
Long term safety	Routine risk minimisation measures: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pegzilarginase active surveillance Additional pharmacovigilance activities: Pegzilarginase registry-based PASS (IMM-PEG-002) To be reported annually (with annual re-assessment) Open-label extension study (Study CAEB1102-102A) Final report due 31Mar2024

Part VI: Summary of the risk management plan

Summary of risk management plan for Loargys (pegzilarginase)

This is a summary of the risk management plan (RMP) for Loargys. The RMP details important risks of Loargys, how these risks can be minimised, and how more information will be obtained about Loargys´ risks and uncertainties (missing information).

The Loargys summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Loargys should be used.

This summary of the RMP for Loargys should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Loargys 's RMP.

I. The medicine and what it is used for

Loargys is authorised for treatment of hyperargininaemia in adults and children >2 years old (see SmPC for the full indication). It contains pegzilarginase as the active substance as a solution for infusion or injection and it is given intravenously or subcutaneously.

Further information about the evaluation of Loargys benefits can be found in the Loargys EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Loargys, together with measures to minimise such risks and the proposed studies for learning more about the risks of Loargys, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Loargys is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Loargys are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Loargys. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table Part VI.1: Important risks and missing information.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Severe hypersensitivity reactions Prolonged hypoargininaemia and its clinical sequelae Medication errors during administration by a non-healthcare professional
Missing information	Safety in pregnancy and lactation Long-term safety

II.B Summary of important risks

Table Part VI.2: Summary of important risks.

Important potential risk: Severe hypersensitivity reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions can occur with enzyme therapy and this risk is supported by epidemiologic evidence and literature reports which also note significant variation in the frequency and severity across different therapies. Furthermore, hypersensitivity reactions were reported in clinical studies. These were solely following IV dosing and there were no reports following SC dosing.
Risk factors and risk groups	Patients with known hypersensitivity to PEG or any of the excipients.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8 PL section 2 and 4 Restricted medical prescription Additional risk minimisation measures: Educational material
Additional pharmacovigilance activities	Pegzilarginase registry-based PASS (IMM-PEG-002) Open-label extension study (Study CAEB1102-102A) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Prolonged hypoargininaemia and its clinical sequelae	
Evidence for linking the risk to the medicine	No risks related to prolonged hypoargininaemia have been observed in the clinical development program. In the nonclinical general and developmental and reproductive toxicology studies, pegzilarginase was well tolerated, with adverse

	findings associated with exaggerated pharmacology characterized by marked and sustained arginine depletion below the normal range. These findings were reversible and likely the result of exaggerated pharmacology in normal animals at baseline and, as such, are a low risk to patients with ARG1-D that have elevated basal levels of arginine.
Risk factors and risk groups	Paediatric patients that are still under development and risk to the foetus during pregnancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and 4.4 PL section 3 Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Pegzilarginase registry-based PASS (IMM-PEG-002) Open-label extension study (Study CAEB1102-102A) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Medication errors during administration by a non-healthcare professional	
Evidence for linking the risk to the medicine	No evidence of risk available from the clinical study programme. The potential risk is based on the theoretical possibility of medication errors when the product is handled by a non-healthcare professional.
Risk factors and risk groups	Patients for whom home administration by the patient or their caregiver will be performed.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 PL section 3 and 7 Restricted medical prescription Additional risk minimisation measures: Educational material
Additional pharmacovigilance activities	Pegzilarginase registry-based PASS (IMM-PEG-002) See section II.C of this summary for an overview of the post-authorisation development plan.

Table Part VI.3: Missing information

Missing Information: Safety in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pegzilarginase registry-based PASS (IMM-PEG-002)

	See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pegzilarginase registry-based PASS (IMM-PEG-002) Open-label extension study (Study CAEB1102-102A) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Title: A European, non-interventional, multicentre registry based post authorisation safety study to evaluate the long-term safety of Loargys treatment in arginase 1 deficiency patients in standard clinical care (IMM-PEG-002)

Rationale: To further evaluate the safety profile of pegzilarginase, including the safety concerns severe hypersensitivity, occurrences of prolonged hypoargininaemia and its clinical consequences, the effectiveness of educational material to minimise the risk for medication errors and to prevent, identify and manage hypersensitivity reactions, use during pregnancy and lactation and other long-term safety data.

Study design: A non-interventional, non-comparative, multi-centre post-authorisation registry based safety study performed in collaboration with the E-IMD designed to collect safety data in patients treated with pegzilarginase.

Population: Adult and paediatric patients aged ≥2 years with a diagnosis of ARG1-D.

Milestones:

Protocol submission to EMA: Draft protocol to be submitted within 3 months after notification of the EC decision

Start of data collection: Planned for Jun 2024 (of note: start of data collection will depend on the availability of a final protocol, the approval by national health authorities and independent ethics committees, the availability of pegzilarginase in the respective country and the consent of the participating patients)

Interim reports: Annually (with annual re-assessment)

End of data collection: Based on annual re-assessments

Final report: Based on annual re-assessments

Title: Analysis of patients with ARG1-D treated with Loargys enrolled in a European, non-interventional, multicentre registry (IMM-PEG-003)

Rationale: To investigate the effectiveness of Loargys in the treatment of ARG1-D in standard clinical care.

Study design: Designed to analyse data in ARG1-D patients treated with Loargys in the real-world setting collected in the E-IMD European, non-interventional, multi-centre registry

Population: Adult and paediatric patients aged ≥2 years with a diagnosis of ARG1-D

Milestones:

Protocol submission to the EMA: Within 3 months after notification of the EC decision

Start of data collection: Registry is ongoing

Interim analysis: Annually (with annual re-assessment)

End of data collection: Based on annual re-assessments

Final report: Based on annual re-assessments

Title: PEACE (Pegzilarginase Effect on Arginase 1 deficiency Clinical Endpoints): a randomized, double-blind, placebo-controlled phase 3 study of the efficacy and safety of pegzilarginase in children and adults with arginase 1 deficiency (Study CAEB1102-300A)

Rationale: To characterize the long-term (>24 to up to 174 weeks) treatment effects of pegzilarginase administration

Study design: After completion of a 24-week double-blind (DB) treatment period, each subject entered the open-label long-term extension (LTE) period of up to 150 weeks. Subjects who received pegzilarginase during the DB period continued to receive their optimized dose of pegzilarginase (20 patients). Subjects who received placebo (11 patients) were transitioned to pegzilarginase at a dose of 0.10 mg/kg that was permitted to be adjusted during the LTE period based on arginine levels. Subjects had the option to receive pegzilarginase by weekly subcutaneous (SC) administration.

Population: Adult and paediatric patients aged ≥2 years with a diagnosis of ARG1-D

Milestones: Final report 31Mar2024

Title: An Open-label, Multicenter Study to Evaluate the Long-term Safety, Tolerability, and Efficacy of AEB1102 in Patients with Arginase 1 Deficiency (Study CAEB1102-102A)

Rationale: To characterize the long-term safety and tolerability of pegzilarginase administered for up to 4 years

Study design: This is an ongoing, open-label long-term extension study of pegzilarginase planned to be conducted for up to 4 years in 14 paediatric and adult subjects with ARG1-D who had previously completed participation in Study 101A. After the initial 24 weeks of IV treatment, it was recommended to transition SC administration.

Population: Adult and paediatric patients aged ≥2 years with a diagnosis of ARG1-D

Milestones: Final report 31Mar2024

II.C.2 Other studies in post-authorisation development plan

None

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Loargys (pegzilarginase) active surveillance questionnaire

Patient Details		
Initials	**Sex**	**Age**

Loargys treatment details			
Indication	**Start date**	**Stop date**	**Batch / Lot #**
Route of administration	**Weekly dose (mg/kg)**	**Weekly dose (mg)**	
☐ IV ☐ Subcutaneous			

Has the patient reported any of the following?			
Hypersensitivity reactions	☐ Yes	(complete section 1 below)	☐ No
Sustained low levels of arginine	☐ Yes	(complete section 2 below)	☐ No
Medication errors when administered	☐ Yes	(complete section 3 below)	☐ No
Other adverse drug reactions	☐ Yes	(complete section 4 below)	☐ No
Pregnancy or lactation	☐ Yes	(complete pregnancy form provided separately by Immedica)	☐ No

If you have responded No to all questions above, please return the questionnaire to Immedica Pharma AB.

If you have responded Yes to any of the questions above, please complete relevant sections and return the questionnaire to Immedica Pharma AB.

Please send this form as soon as possible to safety@immedica.com

The information provided in this form will be processed with support of IT systems and may be shared with partners and authorities within and outside the EU for the purpose protecting patient safety (see www.immedica.com for full data privacy notice).

Reporter information		
Profession	**Name of Health Care Professional**	**Contact details to Health Care Professional (E-mail / address)**
☐ Physician ☐ Nurse ☐ Pharmacist ☐ Other:		

Section 1 - Hypersensitivity reactions	
Question	**Response**
1a. Please describe the clinical course and symptoms of the hypersensitivity reaction	
1b. What was the time to onset for the hypersensitivity reaction?	
1c. Was the reaction considered serious?	☐ Yes ☐ No If Yes, please indicate the seriousness criteria below ☐ Fatal ☐ Life-threatening ☐ Initial or prolonged hospitalization ☐ Persistent disability or incapacity ☐ Other medically important:
1d. Did the patient experience signs or symptoms of a severe hypersensitivity reaction?	☐ Yes ☐ No If yes, please indicate the symptoms below ☐ Hives ☐ Generalised urticaria ☐ Tightness of the chest ☐ Wheezing ☐ Hypotension ☐ Other symptom, please describe:
1e. Was any prophylaxis given prior to the event?	☐ Yes ☐ No If yes, please provide product used and dosage:
1f. Was any treatment given for the hypersensitivity reaction?	
1g. What was the outcome of the hypersensitivity reaction, including results of any dechallenge/rechallenge	☐ Recovered/Resolved ☐ Recovered/Resolved with sequelae ☐ Recovering/Resolving ☐ Not recovered/Not resolved ☐ Fatal ☐ Unknown Results of dechallenge/rechallenge:
1h. Please provide a causality assessment of the hypersensitivity reaction in relation to the Loargys treatment. Provide other alternative causes if applicable.	☐ Related ☐ Not related Description including other causes:
Please include any missing details in the Adverse Drug Reaction report form provided by Immedica.	

Section 2 - Prolonged hypoargininaemia						
Question	**Response**					
2a. Please provide arginine levels at time of prolonged hypoargininaemia	Date of arginine test	Arginine level	Unit	Reference range	Time since last Loargys dose (hours)	Last Loargys dose (mg)
2b. Have nor-NOHA tubes been used when drawing the arginine sample?	☐ Yes ☐ No Comment:					
2c. Please describe further details on the low arginine levels including, but not limited to, the following aspects: - timing in relation to treatment changes - duration of prolonged hypoargininaemia						
2d. Please describe potential causes of the prolonged hypoargininaemia, including Loargys or other concomitant medications, changes in diet, other illnesses etc.						
2e. Has the patient experienced any symptoms or adverse drug reaction(s) in relation to the low levels of arginine?	☐ Yes ☐ No If yes, please list the adverse drug reactions(s):					
2f. Please describe the clinical course of the adverse reactions(s) listed above						
Please include any missing details in the Adverse Drug Reaction report form provided by Immedica.						

Section 3 - Medication errors when administered by a non-healthcare professional	
Question	**Response**
3a. Please describe the medication error(s) reported	
3b. Has the patient been given the educational material provided by Immedica Pharma AB?	☐ Yes ☐ No
3c. Is the medication error suspected to be caused by deficiencies in the educational material?	☐ Yes ☐ No If yes, please provide suggestions for improvement
Please include any missing details in the Adverse Drug Reaction report form provided by Immedica.	

Section 4 - Other adverse drug reactions	
Question	**Response**
4a. Please list any other adverse drug reactions(s) considered related to Loargys	
4b. Please describe the clinical course of the adverse reactions(s) listed above	
Please complete the Adverse Drug Reaction report form provided by Immedica.	

Immedica administrative information	
Date first received by Immedica/partner (day 0)	Immedica case number

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Approved key messages of the additional risk minimisation measures

Prior to launch of Loargys in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to provide instructions to non-healthcare professionals (patients and caregivers) for proper administration techniques to address the potential risk of medication errors as well as to minimize the potential risk of severe hypersensitivity reaction.

The MAH shall ensure that in each Member State where Loargys is marketed, all patients or caregivers who are expected to administer Loargys as a subcutaneous injection in the home-setting are provided with the following educational material:

- Injection guide for patients and caregivers

This educational material, for patients and caregivers, shall contain the following key messages:

- Instructions on importance of proper handling, preparation and administration of Loargys to reduce the risk of medication errors
- A detailed description on how to prepare and administer Loargys
- A description of the signs and symptoms of severe hypersensitivity reactions
- A description of the recommended course of action if signs and symptoms of hypersensitivity occur
- Information on the importance of reporting of side effects including hypersensitivity and medication errors