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

Sponsor study number: IMM-PEG-002
v 1.0 28 May 2025

PASS information

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
Protocol version identifier	IMM-PEG-002 version 1.0
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EMA RWD Catalogues	1000000555
Active substance	Pegzilarginase ATC code: A16AB24
Medicinal product	Loargys
Product reference	H0005484
Procedure number	EMA/PASS/0000258458 (previously assessed as EMEA/H/C/PSP/S/0105)
Marketing authorisation holder	Immedica Pharma AB
Joint PASS	No
Research question and objectives	The primary objective of this study is to further evaluate the safety profile of Loargys, including severe hypersensitivity reactions, occurrences of prolonged hypoargininaemia and its clinical consequences, use during pregnancy and lactation and long-term safety. The effectiveness of product educational material will also be studied
Countries of study	The countries where the study will be conducted are not yet identified; a proposal to join the PASS will be made to all European E-IMD centres in countries where Loargys is available
Author	[redacted] Immedica Pharma AB Solnavägen 3H, 113 63, Stockholm, Sweden

Marketing authorisation holder

Marketing authorisation holder	Immedica Pharma AB Solnavägen 3H, 113 63, Stockholm, Sweden
MAH contact person	[redacted]

SIGNATURE PAGE

Sponsor's Approval

The protocol has been electronically approved by Immedica Pharma AB. The content of this protocol has been reviewed and approved by the MAH´s Qualified Person responsible for Pharmacovigilance (QPPV) and Head of Global Integrated Evidence Generation/Global Head of Genetic and Metabolic Diseases. The electronic signatures are available on file.

Sponsor's signatories:

[redacted]
Head of Global Integrated Evidence Generation,
Global Head of Genetic and Metabolic Diseases, Immedica Pharma AB

[redacted]
Head of Global Drug Safety, EU-QPPV, Immedica Pharma AB

Sponsor's Authorized Officer:

[redacted]
Head of Global Integrated Evidence Generation,
Global Head of Genetic and Metabolic Diseases
Immedica Pharma AB
Solnavägen 3H
113 63 Stockholm
Sweden

INVESTIGATOR'S AGREEMENT

I have read the Study IMM-PEG-002 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. Table of contents

2. List of abbreviations

ADR	adverse drug reactions
AE	adverse event
ARG1	arginase 1
ARG1-D	arginase 1 deficiency
EAA	essential amino acids
E-IMD	European registry and network for intoxication type metabolic diseases
EMA	European medicines agency
EMA RWD Catalogues	EMA Catalogue of real-world data studies (previously known as EU PAS Register).
EU	European union
GVP	good pharmacovigilance practice
ICF	informed consent form
ICSRs	individual case safety reports
IEC	independent ethics committee
IV	intravenous
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities
n	number
PASS	post-authorisation safety study
QPPV	qualified person responsible for pharmacovigilance
RMP	risk management plan
SAE	serious adverse events
SC	subcutaneous
SD	standard deviation
SmPC	summary of product characteristics
UCD	urea cycle disorders

3. Responsible parties

The marketing authorization holder (MAH), Immedica Pharma AB ("Immedica"), is responsible for the design, conduct and data evaluation of this post-authorisation safety study (PASS). This is a non-interventional study, eliciting information from health care professionals completing the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) registry modules.

The PASS is based on collaboration between Immedica and E-IMD. The collaborative approach taken jointly by Immedica and E-IMD will use the established E-IMD registry which includes urea cycle disorders (UCDs) and amend the existing E-IMD data collection by additional data elements pertaining to specific research questions regarding the safety of Loargys. E-IMD consists of a network of collaborating partners from various clinical centres of excellence across Europe. Prior to study start, a contract will be established between Immedica and Heidelberg University Hospital (E-IMD central study office) on behalf of the E-IMD consortium, which determines the tasks and responsibilities of Immedica and E-IMD respectively, deliverables and reporting of study results, as well as the ownership of data. Additionally, individual site contracts will define the responsibilities of Immedica, E-IMD and the clinical sites, respectively.

MAH / Sponsor of the PASS	Immedica Pharma AB Solnavägen 3H SE-113 63 Stockholm Sweden
Collaborating partner	Heidelberg University Hospital (E-IMD central study office) as the coordinating centre of the E-IMD consortium
Coordinating investigator	[redacted] Head of Global Integrated Evidence Generation, Global Head of Genetic and Metabolic Diseases Immedica Pharma AB Solnavägen 3H 113 63 Stockholm Sweden
Data management and data analysis	Central study office of E-IMD at: Centre for Pediatric and Adolescent Medicine Division for Pediatric Neurology and Metabolic Medicine Im Neuenheimer Feld 430 D – 69120 Heidelberg Germany

4. Abstract

Study 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
Study number	IMM-PEG-002
Sponsor	Immedica Pharma AB
Rationale and background	Arginase 1 deficiency (ARG1-D) is a rare, debilitating, progressive, inherited, neurotoxic, metabolic disease associated with increased levels of arginine and its metabolites, with significant reductions in quality of life and increased morbidity. It is an autosomal recessive disease caused by a deficiency in the arginase 1 (ARG1) enzyme which is active in the urea cycle. Manifestation of the disease include progressive spastic paraplegia, cognitive deficiency, epilepsy, and ultimately severe disability and early mortality. Pegzilarginase (Loargys) is a modified, cobalt-substituted, pegylated recombinant human ARG1 enzyme intended for chronic management of patients aged 2 years and older with ARG1-D in conjunction with individualised disease management such as dietary protein restriction, amino acid supplements and pharmacological treatment. In the Loargys ARG1-D clinical development program, mild to moderate hypersensitivity reactions were observed in 6 of 48 (12.5%) treated subjects. Although the hypersensitivity reactions observed in clinical studies where generally mild to moderate in severity it is not known if there is potential for more severe reactions and therefore severe hypersensitivity reactions are included in the EU-RMP as an important potential risk with Loargys treatment. Treatment with Loargys in ARG1-D patients is intended to reduce plasma arginine to normal levels. In nonclinical studies in animals with normal levels of arginine at baseline, prolonged hypoargininaemia was observed which was considered to be due to exaggerated pharmacology following treatment with pegzilarginase. Transient hypoargininaemia is not unexpected with intravenous dosing of Loargys in humans and to a lesser extent with subcutaneous dosing. Prolonged hypoargininaemia and its clinical sequelae is included in the EU-RMP as an important potential risk with Loargys treatment. Administration of subcutaneous Loargys by non-healthcare professionals can be considered following appropriate training of the patient or caregiver. Correct handling and administration procedures are essential to ensure correct dose and effect from treatment, as well as to avoid the risk for medication errors which has been included as an important potential risk in the EU-RMP. An educational material has been developed as an additional risk minimization measure to prevent the risk of medication errors during administration of a non-healthcare professional. The effectiveness of the educational material to avoid the risk for medication errors and to prevent, identify and manage hypersensitivity reactions require follow-up in clinical practice. No data on treatment with Loargys in pregnant or lactating females is available. Furthermore, there are limited number of patients exposed to long-term treatment with Loargys. Therefore, the safety profile of Loargys during pregnancy and lactation and long-term safety has been included as missing information in the EU-RMP. This Post-Authorisation Safety Study (PASS) is established to evaluate the long-term safety of Loargys to fulfil an EMA specific obligation of the EU marketing

	authorisation.
Research questions and objectives	The objective of the study is to evaluate the long-term safety of Loargys treatment in patients with ARG1-D. <u>Specifically, this study is set out to:</u> Evaluate safety in patients treated with Loargys by collecting information on: • severe hypersensitivity reactions • occurrences of prolonged hypoargininaemia and its clinical consequences • medication errors when administered by a non-healthcare professional • the effectiveness of product educational material to minimise the risk for medication errors and to prevent, identify and manage hypersensitivity reactions when administered by a non-healthcare professional • pregnancy and lactation • long-term safety by collection of Adverse Events (AEs)
Study design	This is a non-interventional, non-comparative, multi-centre, prospective, registry-based PASS, which will be conducted in collaboration with the E-IMD. It will be based on registry data using observational methods to collect uniform data prospectively in patients with ARG1-D to monitor the long-term safety of Loargys following granting of the EU marketing authorisation. Health-related personal data concerning treatment and clinical condition of individual patients will be collected at a baseline visit, and prospectively during regular visits or during unscheduled/emergency visits per E-IMD patient registry procedure. The long-term safety of Loargys will be evaluated based on AEs including hypersensitivity reactions, prolonged hypoargininaemia, medication errors when administered by a non-healthcare professional, and pregnancy/lactation exposure. Regular visits collect data from standard care monitoring appointments, recommended to be performed at least every six-months during treatment with Loargys according to the Summary of Products Characteristics (SmPC) but may occur more frequently if medically indicated. Unscheduled visits are all other medical contacts or appointments occurring outside standard monitoring schedule. Visits for acute management of the patient are recorded as emergency visits.
Patient population	Adult and paediatric patients aged 2 years and older enrolled in the PASS with a confirmed diagnosis of ARG1-D and prescribed treatment with Loargys.
Inclusion/ exclusion criteria	<u>Inclusion criteria</u> 1. Enrolled in the main E-IMD registry 2. Diagnosis of arginase 1 deficiency 3. Treated with Loargys 4. Written informed consent for the PASS <u>Exclusion criteria</u> 1. Enrolled in an interventional clinical trial with Loargys In addition, the exclusion criteria listed as per the main E-IMD registry protocol apply: 2. Individuals with rare and unrelated serious comorbidities, e.g. Down syndrome, severe intraventricular haemorrhage (°III-IV) in the newborn period, extreme low birth weight (<1,500 grams), Kernicterus, embryofoetal disease due to maternal alcohol or drug abuse
Variables	The registry collects demographic data on the initial presentation, such as medical history and family history at baseline. Additional data on the current overall health status, including physical examination and concomitant medications is collected at baseline and in subsequent follow-up visits. Follow-up visits encompass regular

	patient visits as well as unscheduled visits and emergency visits. The study will further collect variables for the long-term safety of Loargys such as AEs (including all hypersensitivity reactions), medication errors, changes in clinical laboratory tests (arginine) and lack of efficacy. Parameters to be collected: • Demographics (patient age at date of baseline, sex, country, ethnicity) • Patient characteristics (height, weight, medical history at baseline) • AEs • Severe hypersensitivity reactions (as defined in Section 9.3) • Prolonged hypoargininaemia • Medication errors • Information of pregnancy and lactation, as applicable • Dose and exposure to Loargys (start/stop, reason for stopping) and other potential therapeutic and supportive interventions • Plasma arginine levels (baseline prior to Loargys treatment, and follow-up during treatment)
Data sources	Participating investigators will enter the data in the electronic registry record forms provided by the E-IMD. Patients/caregivers will receive paper-based logs for recording of Loargys administrations by a non-health care professional and any AEs experienced to support recollection of events between visits. The patients' hospital case records will be the source for all data. The Sponsor's global safety database will be used for management of SAEs, ADRs and pregnancy/lactation exposure. Prospective post authorisation safety data since the EU approval of Loargys will be collected in this study.
Study size	All ARG1-D patients treated with Loargys in Europe at treatment sites included in the PASS, are eligible to be enrolled in the study.
Countries	A proposal to join the PASS will be made to all EU E-IMD centres in countries where Loargys is available.
Data analysis	A formal statistical analysis plan that will provide details of all analyses and presentation of data will be approved prior to data analysis. Descriptive statistics will comprise the number (n) of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables. Data will be presented for ARG1-D patients enrolled in the PASS. Additional subgroups may be examined, as deemed appropriate (paediatric, adult and elderly). All AEs will be coded to System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA). Tables including overview or AEs, common AEs, related AEs, SAEs and related SAEs will be presented. Narratives will be prepared for cases of severe hypersensitivity reactions, prolonged hypoargininaemia and pregnancy/lactation. These may include individual patient graphs (e.g. arginine values over time for cases of prolonged hypoargininaemia). Demographic, disposition and clinical data will be summarised with descriptive statistics. Post-baseline values and/or change from baseline in the outcome variables will be summarised with descriptive statistics, and, where appropriate, graphical presentations.

Timelines	**Milestone**	**Planned date**
	Protocol submission to EMA	Draft protocol to be submitted within 3 months after notification of the EC decision
	Start of data collection	Planned for Nov 2025 (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 Loargys in the respective country and the consent of the participating patients)
	End of data collection	Based on annual EMA reassessment

5. Amendments and updates

Not applicable.

6. Milestones

Milestone	Planned date
Study protocol to be agreed by EMA, Immedica, and E-IMD	May 2025 (actual date 8 May 2025)
Start of data collection	Planned for Nov 2025 (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 Loargys in the respective country and the consent of the participating patients)
End of data collection	Based on annual EMA reassessment
Interim reports	Annually with annual re-assessment
Registration in the EMA RWD Catalogues	June 2025
Final report of study results	Based on annual EMA reassessment

7. Rationale and background

Arginase 1 deficiency (ARG1-D) is a rare, debilitating, progressive, inherited, neurotoxic, metabolic disease associated with increased levels of arginine and its metabolites, with significant reductions in quality of life and increased morbidity. It is an autosomal recessive disease caused by a deficiency in the arginase 1 (ARG1) enzyme which is active in the urea cycle [1-4]. Manifestation of the disease include progressive spastic paraplegia, cognitive dysfunction, epilepsy, and ultimately severe disability and early mortality [2].

Standard management approaches, prior to the availability of Loargys, included individualized combinations of protein restriction to reduce arginine, essential amino acid (EAA) supplementation, and concomitant medications to manage other clinical symptoms such as nitrogen scavengers to help control the ammonia level. Dietary modification can produce modest reductions in plasma arginine levels, but reducing plasma arginine to normal levels is difficult to achieve via dietary restriction alone as arginine flux is largely dependent on whole body protein turnover and is minimally affected by dietary intake. More importantly, this treatment option does not halt the disease progression. [5-6]

Loargys (pegzilarginase) is a modified, cobalt-substituted, pegylated recombinant human ARG1 enzyme intended for chronic management of patients aged 2 years and older with ARG1-D in conjunction with individualised disease management such as dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers. Loargys has been shown to rapidly and sustainably reduce plasma arginine and convert it to urea and ornithine with associated clinically meaningful improvements in functional mobility.

In the Loargys ARG1-D clinical development program, mild to moderate hypersensitivity reactions were observed in 6 of 48 (12.5%) treated subjects. Dyspnoea was reported in a limited number of subjects, however none of the hypersensitivity reactions resulted in haemodynamic

changes. All reactions were immediate and not delayed and responded to treatment with antihistamines or corticosteroids. Although the hypersensitivity reactions observed in clinical studies where generally mild to moderate in severity it is not known if there is potential for more severe reactions and therefore severe hypersensitivity reactions are included in the Loargys EU Risk Management Plan (RMP) as an important potential risk with Loargys treatment.

Treatment with Loargys in ARG1-D patients is intended to reduce plasma arginine to normal levels. In nonclinical studies in animals with normal levels of arginine at baseline, prolonged hypoargininaemia was observed which was considered to be due to exaggerated pharmacology following treatment with pegzilarginase. Transient hypoargininaemia is not unexpected with intravenous (IV) dosing of Loargys in humans and to a lesser extent with subcutaneous (SC) dosing. Depletion of arginine to very low levels, and for extended periods as studied in the nonclinical programme, is very unlikely to occur in clinical practice due to daily multiple food intake and regular monitoring of arginine levels. Prolonged hypoargininaemia, defined as "arginine values <lower limit of normal (LLN) for more than 14 days or for two or more consecutive arginine measurements (if there was more than 14 days between measurements)", occurred infrequently in the clinical trials. No treatment emergent adverse events assessed as related were reported in relation to the hypoargininaemia. Prolonged hypoargininaemia and its clinical sequelae is included in the EU-RMP as an important potential risk with Loargys treatment.

SC administration of Loargys by non-healthcare professionals (patients or caregivers) can be considered following appropriate training of the patient or caregiver. Correct handling and administration procedures are essential to ensure correct dose and effect from treatment, as well as to avoid the risk for medication errors which has been included as an important potential risk in the EU-RMP. An educational material has been developed as an additional risk minimization measure to prevent the risk of medication errors during administration of a non-healthcare professional. The effectiveness of the educational material to avoid the risk for medication errors and to prevent, identify and manage hypersensitivity reactions require follow-up in clinical practice.

The clinical development program did not include pregnant or lactating females. Furthermore, there are limited number of patients exposed to long-term treatment with Loargys. Therefore, the safety profile of Loargys during pregnancy and lactation and long-term safety has been included as missing information in the EU-RMP.

8. Research question and objectives

This is a non-interventional post-authorisation safety study (PASS) evaluating the long-term safety of Loargys treatment in patients with ARG1-D.

Specifically, this study is set out to:

Evaluate safety in patients treated with Loargys by collecting information on:

- severe hypersensitivity reactions
- occurrences of prolonged hypoargininaemia and its clinical consequences
- medication errors when administered by a non-healthcare professional
- the effectiveness of product educational material to minimise the risk for medication errors

and to prevent, identify and manage hypersensitivity reactions when administered by a non-healthcare professional
- pregnancy and lactation
- long-term safety by collection of Adverse Events (AEs)

9. Research methods

9.1 Study design

This is a non-interventional, non-comparative, multi-centre, prospective, registry-based PASS, conducted in collaboration with E-IMD. It will be based on registry data using observational methods to collect uniform data on specified outcomes prospectively in patients with ARG1-D to monitor the long-term safety of Loargys following granting of the EU marketing authorisation.

The E-IMD has been co-funded by the European Union (via the European Agency for Health and Consumers [EAHC]; agreement no. 2010 12 01) from 1st January 2011 to 30th April 2014, in the framework of the Health Programme 2008-2013. E-IMD has established a patient-based registry including comprehensive basic and follow-up data of more than 1400 patients with organic acidurias (890) or urea cycle disorders (590). After the EU funding period has ended, E-IMD Partners and Members have continued with these activities within the legal framework of a collaboration agreement, sustaining the E-IMD network, its instruments and activities as a scientific consortium encompassing over 40 metabolic expert centres throughout Europe and worldwide.

The current (main) E-IMD registry protocol does not capture AEs or other safety data as required in this PASS. This current study will therefore be an add-on study to the existing E-IMD registry.

This study will use the main E-IMD registry as the basis. Health-related personal data concerning treatment and clinical condition of individual patients will be collected at a baseline visit, and prospectively during regular visits or during unscheduled/emergency visits per E-IMD patient registry procedure.
Regular visits collect data from standard care monitoring appointments, recommended to be performed at least every six-months for Loargys according to the EU Summary of Product Characteristics (SmPC) but may occur more frequently if medically indicated. Unscheduled visits are all other medical contacts or appointments occurring outside standard monitoring schedule. Visits for acute management of the patient are recorded as emergency visits.

The E-IMD registry has established standardized follow-up examinations of children and adults with ARG1-D. Patients are followed using a standardized assessment schedule including basic data, family history, age at diagnosis, first symptoms, frequency and duration of hospitalization, medical and developmental history, physical and neurological examination, and neuropsychological tests (see www.e-imd.org).

The Loargys PASS extends the existing E-IMD registry by collecting additional safety related data in patients with ARG1-D treated with Loargys. The existing data collection is augmented by

collection of additional data to gather information from patients with characteristics not previously studied or underrepresented in the clinical program for Loargys. Additional form(s) have been developed, whereby AEs and information on the safety concerns included in the Loargys' RMP will be collected.

9.2 Setting

This study is conducted in countries in Europe where Loargys is available to patients. A proposal to join the PASS will be made to all European E-IMD centres in countries where Loargys is available.

Inclusion criteria

The study will enrol adult and paediatric patients who fulfil all of the following criteria:

1. Enrolled in the main E-IMD registry
2. Diagnosis of ARG1-D
3. Treated with Loargys
4. Provided PASS specific written informed consent

Exclusion criteria

1. Enrolled in an interventional clinical trial with Loargys

In addition, the exclusion criteria listed as per the main E-IMD registry protocol apply:

2. Individuals with rare and unrelated serious comorbidities, e.g. Down syndrome, severe intraventricular haemorrhage (°III-IV) in the newborn period, extreme low birth weight (<1,500 grams), Kernicterus, embryofoetal disease due to maternal alcohol or drug abuse.

9.3 Variables

The E-IMD registry collects demographic data on the initial presentation, such as medical history at baseline. Additional data on the current overall health status, including physical examination and concomitant medications is collected at baseline and in subsequent follow-up visits. Follow-up visits encompass regular patient visits as well as unscheduled visits and emergency visits. The E-IMD registry will further collect variables for the long-term safety of Loargys such as AEs (including all hypersensitivity reactions), medication errors, and changes in clinical laboratory tests (arginine).

Section 1.01

Study endpoints:

- Occurrence of AEs
- Occurrence of SAEs
- Occurrence of ADRs
- Occurrence of severe hypersensitivity reactions which includes anaphylactic reactions and would usually be acute reactions with involvement of skin and/or mucosal tissue accompanied by either respiratory, cardiovascular, or gastrointestinal compromise, which require intervention or treatment
- Occurrences of prolonged hypoargininaemia, defined as "arginine values <LLN for more than 14 days or for two or more consecutive arginine measurements (if there was more than 14 days between measurements)" and associated SAEs and/or ADRs
- Occurrence of medication errors during non-healthcare professional administration
- Occurrence and clinical course of hypersensitivity reactions during non-healthcare

professional administration
- Exposure and outcomes of pregnancy and lactation

Parameters to be collected:
- Demographics (patient age at date of baseline, sex, country, ethnicity)
- Patient characteristics (height, weight, medical history at baseline)
- AEs
- Severe hypersensitivity reactions
- Medication errors when administered by non-healthcare professionals
- Information of exposure during pregnancy and lactation, as applicable
- Dose and exposure to Loargys (start/stop, reason for stopping) and other potential therapeutic and supportive interventions (for example dietary prescription, concomitant medications)
- Plasma arginine levels (baseline prior to Loargys treatment, and follow-up during treatment)

Within the E-IMD registry, data is collected at the below visits:
1. Baseline visit; Once at the beginning for a new study patient
2. Regular visit; Scheduled visits (inpatient or outpatient). In accordance with clinical practice; all regular visits are expected to be entered into the registry database, and at least once yearly. For Loargys-treated patients, the SmPC recommend monitoring visits to be performed at least every six-months but may occur more frequently if medically indicated
3. Emergency (or any other unscheduled) visit; All unscheduled visits (inpatient or outpatient) to be entered into the database
4. Fatal disease course; To be entered for study patients in case of fatal disease course.

9.4 Data sources

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed, and only these data will be collected as part of the study. The treating physician is asked to complete the appropriate E-IMD modules at every patient visit recommended by the data collection schedule.

This study will use available data documented at the participating site for the enrolled patient during each patient contact as specified above. Patients/caregivers will receive paper-based logs for recording of Loargys administrations by a non-healthcare professional and any AEs experienced to support recollection of events between visits. The logs (Annex 1) will be handed out at every visit. The patients will be instructed to bring completed logs to their next visit. The physician will review completed logs with the patient to identify any potential medication errors and AEs including potential hypersensitivity reactions. Data, as documented in the patient's medical record including physician's or nurse's notes, consultancy reports, discharge summaries, laboratory sheets, etc, will be entered by the participating sites in the electronic registry record forms provided by E-IMD. The patients' medical records will be the source for all data.

The Sponsor's global safety database will be used for management of ADRs, SAEs and

pregnancy/lactation exposure to ensure compliance with the Sponsor regulatory reporting requirements. Data from the safety database will be included in the study reports, e.g. for information to be included in safety narratives, as applicable.

9.5 Study size

All ARG1-D patients treated with Loargys in the EU, at treatment sites included in the E-IMD registry, are eligible to be enrolled in the study. However, approximately 10-15 patients are estimated to be included in the study the first 5 years. The number of anticipated patients is based on the estimated prevalence of the orphan indication and assumptions regarding the availability of Loargys at sites willing to be included in the PASS.

9.6 Data management

The E-IMD registry use a web-based secured data collection tool. The server is maintained by the Central Study Office (University Hospital Heidelberg) and has an ISO 27001 certified security concept.

Health-related personal data concerning treatment and clinical condition of individual patients will be collected at baseline, and prospective regular, unscheduled and emergency visits per the E-IMD registry protocol.

All study-related data in the E-IMD database will continuously be checked for accuracy and consistency according to the study procedures of the Central Study Office.

Medical diagnoses will be coded according to ICD-10. All AEs collected will be coded by the Sponsor using the current Medical Dictionary for Regulatory Activities (MedDRA) at least once yearly prior to the annual interim analyses as well as before the database lock. Drugs used to treat ARG1-D and concomitant medications will not be coded but entered according to pre-specified drug categories.

Data transferred from the E-IMD or collected directly by the Sponsor will be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist.

9.7 Data analysis

A formal statistical analysis plan that will provide details of all analyses and presentation of data will be approved prior to data analysis. Descriptive statistics will comprise the number (n) of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables.

Data will be presented for ARG1-D patients enrolled in the PASS. Additional subgroups may be examined, as deemed appropriate (paediatric, adult and elderly).

All AEs will be coded to System Organ Class and Preferred Term using MedDRA. Tables including overview or AEs, common AEs, related AEs, SAEs and related SAEs will be presented. Narratives will be prepared for cases of severe hypersensitivity reactions, prolonged

hypoargininaemia and pregnancy/lactation. These may include individual patient graphs (e.g. arginine values over time for cases of prolonged hypoargininaemia).

Clinical data will be summarised with descriptive statistics. Post-baseline values and/or change from baseline in the outcome variables will be summarised with descriptive statistics, and, where appropriate, graphical presentations.

Statistical analysis will be performed using the recent version of SPSS and recent version of R environment for statistical computing and graphics.

9.8 Quality control

The E-IMD registry has been used since 2011 for collecting longitudinal observational data of intoxication type metabolic disease. It was developed for this specific task, has been continually improved and already proved its capabilities by providing data for several scientific publications. The data is entered by qualified staff supervised by metabolic experts with long standing experience in using the E-IMD interface.

Collection of data will follow the standard clinical practice in treatment of the patient. The source for all collected data will be the patients' medical records. It is the responsibility of the investigator to ensure completion and to review and approve all entered data. At all times, the investigator has the final responsibility for the accuracy and authenticity of all patient data entered into the registry.

Wherever possible the registry verifies data during entry by employing valid ranges for individual data variables. Additionally, prior to each analysis and at regular intervals in between, the entered data is checked for plausibility by qualified study physicians at the Central study office and queries are issued as needed. The study centres are informed at regular intervals about the completeness of entered datasets and motivated to resolve data queries.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). Investigators will be trained in the collection of safety data by the Sponsor at the site initiation visit.

9.9 Limitations of the research methods

This PASS is being performed to generate longitudinal safety data in patients with ARG1-D treated with Loargys. It is expected to provide further insight into the long-term safety of Loargys as well as indicate any new safety signals.

However, the following limitations apply:

Study size and power to detect new risks:

By necessity, clinical trials in rare disorders enrol small sample sizes. In combination with high inter-individual variability in clinical course observed in ARG1-D, this diminishes a study's power. This study is not immune to this dual disadvantage given that ARG1-D is an ultra-orphan disease with an estimated incidence of 1 in 950,000 births [3]. Therefore, with the small number of patients expected to be enrolled in this study, ability to detect rare new risks is estimated to be

inevitably low. However, in general, new risks cannot only be detected by increasing the number of patients but also by long-term follow-up of individual patients.

Selection bias regarding disease severity

From data collected in the E-IMD registry until today, it was noted that patients who are severely ill from UCDs are to a lesser extent enrolled than patients with less severe manifestations, presumably due to the high risk of early mortality in this patient population. Thus, the generalisability of data collected in the registry to the entire population may be limited and may not include patients who are critically ill. However, all patients treated with Loargys are invited to participate in the registry. In order to minimize bias in the selection of patients, the investigators are encouraged to consecutively enrol all patients who consent and meet the selection criteria, regardless of health status, or other considerations.

Missing data

Like all non-interventional studies, data collected are generated according to the patient's medical needs upon discretion of the treating physician. It is likely that some data will be missing during the patient's participation in the registry, e.g. laboratory test results if they are not required according to the individual treatment plans of the patient. Furthermore, it must be considered that some patients may be lost to follow up, as patients may withdraw from the registry any time or move to another health care provider.

9.10 Other aspects

Not applicable. The relevant aspect of the study is covered by previous sections.

10. Protection of human subjects

This is a non-interventional study where data is documented during routine visits of participating patients. No additional visits, examinations or treatments are performed for the purpose of this study. Therefore, it is to be expected that no additional risk exists for participants.

10.1 Study conduct

This study will comply with the definition for Post-Authorisation Safety Studies in Directive 2001/83/EC Art 1 [7], and its refinement provided in the Guideline of Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies [8]. Further, this study will be conducted in compliance with this protocol and in accordance with the ethical principles for Medical Research Involving Human Subjects in the Declaration of Helsinki [9] and will be consistent with the International Ethical Guidelines for Biomedical Research Involving Human Subjects [10], as well as all other applicable regulatory requirements.

The investigator will also ensure that this study is conducted in accordance with the laws and regulations of the country in which the research is conducted.

10.2 Independent Ethics Committee review

The investigator will submit this protocol, informed consent forms (ICF), and any accompanying material to be provided to the patient (such as patient information sheets, or descriptions of the study used to obtain informed consent) to an Independent Ethics Committee (IEC), where

applicable. The investigator will not begin any study activities until approval from the IEC has been documented and provided as a letter to the investigator. If required, the investigator is responsible for providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC. Investigators are also responsible for promptly informing the IEC of any protocol amendments. Any subsequent changes to the IEC submitted study documents, including amendments, will require resubmission and reapproval by the IEC prior to implementation, with the exception of those necessary to reduce immediate risk to study subjects. It is the responsibility of the investigator to ensure that all interactions with IEC are conducted in accordance with current governmental regulations.

10.3 Informed consent

Patients or their caregiver(s) will already have consented to participating in the collection of data in the main E-IMD registry. An additional ICF will be required to be completed for the participation in this specific PASS.

It is the responsibility of the investigator to give each patient (or the patient's representative) prior to any study-related activities, full and adequate verbal and written information in local language regarding the study, including aims, methods, objectives, study activities/procedures, the possible risks/hazards involved in participation, data protection, and alternatives of the study. The investigator must utilize the most current Sponsor and IEC approved ICF for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative, in accordance with local regulations, and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements. The medical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

Patients may decline the invitation and refuse consent without giving a reason and without prejudice to any treatment that is proposed. The patients must be informed about their right to withdraw from the study at any time.

The written patient information and/or consent form must not be changed without prior agreement with the Sponsor. Before any revisions are implemented, the revised written patient information and/or consent form must be approved by the IEC.

10.4 Confidentiality

All procedures in data collection and documentation will ensure that data privacy laws are adhered to. The names of the participants and all other confidential information are subject to medical confidentiality and the statutory data protection provisions. Participant data are forwarded to the central database of the study only in key-coded form.

The main coordinator of the study has access to the key-coded data, but not the key list, of all participants. The study centres have access only to the data of the participants under their management. Access to the database is restricted to the study investigators and site personnel and

is protected by a personal password generated by the study coordinator, which must be changed by the responsible employees at regular intervals. All data sent via the internet are cryptographically encoded. Thus, no-one apart from the sender (study centre) and the recipient (Central Study Office) has access to readable data. The server with the database is protected by a professional security concept. Neither the data transmission nor the central database contains any identifying data, only the key-code.

Extracted data are pseudonymised, with patient identifiers restricted to age and gender. E-IMD will provide tables and listings and respective analysis results to Immedica in anonymized data outputs which will not permit the identification of the individual participants.

Patients and/or caregivers (as applicable) are informed about data access, management, storage and protection. They are informed that all data in the registry are pseudonymised (and what pseudonymisation means). Patients and/or caregivers give written informed consent before inclusion in the E-IMD registry. The PASS specific informed consent includes an explicit statement that patients/caregivers allow E-IMD to provide pseudonymised data to third parties. In case of publication, personal data may only be used in anonymised form.

11. Management and reporting of adverse events / adverse reactions

Data regarding AEs (including hypersensitivity, medication errors, prolonged hypoargininaemia and pregnancy/lactation exposure) of patients treated with Loargys will be added in the study specific registry module. AEs will be documented by the Investigator in the additional Loargys forms available in the E-IMD registry. Serious Adverse Events (SAEs) will also be reported directly to Immedica Global Drug Safety. Loargys suspected non-serious ADRs and pregnancy/lactation reports will be included in the Global Safety Database by Immedica Global Drug Safety via a monthly review of reported AEs within the E-IMD registry module. The reporting of suspected ADRs, SAEs and pregnancy/lactation exposure for patients treated with Loargys with regard to fulfilling critical timelines in compliance with legal requirements will remain the sole responsibility of the treating physicians at the various study sites.

Immedica Global Drug Safety will provide appropriate reporting forms to be completed by the treating physician and sent directly to Immedica Pharmacovigilance for patients on Loargys who experience an SAE. The E-IMD registry will help to facilitate this process by making these reporting forms available for download and by implementing a system of automatic warning messages that are triggered when entering data suspected as an SAE however none of these measures will assume any of the responsibilities of the treating physician and will remain strictly supportive in nature.

Definition of an AE

An adverse event is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition of an SAE

A SAE is any untoward medical occurrence that at any dose (including overdose):

- Results in death
- Is life-threatening
  "Life-threatening" means that the patient was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the adverse event (AE), or that they occurred as a consequence of the event. Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfils any other of the serious criteria
- Results in persistent or significant disability or incapacity
  "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions
- Is a congenital anomaly or birth defect
- Is an important medical event
- Other important medical events which based on medical/scientific judgement may jeopardise the patient or may require medical/surgical intervention to prevent any of the above listed outcomes.

Definition of a suspected ADR

A suspected ADR is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. For the purpose of this study an AE which was judged either by the investigator as having a reasonable causal relationship to Loargys will be considered a suspected ADR.

Causality

The investigator will provide an assessment of the causal relationship between the event and Loargys.

The investigator will primarily apply a binary form of causality assessment:

- Related: There is a reasonable causal relationship between the medicinal product and the event; or
- Not related: There is no reasonable causal relationship between the medicinal product and the event.

The investigator should use medical judgment to determine whether he/she/they assumes a reasonable causal relationship, and include into his/her/their evaluation all relevant factors and factual evidence such as:

- temporal course and latency;
- results from de-challenge or re-challenge;

- pattern of the reaction;
- known pharmacological properties of the product; and
- alternative explanations (e.g. other drugs, medical history, concomitant diseases).

The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship. Participating investigators shall report any SAEs which occurs in a patient who is treated with Loargys within 24 hours of learning of the event. This is done by completing the SAE reporting form which is sent via e-mail directly to the Immedica Global Drug Safety department at safety@immedica.com.

Every attempt should be made to describe all SAEs in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms should not be reported unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be reported individually. The report should be as complete as possible, including details of the current illness and SAE, date of onset and stop date (if applicable), diagnostic procedures and treatment of the event, relevant medical history and concomitant medication and action taken with Loargys.

In the event of a pregnancy occurring during the course of this particular study, the patient should be closely followed-up during the entire course of the pregnancy and postpartum period, regardless whether the product was continued or withdrawn, as long as they participate in the study. Pregnancy outcomes must be recorded even if they are completely normal and without AEs. Infant outcomes will be collected after birth as well as followed up for at least one year following the birth to ensure all potential outcomes are collected. Exposure during pregnancy should also be recorded.

Information not available at the time of the initial report (e.g., an end date for the event or laboratory values received after the report) will be documented and sent as a follow-up report.

All patients who have AEs must be monitored to determine the outcome. The clinical course of the AEs will be followed up according to accepted standards of medical practice until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up.

Immedica will identify missing information for each report. Requests for follow-up will be sent directly to the investigator. Immedica will require follow-up information until all queries are resolved or no further information can be reasonably expected.

<u>Reporting to Health Authorities</u>

Immedica will report cases of suspected ADRs in the form of valid individual case safety reports (ICSRs) to Health Authorities in line with legal requirements taking account of the guidance set out in Good Pharmacovigilance Practice (GVP) Module VI to ensure that the ICSRs are reported in accordance with the appropriate timeframes. The investigator is responsible for reporting of suspected ADRs to Health Authorities as per national requirements. If any reporting is performed by the investigator to Health Authorities, Immedica would like to be informed.

12. Plans for disseminating and communicating study results

Safety data collected while the study is ongoing will be reported in the annual re-assessment procedure for a product approved under exceptional circumstances. A final report will be prepared on study completion and submitted to the EMA as per GVP module VIII.

The final results of this study will be posted in the EMA Catalogue of real-world data studies (EMA RWD Catalogues).

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with E-IMD and the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues.

13. References

[1] Diez-Fernandez C, Rüfenacht V, Gemperle C, Fingerhut R, Häberle J. Mutations and common variants in the human arginase 1 (ARG1) gene: impact on patients, diagnostics, and protein structure considerations. Hum Mutat. 2018;39(8):1029-1050

[2] 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;47:1751-1762

[3] Summar ML, Koelker S, Freedenberg D, Le Mons C, Häberle J, Lee HS. The incidence of urea cycle disorders. Mol Genet Metab. 2013;110(1-2):179-180

[4] Waisbren SE, Cuthbertson D, Burgard P, et al. Biochemical markers and neuropsychological functioning in distal urea cycle disorders. J Inherit Metab Dis. 2018;41(4):657-667

[5] Bin Sawad A, Pothukuchy A, Badeaux M, Hodson V, Bubb G, Lindsley K, Uyei J, Diaz GA. Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. JIMD Rep. 2022 Mar 25;63(4):330-340

[6] Wu G, Morris SN Jr. Arginine metabolism: nitric oxide and beyond. Biochem J. 1998;336:1-17

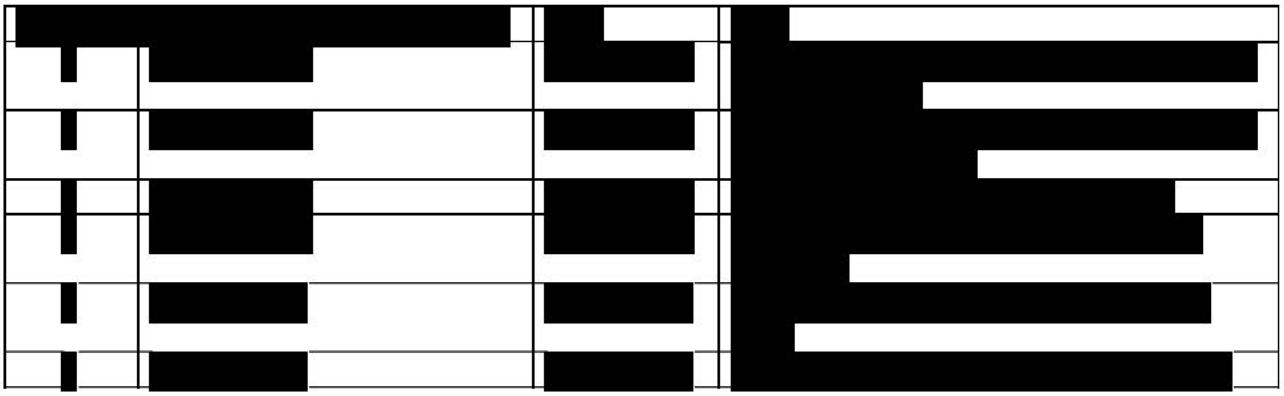
[7] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, on the Community code relating to medicinal products for human use, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010

[8] European Medicines Agency (EMA): Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies, current version dated 9 July 2012

[9] World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, latest amendment at the 59th WMA General Assembly, Seoul, South Korea, October 2008

[10] Council for International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects. 3rd ed. Geneva: CIOMS

Annex 1. List of stand-alone documents



Annex 2. ENCePP Checklist for study protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study 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

Sponsor study number: IMM-PEG-002

EU PAS Register® number: 1000000555
Study reference number (if applicable): N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	Section No 6
1.1.2 End of data collection[2]	☒	☐	☐	Section No 6
1.1.3 Progress report(s)	☒	☐	☐	Section No 6
1.1.4 Interim report(s)	☒	☐	☐	Section No 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Section No 6
1.1.6 Final report of study results.	☒	☐	☐	Section No 6 & 12

Comments:

Study start planned for Nov 2025 (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 Loargys in the respective country and the consent of the participating patients)

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section No 7
2.1.2 The objective(s) of the study?	☒	☐	☐	Section No 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section No 9.2, 9.5 & 9.9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a non-interventional post-authorisation safety study (PASS) evaluating the long-term safety of Loargys treatment in patients with ARG1-D.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	Section No 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section No 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	Section No 7 & 9.9
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	Section No 11

Comments:

This is a non-interventional, non-comparative, multi-centre, prospective, registry-based PASS, conducted in collaboration with E-IMD. It will be based on registry data using observational methods to collect uniform data on specified outcomes prospectively in patients with ARG1-D to monitor the long-term safety of Loargys following granting of the EU marketing authorisation.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	Section No 9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	Section 6
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	Section No 9.2 & 9.5
4.2.4 Disease/indication	☒	☐	☐	Section No 8 & 9.2
4.2.5 Duration of follow-up	☒	☐	☐	Section No 9.3 & 9.9
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section No 9.2

Comments:

All patients with ARG1-D treated with Loargys at E-IMD centres in Europe are eligible. Patients will be treated according to the prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed, and only these data will be collected as part of the study. The treating physician is asked to complete the appropriate E-IMD modules at every patient visit recommended by the data collection schedule.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section No 9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section No 9.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Section No 8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section No 11
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	Section No 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	Section No 9.9

Comments:

All patients treated with Loargys at E-IMD centres are invited to participate in the registry. In order to minimize bias in the selection of patients, the investigators are encouraged to consecutively enrol all patients who consent and meet the selection criteria, regardless of health status, or other considerations

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Section 9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 9.3
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 9.1 & 9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9.1, 9.3 & 11
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Section 9.7
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Section 9.4 & 9.8

Comments:

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed, and only these data will be collected as part of the study. The treating physician is asked to complete the appropriate E-IMD modules at every patient visit recommended by the data collection schedule.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section No 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Section No 9.5
10.3 Are descriptive analyses included?	☒	☐	☐	Section No 9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	Section No 9.7 & 9.9
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Like all non-interventional studies, data collected are generated according to the patient's medical needs upon discretion of the treating physician. It is likely that some data will be missing during the patient's participation in the registry, e.g. laboratory test results if they are not required according to the individual treatment plans of the patient. Furthermore, it must be considered that some patients may be lost to follow up, as patients may withdraw from the registry any time or move to another health care provider. A formal statistical analysis plan that will provide details of all analyses and presentation of data will be approved prior to data analysis.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Section No 9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section No 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	Section No 9.6 & 9.7

Comments:

The E-IMD registry use a web-based secured data collection tool. The server is maintained by the Central Study Office (University Hospital Heidelberg) and has an ISO 27001 certified security concept.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	Section No 9.9
12.1.2 Information bias?	☒	☐	☐	Section No 9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	Section No 9.5

Comments:

This PASS is being performed to generate longitudinal safety data in patients with ARG1-D treated with Loargys. It is expected to provide further insight into the long-term safety of

Loargys as well as indicate any new safety signals.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	Section No 10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Section No 10.3 & 10.4

Comments:

The investigator will submit this protocol, informed consent forms (ICF), and any accompanying material to be provided to the patient (such as patient information sheets, or descriptions of the study used to obtain informed consent, and the patient logs) to an Independent Ethics Committee (IEC), where applicable.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section No 5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	Section No 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section No 12

Comments:

Safety data collected while the study is ongoing will be reported in the annual re-assessment procedure for a product approved under exceptional circumstances. A final report will be prepared on study completion and submitted to the EMA as per GVP module VIII. The final results of this study will be posted in the EMA Catalogue of real-world data studies (EMA RWD Catalogues). After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with E-IMD and the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues.

Name of the main author of the protocol: [redacted]

Date: 22/April/2025

Signature: [redacted]