# RISK MANAGEMENT PLAN

# ELFABRIO®
# [PEGUNIGALSIDASE ALFA]

**RMP Version Number:** **1.5**

**Data Lock Point for this RMP:** **15 JUL 2024**

# EU Risk Management Plan for
## ELFABRIO®
## (Pegunigalsidase alfa)

**RMP version to be assessed as part of this application:**

**RMP Version number:** 1.5

**Data lock point for this RMP:** 15 JUL 2024
**Date of final sign-off:** 28 JAN 2026

**Rationale for submitting an updated RMP:**

- Changes related to address PRAC's preliminary assessment report
- Proposed new alternative dosing regimen of 2 mg/kg E4W

**Summary of significant changes in this RMP**:
Update on the proposed new alternative dosing regimen of 2 mg/kg E4W

- Part I – addition of proposed posology and update of ATC
- Part II: SI - minor changes in Epidemiology of the indication section
- SIII – updates related to clinical trial exposure

Minor changes as per PRAC Rapporteur's recommendation in:

- Part II: SIII – update information on Cohort 3
- Part II: SV.1.2- Removal of country-specific data
- Part II: SVII.3, Part VI - harmonization of the text according to the Guidelines - GVP Module V Rev.2
- Part II: VII.3.1- Removal of individual patient information

**Other RMP versions under evaluation:** None

**Details of the currently approved RMP:**

**Version number:** 1.0
**Approved with procedure:** EMEA/H/C/005618
**Date of approval (opinion date):** 04 MAY 2023

**QPPV name:** Stella FIORINI

**Signature:** Signed by Stella Fiorini on 28/01/2026 at 17:18:52 CET Reason: Approval

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse event |
| α-GAL-A | alpha Galactosidase-A |
| BL | Baseline |
| BY2 | *Nicotiana tabacum* Bright Yellow 2 |
| CI | confidence interval |
| cm | centimetre(s) |
| Cmax | maximum concentration |
| dL | decilitre |
| DNA | Deoxyribonucleic acid |
| DRF | Dose range-finding |
| EAP | Early Access Programme |
| ECG | Electrocardiogram |
| EEA | European Economic area |
| eGFR | Estimated glomerular filtration rate |
| E2W | Every other week |
| EOW | Every other week |
| EPAR | European Public Assessment Report |
| ERT | Enzyme replacement therapy |
| ESRD | end-stage renal disease |
| EU | European Union |
| E4W | Every 4 weeks |
| FD | Fabry disease |
| FDA | Food and Drug Administration |
| Gb3 | Globotriaosylceramide |
| GD | Gestational day |
| GFR | glomerular filtration rate |
| GLA | α-galactosidase A gene |
| GLP | Good laboratory Practice |
| H | hour(s) |
| ICR | Institute of Cancer Research |
| ICR (CD-1®) | Outbred mice |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IRR | Infusion related reactions (within 2 hours of infusion) |
| ISR | Injection site reaction |
| IV | Intravenous |

| | |
|---|---|
| kg | kilogram(s) |
| L | litre(s) |
| Lyso-Gb3 | Globotriaosylsphingosine |
| M | month |
| MAA | Marketing Authorisation Application |
| MedDRA | Medical Dictionary for Regulatory Activities |
| max | maximum |
| mg | milligram(s) |
| mg/kg | milligram(s) per kilogram(s) |
| mg/mL | milligram(s) per millilitre(s) |
| min | minimum |
| mL | millilitre(s) |
| mL/kg | millilitre(s) per kilogram(s) |
| n | Number of patients with data in the category |
| N | Number of patients in the analysed population |
| n (%) | percentage based on N |
| NA | not applicable |
| OLE | open-label extension |
| OR | odds ratio |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PEG | Polyethylene glycol |
| PK | Pharmacokinetic(s) |
| PL | package leaflet |
| PRX-102 | Pegunigalsidase alfa |
| PSUR | Periodic Safety Update Report |
| PV | pharmacovigilance |
| QoL | quality of life |
| QPPV | Qualified Person Responsible For Pharmacovigilance |
| SD | Standard deviation |
| SmPC | Summary of Product Characteristics |
| TEAE | Treatment-emergent adverse events |
| TK | toxokinetics |
| US | United States of America |

# Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Pegunigalsidase alfa<br>(PRX-102) |
| **Pharmacotherapeutic group(s) (ATC Code)** | Alimentary Tract and Metabolism; Other Alimentary Tract and Metabolism products; Enzymes.<br>(A16AB20) |
| **Marketing Authorisation Applicant** | Chiesi Farmaceutici S.p.A. |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | Elfabrio 2 mg/mL concentrate for solution for infusion |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | **Chemical class:**<br>Hydrolytic lysosomal neutral glycosphingolipid-specific enzyme.<br>(Pegunigalsidase alfa is a PEGylated homodimeric, covalently cross-linked recombinant human α-Gal-A enzyme expressed in plant (*Nicotiana tabacum* Bright Yellow 2, BY2) cells.) |
| | **Summary of mode of action:** Pegunigalsidase alfa is categorized as an enzyme replacement therapy (hereafter referred to as ERT) to supplement biological active alpha-galactosidase A (α-GAL-A) enzyme to Fabry disease patients characterized by deficient/absent enzyme activity. α-GAL-A is a lysosomal enzyme which primarily catalyses the hydrolysis of the terminal α-galactosyl moieties of oligosaccharides and polysaccharides in the lysosome, reducing the amount of accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3) in cells of the vascular system, cardiomyocytes, neuronal cells and kidney cells as well as elevated levels in circulation.<br>The ultimate consequence of glycosphingolipid deposition in the vasculature and other tissues is end-organ failure, particularly of the kidney, but also of the cardiac and cerebrovascular system. |

| | |
|---|---|
| | Pegunigalsidase alfa is a pegylated recombinant form of human α-GAL-A. The production in plant cells results in mannose terminated glycosylation that targets pegunigalsidase alfa to disease-relevant tissues, and the PEGylation decreases the immunogenicity and further enhance enzyme exposure to target organs, thus improving PK properties. |
| | **Important information about its composition:**<br><br>It contains pegunigalsidase alfa as an active substance |
| **Hyperlink to the Product Information** | Please refer to the proposed PI available in the eCTD sequence |
| **Indication(s) in the EEA** | **Current:**<br><br>Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase). |
| | **Proposed:** NA |
| **Dosage in the EEA** | **Current:**<br><br>The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once every two weeks. |
| | **Proposed:**<br><br>The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once every two weeks.<br><br>The treatment can be also administered at the dose of 2 mg/kg of body weight once every four weeks in patients stable with an ERT treatment. |
| **Pharmaceutical form(s) and strengths** | **Current:**<br><br>Concentrate for solution for infusion<br><br>Each vial contains 20 mg of pegunigalsidase alfa in a volume of 10 mL or 5 mg of pegunigalsidase alfa in a volume of 2.5 mL, at a concentration of 2 mg/mL. |
| | **Proposed:**<br><br>N/A |

| | |
|---|---|
| **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).

## Indication.

Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

## Epidemiology and Genetics.

## Incidence and Prevalence.

Fabry disease is an X-linked lysosomal storage disorder caused by alterations in the gene that encodes the enzyme α-GAL-A (GLA) leading to deficient/absent enzymatic activity and resulting in glycosphingolipid accumulation with life-threatening complications [Ortiz 2018].

Fabry disease is regarded as a rare disease and it was originally estimated that 1 in 40,000 males has the disease [Meikle 1999], the global prevalence estimates of FD based on clinical ascertainment range from 1 in 40 000 to 1 in 170 000 [Gilchrist 2022].

However, following the development of better diagnostic tools and increasing awareness, newer studies suggest that Fabry disease has a much higher prevalence [Hoffmann 2009]. Due to the nonspecific nature of the clinical manifestations of Fabry disease and the common occurrence of a single complication, it is likely that many undiagnosed patients exist, which explains the discrepancy in frequency. Furthermore, the presence of equal numbers of females and males in large populations studied suggests that up to 50% of the females with Fabry disease may be not identified [Eng 2007; Mehta 2004]. An α-GAL-A enzyme activity screening of 37,104 consecutive newborn males confirmed by sequencing of genomic DNA indicated the prevalence for Fabry disease in Italy to be 1 in 3,100 males. This study identified and included often undiagnosed patients with the non-classic form of Fabry disease; the ratio of non-classic to classic was determined to be 11 to 1 [Spada 2006]. A random screening of 110,027 newborns in Taiwan discovered the incidence in males to be about 1 in 1,500 [Lin 2009]. This study also determined there were still significantly fewer females affected than males, with approximately 1 in 17,000 affected; however, this prevalence is still a much greater incidence than was previously thought for males [Lin 2009]. Screening for Fabry disease reveals a high prevalence of individuals with *GLA* genetic variants of unknown significance. The prevalence of *GLA* variants in newborns was found to be 0.04%, while in high-risk populations, the overall prevalence of individuals with *GLA* variants was 0.62%, with the prevalence of a definite diagnosis of Fabry disease as 0.12% [van der Tol 2016].

## Main Existing Treatment Options.

There are currently two approved classes of therapies available for patients with Fabry disease, ERT and pharmacological Chaperone as described below:

- **ERT:**

  The mechanism of action for this treatment is by exogenous IV administration of purified recombinant enzyme. ERT is the longest and most successfully employed drug treatment for lysosomal storage disorders indicated across the entire spectrum of disease-causing mutations. Recombinant human α-GAL-A has the ability to ameliorate the $Gb_3$ accumulation in patients and has recently been shown to be accompanied by reduction of plasma Lyso-Gb3 [Aerts 2008].

  Currently the following ERTs using this enzyme are commercially available:

  - Fabrazyme® (agalsidase beta 1.0 mg/kg every other week [EOW]), produced in Chinese hamster ovary (CHO) cells and approved in the United States, European Union and other countries.
  - Replagal® (agalsidase alfa 0.2 mg/kg EOW), produced in a human cell line (human fibrosarcoma cells HT-1080) and approved outside of the United States only.

  Both recombinant enzymes are comparable in their properties and differ only slightly in glycan composition [Blom 2003].

  Further, both enzymes have shown effects in clinical studies with regard to clearance of Gb3 from kidney cells (such as capillary endothelial cells, glomerular endothelial cells, noncapillary endothelial cells and noncapillary smooth muscle cells), and capillary endothelial cells of the myocardium and skin plasma, [Eng 2001; Germain 2007; Schaefer 2009]. In addition, ERT with both products leads to some improvement in quality of life (QoL), reduction or stabilization of cardiac mass, and potentially the preservation of renal function [Wilcox 2004; Schiffmann 2006; Germain 2007; Schiffmann 2009].

  Fabrazyme® is the only ERT approved in the US and received full approval based on reduction of renal Gb3 inclusions.

- **Pharmacological Chaperone:**

  Galafold® (migalastat) is the only approved molecular Chaperone and is only effective for a subgroup of ~30% of Fabry disease patients with amenable mutations. The mechanism of action of this oral therapy is to facilitate the folding of the patient's endogenous α-GAL-A and therefore increasing the activity of the enzyme [Lenders 2019].

  Galafold®, similar to Fabrazyme®, was approved under the Accelerated Approval pathway based on reduction of renal Gb3 inclusions.

**Natural history of the indicated condition in the Fabry disease untreated population, including mortality and morbidity.**

Fabry disease is characterized by mutations in the *GLA* gene, resulting in decreased/undetectable levels of α-Gal-A activity in plasma or leukocytes, typically observed together, with high concentrations of the substrate $Gb_3$ and its degradation product, Lyso-Gb3 in tissues and plasma, which both correlate with organ damage [Aerts 2008; Boutin 2014; Ouyang 2017; Kramer 2018].

Progressive accumulation of $Gb_3$, Lyso-Gb3, and related lipids, leads to impaired tissue and organ function, particularly in the kidney, heart, and cerebrovascular system. In addition, involvement of the central, peripheral, and autonomic nervous systems result in episodes of pain and impaired peripheral sensation [Aerts 2008; Schiffmann 2009]. The Lyso-Gb3 has been identified as a biomarker with clinical applicability from the perspective of Fabry disease-specific biomarkers. A review of 70 papers found that reductions in plasma Lyso-Gb3 could be an indicative of treatment response, i.e., of ERT performance [Kramer 2018]. Furthermore, when anti-drug antibodies (ADAs) to ERT form, they decrease the ability of ERT to reduce plasma Lyso-Gb3 concentration [Sakuraba 2018; Mauhin 2018; Rombach 2012]. Fabry disease comprises two subtypes, classic and non-classic, based on age of symptom onset and extent of organ involvement. Clinical onset of the classic form of disease typically occurs during childhood or adolescence [Schaefer 2009] and progresses to end-stage renal disease (ESRD), cardiac complications, and/or cerebrovascular disease in the fourth or fifth decade of life [Branton 2002]. Non-classical Fabry disease, also referred to as late-onset or atypical disease, is characterized by a more variable disease course, in which patients are generally less severely affected and disease manifestations may be limited to a single organ. Males with non-classical disease typically have >5% residual enzyme activity and lower levels of the deacetylated substrate (Lyso-Gb3) [Arends 2017].

**Definition of classic Fabry disease.**

The discussion and parameters regarding the definition of a classic Fabry disease patient is evolving and, in some cases, challenging. Currently, there is no consensus in the published literature regarding the definition of classic Fabry disease in either males or females [Arends 2017; van der Tol 2014; Mehta 2002; Smid 2013; Chien 2012; Nakao 2003; Salviati 2010]. Patients with the classic, most severe, form of Fabry disease almost always have a mutation that causes a severe decrease or absence of α-GAL-A activity (≤5% of the laboratory normal mean), while some non-classic patients with missense mutations often have some residual enzyme activity ranging from 2% to 25% [Schiffmann 2009; Ortiz 2018].

The following definition was used for the allocation to classic or non-classic phenotypes for the analysis of studies correlating phenotypes with immunogenicity profiles. Males were considered to be classic when the following criteria are met: (1) a *GLA* disease-causing mutation, (2) enzyme activity ≤5% of the mean reference range, and (3) one or more characteristic Fabry disease symptoms (i.e., neuropathic pain, angiokeratoma, and/or cornea verticillata). Women were classified as having a classic phenotype if they had a *GLA* disease-causing mutation and one or more of the characteristic Fabry disease symptoms listed above.

**Disease manifestations in males.**

Primary clinical manifestations of Fabry disease in males are neuropathic pain and acroparaesthesia; angiokeratomas; hypohidrosis; cornea verticillata; hearing loss and gastrointestinal symptoms.

Renal disease is associated with progressive proteinuria accompanied by a decline in estimated glomerular filtration rate (eGFR), leading over a number of years to ESRD requiring dialysis and/or kidney transplantation [Branton 2002; Ortiz 2008]. There is evidence that hyperfiltration often

precedes the decline in renal function, particularly in childhood; hyperfiltration will present as greater than normal eGFR but represents evolving glomerulopathy [Ries 2005; Vedder 2007].

Cardiac disease is associated with progressive hypertrophic cardiomyopathy with diastolic dysfunction, a variety of conduction defects and arrhythmias such as short P–R interval, and supraventricular and ventricular tachycardia. Other complications are valvular disease (insufficiency or stenosis) and coronary artery stenosis of large or, more commonly, of small vessels [Kampmann 2008; Weidemann 2005]. Progressive bradycardia and decreased exercise capacity are also very common [Lobo 2008]. It has been estimated that patients with Fabry disease have a 20-fold increased risk of ischemic stroke and transient ischemic attacks compared to the general population. Both small and large vessel strokes occur, with brain regions perfused by the posterior circulation being affected more commonly than anterior circulation [Moore 2001; Moore 2003].

**Disease manifestations in females.**

Due to the X-linked nature of the disease, males are hemizygotes and females are heterozygotes. It is now widely accepted that females may express a range of clinical features including life-threatening manifestations such as cardiomyopathy, renal disease and stroke [MacDermot 2001; Whybra 2009; Sunder-Plassmann 2006]. As the disorder is X-linked, the prevalence of the mutation is predicted to be twice as high in females compared with males. There is considerable variation in the phenotype in heterozygous females. Age has the strongest correlation with the presence of symptoms, with the proportion of women suffering from a particular symptom manifesting approximately a decade after that symptom is found in males. The median age of onset of symptoms is 13 years in female as compared to 9 years in males [Hughes 2011]. Only 7.6% of females were diagnosed prior to symptom onset, largely due to screening of families. Forty-three percent (43%) of diagnosed females are receiving ERT with median age of initiation of 44.8 years. ERT has been shown to have an advantageous effect on $Gb_3$ levels, cardiac outcomes, and may improve QoL in adult female patients [Germain 2018].

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

**Toxicology:**

Good laboratory Practice (GLP) compliant 26-week toxicology studies were carried out in ICR mice and cynomolgus monkeys. As part of these studies, toxokinetics (TK) was assessed. TK data are presented for Day 1, 3 months, and after 6 months of IV drug administration. For the TK evaluation, three groups of 54 male and 54 female mice each received 2, 10, or 40 mg/kg/dose pegunigalsidase alfa as approximately 90-second IV injections into the tail vein once every two weeks. There were no consistent gender differences. Although there were exceptions, probably due to inter-animal variability, the relationships between the TK parameters did not show any clear evidence of non-linearity.

**Key issues identified from acute or repeat-dose toxicology studies:**
Toxicology.

To evaluate the toxicity of pegunigalsidase alfa, toxicology studies were performed in ICR (CD-1®) mice and cynomolgus monkeys. Safety pharmacology parameters were incorporated into the repeat-dose toxicology studies (e.g., clinical signs and electrocardiogram (ECG) [monkeys]). Rats and rabbits were studied in reproductive toxicology studies. Using a maximum dose volume of 10 mL/kg, this limits the high dose in most of the toxicology studies to 40 mg/kg, which is considered the maximum feasible dose. Therefore, in many of the toxicology studies, the high dose was set at this maximum feasible dose. Table 1 lists of all the toxicology studies performed.

**Preliminary Toxicology Studies.**

Non-GLP compliant repeat-dose toxicity studies were conducted in mice and cynomolgus monkeys to provide preliminary repeat-dose information on pegunigalsidase alfa after IV dosing.

**Pilot Mouse Study (Study PRT/037/RIT).**

Pegunigalsidase alfa or placebo were administered by slow IV bolus injection (over approximately 1 minute) into the tail vein of ICR mice (n = 3/sex/group) on study days 0, 5, 10, 15 at a dose volume of 10 mL/kg. No adverse clinical signs or effects were observed in any of the animals from any of the groups. Therefore, it was concluded that pegunigalsidase alfa intravenously at doses of 20 and 40 mg/kg/dose to mice was well tolerated.

**Pilot Monkey Study (Study 1171-010).**

Two treatment groups of one cynomolgus monkey/sex each were administered pegunigalsidase alfa at dose levels of 20 and 40 mg/kg/dose (20X and 40X intended dose for clinical studies, respectively) and placebo. Pegunigalsidase alfa was administered to all groups via 1-hour IV infusion on Days 5, 10, 15, and 20 at a dose volume of 10 mL/kg. No deaths occurred and there were no pegunigalsidase alfa -related clinical signs or other adverse events (AEs) in any of the animals in either of the groups throughout the entire study period. The IV infusion of pegunigalsidase alfa at dose levels of 20 and 40 mg/kg/dose was well tolerated by the cynomolgus monkeys.

**Toxicology Studies Supporting Clinical Development.**

GLP-compliant repeat-dose toxicity studies were conducted in mice and cynomolgus monkeys to assess toxicity and TKs. IV dosing was every two weeks to mirror clinical utility.

**Repeated Intravenous (IV) Toxicology study in the Mouse with Recovery (Study PRT/040/RIT).**

Mice administered pegunigalsidase alfa via slow bolus IV administration into the tail vein over a period of approximately 90 seconds. Three dose levels of pegunigalsidase alfa were evaluated: low-dose (2 mg/kg/injection), mid-dose (10 mg/kg/injection), and high-dose (40 mg/kg/injection) which correspond to 2X, 10X, and 40X the maximal intended clinical dose, respectively. The main findings in the 26-week repeat-dose mouse study were unexpected mortality primarily after the third dose (which was largely controlled by pre-dosing with diphenhydramine [Benadryl]) and transient clinical signs (decreased activity and dyspnea). Nephropathy occurred at the following incidence and severity: minimal in 7 of 18 placebo males, minimal to mild in 15 of 19 high-dose males, minimal to mild in 7 of 20 placebo females, and minimal to mild in 14 of 20 high-dose females. Lymphocytic infiltration was noted in 16 of 18 placebo males (minimal), all 19 high-dose males (minimal to mild), 17 of 20 placebo females (minimal to mild), and 19 of 20 high-dose females (minimal to mild). No effects were noted on the kidneys from the low- and mid-dose animals. No test article-related renal changes were noted in the recovery animals, highlighting the reversibility of the effect observed at the high dose. There was no evidence of systemic toxicity at any dose. There was no indication of adverse local injection site reactions based on clinical signs or histopathology at any dose. Antibodies were detected in most of the satellite animals at both the 13-week interim and 26-week terminal timepoints. Neutralizing antibodies were detected in only one sample. The presence of antibodies did not affect the TKs of the drug.

**6-Month Intravenous Infusion Toxicology Study in Cynomolgus Monkeys (Study 1171-011).**

Pegunigalsidase alfa or placebo were administered once every two weeks to cynomolgus monkeys for 26 weeks. Three dose levels of pegunigalsidase alfa were evaluated in the study: low-dose (2 mg/kg/injection), mid-dose (10 mg/kg/injection), and high-dose (40 mg/kg/injection) which correspond to 2X, 10X, and 40X the maximal intended clinical dose, respectively. The main findings in the 26-week repeat-dose monkey study were limited to a minor, sporadically occurring clinical sign (red discoloration of the face) and minor microscopic changes in the liver. There was one death (mid-dose male, cause not determined but not likely to be test article-related due to the lack of a dose-response) and one moribund sacrifice (due to fractured humerus, not related to the test article). No evidence of systemic toxicity was observed at any dose. Minimal to mild Kupffer cell hypertrophy occurred in 3 males and 2 females at 40 mg/kg/dose at the terminal necropsy and one male at 40 mg/kg/dose at the interim necropsy. These findings did not constitute significant adverse effects and were not present in the livers of males and females at the recovery examinations.

**Reproductive Toxicology Studies.**

GLP-compliant reproductive toxicology studies, including fertility and early embryonic development (rats) and embryo fetal development (rats and rabbits), have been completed.

**28-Day Repeated Dose Intravenous Toxicology Study in Sprague Dawley Rats (Study G9423).**

A pilot, repeat-dose study was conducted to evaluate the toxicity potential of the test item, pegunigalsidase alfa, when administered intravenously twice a week for four weeks to Sprague Dawley rats and in order to select dose levels for the definitive fertility and early embryonic development study. Three dose levels of pegunigalsidase alfa were evaluated: low dose (2 mg/kg/injection), mid-dose (20 mg/kg/injection) and high dose (40 mg/kg/injection). The results of this study indicated that pegunigalsidase alfa administration by IV injection twice a week for four weeks to Sprague Dawley rats at 2, 20, and 40 mg/kg/dose did not cause any toxicological effects on general health, growth and feed consumption, organ weights, and gross pathology.

**Male and Female Fertility Study (Segment-I) by Intravenous Route in Sprague Dawley Rats (Study G9414).**

In this GLP study, Sprague-Dawley rats (n = 25/sex/group) were administered pegunigalsidase alfa via IV injection at doses of 0, 2, 10, and 40 mg/kg/dose twice per week. pegunigalsidase alfa did not affect any parameters including mating, fertility, and sperm analyses. No gross-pathology anomalies were observed.

**Preliminary Embryo-Foetal Development Study in Sprague Dawley Rats via Intravenous Injection (Study N2188).**

Pegunigalsidase alfa was administered intravenously to pregnant rats (n = 7/group) on GD 6, 9, 12, and 15. Parameters evaluated included clinical signs, mortality and morbidity, body weights and food intake, gross pathology, uterine evaluations, and fetal examinations (viability, body weight, and external malformations).

Pegunigalsidase alfa did not produce any adverse effects on the dams or on the fetuses. Maternal body weight and uterine parameters were unaffected and there was no evidence of external fetal malformations or effects on fetal body weight.

**Embryofoetal Development Toxicology Study in Sprague Dawley Rats by Intravenous Injection (Study G9415).**

In a GLP study, Sprague-Dawley rats (n=24) were administered pegunigalsidase alfa by IV injection at doses of 0, 2, 10, and 40 mg/kg/dose on GD 6, 9, 12, and 15. Parameters evaluated included clinical signs, body weight, food consumption, gross pathology, uterine parameters, and fetal parameters. There were no adverse effects on any parameters including no effects on fetal body weight and malformations.

**Preliminary Embryo-Foetal Development Study in New Zealand White Rabbits via Intravenous Injection (Study N2189).**

New Zealand White rabbits (n = 5/group) were administered pegunigalsidase alfa intravenously at doses of 0, 2, 10, 20, and 40 mg/kg/dose on GD 6, 9, 12, 15, and 18. Animals were sacrificed on GD 29. Maternal toxicity was observed at 20 mg/kg/dose (abortion, increased late resorptions, and post-implantation loss) and 40 mg/kg/dose (adverse clinical signs, mortality, and abortion). Fetal parameters were unaffected.

**Embryo-Foetal Development Study in New Zealand White Rabbits via Intravenous Injection (Study G9416).**

In a GLP study, New Zealand white rabbits (n=24/group) were administered pegunigalsidase alfa intravenously at doses of 0, 2, 10, and 20 mg/kg/dose on GD 6, 9, 12, 15, and 18. Animals were sacrificed on GD 29. Maternal toxicity was noted at 10 and 20 mg/kg/dose. Mortality was observed at the mid and high doses as was abortion, decreased body weight gain, and/or food consumption. At 20 mg/kg/dose, an increase in late resorptions was reported. Other uterine parameters were not affected. In the fetuses, body weight was reduced at 10 and 20 mg/kg/dose, likely as a secondary response to maternal toxicity. There was no increase in external, skeletal, or visceral malformations.

**Conclusions on non-clinical data.**

Two GLP-compliant toxicology studies were conducted in mice and cynomolgus monkeys to assess repeat-dose toxicity and TK. No systemic toxicity was observed in either species. There were also no significant differences in the toxicity profile between 13 weeks and 26 weeks in the two species. In monkeys, no safety concerns were identified at a dose 40 times higher than 1mg/kg, the intended clinical dose. Notably, liver and kidney-related adverse effects were mild to moderate and resolved in survival animals. In mice, the adverse effects observed were related to an allergic response to the administration of the drug which is a recombinant human protein. This type of allergic response is not unexpected and has been observed with other recombinant human proteins including recombinant human proteins for treating Fabry disease (Fabrazyme (EMA 2003), Replagal (EMA 2004), Naglazyme (FDA 2004), Myozyme (FDA 2006), and becaplermin [Knight 1998]). All of these protein drugs are currently approved for use in humans. A comparison of the amino acid sequence of α-GAL A in mice versus humans reveals a 78% similarity in the sequence which explains the allergic response in the rodent species to the human α-GAL A. Therefore, the allergic response to pegunigalsidase alfa observed in mice is not likely to represent safety concern to humans (see Table 2). The potential adverse effects of pegunigalsidase alfa on fertility and development were assessed in both rats and rabbits. There was no adverse effect on any of the reproductive parameters and no evidence of teratogenicity in either rats or rabbits. Maternal toxicity (mortality, decreased body weight, food consumption, and abortions) and fetotoxicity (decreased fetal weights) were observed in rabbits only, at doses of 10 and/or 20 mg/kg/dose. No similar findings were observed in rats, at doses up to 40 mg/kg/dose. No additional effects on kidney or liver were observed in developmental toxicology studies in these species.

**Table 1: Toxicology and Reproductive Toxicology: Overview of Studies.**

| Type of Study | Species and Strain | Method of Administration | Duration of Dosing | Doses (mg/kg) |
|---|---|---|---|---|
| Repeat-dose toxicity | CD-1 Mice | IV Injection | 15 Days a | 0, 20, 40 |
| | CD-1 Mice | IV Injection | 26 Weeks b | 0, 2, 10, 40 |
| | CD-1 Mice | IV Injection | 41 Days b | 0, 10 |
| | Cynomolgus Monkeys | IV Infusion | 20 Days a | 0, 20, 40 |
| | Cynomolgus Monkeys | IV Infusion | 26 Weeks b | 0, 2, 10, 40 |
| DRF study for fertility study | Sprague-Dawley Rats | Slow IV Bolus | 28 Days c | 0, 2, 10, 40 |
| Fertility study | Sprague-Dawley Rats | Slow IV Bolus | ~9 weeks c | 0, 2, 10, 40 |
| DRF study for embryofoetal development study | Sprague-Dawley Rats | Slow IV Bolus | 10 days d | 0, 2, 10, 40 |
| Embryofoetal development study | Sprague-Dawley Rats | Slow IV Bolus | 10 days d | 0, 2, 10, 40 |
| DRF study for embryofoetal development study | New Zealand White Rabbits | Slow IV Bolus | 13 days d | 0, 2, 10, 20, 40 |
| Embryofoetal development study | New Zealand White Rabbits | Slow IV Bolus | 13 days d | 0, 2, 10, 20 |

DRF = Dose range-finding; IV = Intravenous
a - Dosing once every 5 days.
b - Dosing once every two weeks.
c- Dosing twice a week.
d – Dosing on Gestation Days 6, 9, 12, 15 and 18 (rabbits only).

**Table 2: Overview on safety from Non-clinical Studies with pegunigalsidase alfa**

| **Safety concerns** |
|---|
| **Important identified risks (confirmed by clinical data)** |
| None |
| **Important potential risks (not refuted by clinical data or which are of unknown significance)** |
| None |
| **Important missing information** |
| The PPND study has not yet been initiated, pending Agency approval of the final protocol. |

# Part II: Module SIII - Clinical trial exposure

## SIII.1 Brief overview of development

The clinical plan for the development of pegunigalsidase alfa at the dose of 1.0 mg/kg every two weeks (E2W) administered by intravenous (IV) infusion for Fabry disease included a combined Phase 1/2 study in adult ERT-naïve male and female Fabry patients (3-months in PB-102-F01 and 9-months in PB-102-F02) followed by an extension study (PB-102-F03), and 3 Phase 3 studies in pre-treated adult Fabry patients (PB-102-F20, PB-102-F30, and PB-102-F60). Study CLI-06657AA1-04 (formerly PB-102-F60) is an ongoing long-term extension study with 1.0 mg/kg pegunigalsidase alfa E2W for patients who successfully completed PB-102-F03, PB-102-F20, or PB-102-F30. As of the cut-off date of 15 July 2021, 87 patients were included in the study and their safety data have been included in the integrated analyses of safety.

The clinical development plan for pegunigalsidase alfa also included two studies, study PB-102-F50 and its extension CLI-06657AA1-03 (formerly PB-102-F51), that have investigated pegunigalsidase alfa at the dose of 2 mg/kg administered every four weeks (E4W). The aim of these studies was to assess the safety and efficacy of this additional less frequent E4W dosing regimen of pegunigalsidase alfa.

Study PB-102-F50 was an open-label, switchover study to assess the safety and efficacy of pegunigalsidase alfa 2.0 mg/kg E4W for 12 months (52 weeks) in adult Fabry patients previously treated with ERT: Fabrazyme or Replagal. Study CLI-06657AA1-03 (formerly PB-102-F51), is an ongoing, open-label extension study of Study PB-102-F50 to evaluate the long-term safety and efficacy of 2.0 mg/kg pegunigalsidase alfa E4W for up to an additional 48 months. All 29 patients who completed PB-102-F50 enrolled in this extension study. Safety data as of the cut-off date 31 December 2022 for dosing regimen 2mg/kg E4W and the overview on studies from Clinical Development Plan and the Safety Endpoints are provided in Table 3.

**Table 3: Overview of Safety-relevant Clinical Studies and Safety Endpoints**

| Study Number | Status | Number of Treated Patients | Dose (mg/kg) | Baseline Treatment | Safety Endpoints |
|---|---|---|---|---|---|
| PB-102-F01/ PB-102-F02 [Schiffmann 2019] | Completed | 18 | 0.2, 1.0, 2.0 E2W | Naïve[a] | • TEAEs<br>• Clinical laboratory (haematology, coagulation profile, biochemistry and urinalysis) safety tests<br>• ADA<br>• ECG<br>• Physical examination findings<br>• Injection site reactions[b] |

| Study Number | Status | Number of Treated Patients | Dose (mg/kg) | Baseline Treatment | Safety Endpoints |
|---|---|---|---|---|---|
| PB-102-F03 [Hughes 2023] | Completed | 15 | 1.0 E2W (0.2, 2.0 during gradual dose adjustment) | Extension of F01/F02 | • TEAEs (including IRR)<br>• Clinical laboratory safety tests<br>• ADA<br>• ECG<br>• Physical examination findings<br>• Injection site reactions[b]<br>• Cerebrovascular disease assessment at M 24 and end of study (60 M). |
| PB-102-F20 [Wallace 2024] | Completed | 77 (52 with pegunigalsidase alfa, 25 with Fabrazyme) | 1.0 E2W | Fabrazyme | • TEAEs (including IRR)<br>• Clinical laboratory safety tests<br>• ADA<br>• ECG<br>• Physical examination findings<br>• Injection site reactions[b]<br>• Ability to taper off infusion premedication up to Month 2<br>• Requirement for use of premedication overall to manage infusion reactions |
| PB-102-F30 [Linhart 2023] | Completed | 22 | 1.0 E2W | Replagal | Same as in PB-102-F20 |
| CLI-06657AA1-04 (PB-102-F60) | Ongoing Interim data included in integrated analyses, cut-off date 15 July 2021 | 87 (n=10 from F03, n=18 from F30, n=59 from F20[c]) | 1.0 E2W | OLE of F20, F30, and F03 | Same as in PB-102-F20 |
| PB-102-F50 [Holida 2024] | Completed | 30 | 2.0 E4W | Fabrazyme or Replagal | Same as in PB-102-F20 |
| CLI-06657AA1-03 (PB-102-F51) | Ongoing Interim data (CSR) covering 12 months (24 months overall) included, cut-off date is 31 December 2022 | 29 | 2.0 E4W | OLE of F50 | Same as in PB-102-F20 |

ADA: anti-drug antibodies; ECG: Electrocardiogram; E2W: every two weeks; E4W: every 4 weeks; IRR: infusion related reactions; OLE: open-label extension; M: month; MAA: Marketing Authorisation Application; TEAE: Treatment-emergent adverse event;

a. Naïve: patients not previously exposed to an ERT or off-treatment for at least 6 months
b. For definition of injection site reactions see 2.7.4.1.4, table 2 of and 2.7.4.3.5.1 results for the relevant safety endpoint Infusion Related Reactions (IRRs)
c. 39 patients coming from pegunigalsidase alfa arm and 20 from Fabrazyme arm of study F20

## SIII.2 Clinical Trial exposure.

As of 31 December 2022, 142 individual patients (94 male and 48 female) have been treated with pegunigalsidase alfa at any dose or posology in clinical studies. Three cohorts were defined for the integrated analysis of safety to be able to compare the 2 mg/kg E4W dosing regimen to the standard approved 1 mg/kg E2W. Cohort 1 included 111 patients treated with 1 mg/kg pegunigalsidase alfa E2W (all studies), Cohort 2 included 30 patients/switchers from other ERTs to 2 mg/kg pegunigalsidase alfa E4W, and Cohort 3 included 142 patients with any dose and frequency of pegunigalsidase alfa. Overall, cumulative exposure amounted to 5347.12 patient months (about 445.6 patient years). Maximum individual exposure was 91 months (7.6 years).

Most of the exposure was from treatment with 1 mg/kg pegunigalsidase alfa E2W (3519.77 patient months; about 293.3 patient years). Exposure to the 2 mg/kg E4W dosing regimen, albeit lower, was still substantial with 1582.42 patient months (about 131.9 patient years). Most of the exposure with 1 mg/kg E2W occurred in ERT-experienced patients (2835.52 patient months including switch studies PB-102-F20 (pegunigalsidase alfa arm), -F30, and -F60), while naïve patients (studies PB-102-F01, -02, and -03) received 1 mg/kg E2W for a total of 528.00 patient months.

As expected for Fabry patients, and in line with inclusion criteria, fewer female than male patients were included in the clinical studies. Individual mean exposure was similar in male and female patients and in ADA positive and negative patients. Generally, the numbers of patients developing induced ADA was low especially with 2 mg/kg E4W where only a single patient developed ADA de novo.

Table 4 and Table 5 summarize the overall exposure and of the subgroups for the two dosages regiments (1 mg/kg E2W and 2 mg/kg E4W). One additional patient received a different dose in studies PB-102-F01/-F02/-F03 and was included in Cohort 3 only.

**Table 4: Clinical Trial Cumulative and Individual Exposure and the Corresponding Subgroups**

| Exposure (months) | Overall | Gender | | ADA Status[a] | | |
|---|---|---|---|---|---|---|
| **Cohort 1 (1 mg/kg pegunigalsidase alfa E2W)** | | | | | | |
| | **N=111** | **Male N=70** | **Female N=41** | **Positive N=27** | **Induced N=17** | **Negative N=63** |
| Cumulative exposure | 3519.77 | 2167.72 | 1352.05 | 897.71 | 706.23 | 1915.14 |
| Individual exposure Mean (SD) | 31.7 (17.2) | 31.0 (17.9) | 33.0 (16.0) | 33.2 (16.0) | 41.5 (17.7) | 30.4 (15.6) |
| Median | 31.1 | 29.4 | 31.8 | 31.1 | 44.9 | 28.2 |
| Range (min, max) | 0; 83 | 0; 83 | 1; 58 | 1; 58 | 0; 83 | 2; 61 |

| **Cohort 2 (2 mg/kg pegunigalsidase alfa E4W)** | | | | | | |
|---|---|---|---|---|---|---|
| | **N=30** | **Male N=24** | **Female N=6** | **Positive N=10** | **Induced N=1** | **Negative N=19** |
| Cumulative exposure | 1582.42 | 1265.91 | 316.52 | 522.55 | 59.07 | 1000.80 |
| Individual exposure Mean (SD) | 52.7 (11.8) | 52.7 (12.5) | 52.8 (10.0) | 52.3 (18.4) | 59.1 (-) | 52.7 (7.3) |
| Median | 57.4 | 57.4 | 54.8 | 58.0 | 59.1 | 52.6 |
| Range (min, max) | 0; 62 | 0; 61 | 36; 62 | 0; 60 | 59; 59 | 36; 62 |

E2W: Every 2 weeks; E4W: Every 4 weeks; N: Number of patients in group; SD: Standard deviation.

a. Positive = ADA positive at BL; Negative = ADA negative at BL and all post-BL assessments, Induced = ADA negative at BL and at least 1 ADA positive post-BL. Please note information was not available for all patients and timepoints.

Note: due to rounding patients discontinued after 1 infusion are presented with an exposure of 0 (1 day = 0.03 months)

Reference: 2.7.4.1.6, Source: Addendum ISS Table 5.1.1 and Table 5.1.2

Seventy (70) patients, i.e., more than 63% of the patients treated with 1 mg/kg pegunigalsidase alfa E2W have received treatment for more than 2 years and 29 patients, about 97% of the patients treated with2 mg/kg pegunigalsidase alfa E4W, have received this dosing regimen for more than 2 years. Sixteen (16) patients, i.e., about 14% of the patients with 1 mg/kg pegunigalsidase alfa E2W, have received treatment for more than 4 years and 25 patients, about 83% of the patients with 2 mg/kg pegunigalsidase alfa E4W, have received this dosing regimen for more than 4 years.

**Table 5: Clinical Trial Exposure and the Corresponding Subgroups by Exposure Categories**

| n (%) in exposure categories | Overall | Gender | | ADA status[a] | | |
|---|---|---|---|---|---|---|
| **Cohort 1 (1 mg/kg pegunigalsidase alfa E2W)** | | | | | | |
| | **N=111** | **Male N=70** | **Female N=41** | **Positive N=27** | **Induced N=17** | **Negative N=63** |
| ≤6 months | 10 (9.0%) | 6 (8.6%) | 4 (9.8%) | 1 (3.7%) | 1 (5.9%) | 4 (6.3%) |
| 6 - 12 months | 7 (6.3%) | 6 (8.6%) | 1 (2.4%) | 3 (11.1%) | 0 | 4 (6.3%) |
| 12 - 24 months | 24 (21.6%) | 15 (21.4%) | 9 (22.0%) | 5 (18.5%) | 1 (5.9%) | 18 (28.6%) |
| 24 - 36 months | 19 (17.1%) | 12 (17.1%) | 7 (17.1%) | 5 (18.5%) | 3 (17.6%) | 11 (17.5%) |
| 36 - 48 months | 35 (31.5%) | 21 (30.0%) | 14 (34.1%) | 7 (25.9%) | 9 (52.9%) | 19 (30.2%) |
| 48 - 60 months | 14 (12.6%) | 8 (11.4%) | 6 (14.6%) | 6 (22.2%) | 2 (11.8%) | 6 (9.5%) |
| >60 months | 2 (1.8%) | 2 (2.9%) | 0 | 0 | 1 (5.9%) | 1 (1.6%) |

| **Cohort 2 (2 mg/kg pegunigalsidase alfa E4W)** | | | | | | |
|---|---|---|---|---|---|---|
| | **N=30** | **Male N=24** | **Female N=6** | **Positive N=10** | **Induced N=1** | **Negative N=19** |
| ≤6 months | 1 (3.3%) | 1 (4.2%) | 0 | 1 (10.0%) | 0 | 0 |
| 6 - 12 months | 0 | 0 | 0 | 0 | 0 | 0 |
| 12 - 24 months | 0 | 0 | 0 | 0 | 0 | 0 |
| 24 - 36 months | 1 (3.3%) | 0 | 1 (16.7%) | 0 | 0 | 1 (5.3%) |
| 36 - 48 months | 3 (10.0%) | 3 (12.5%) | 0 | 0 | 0 | 3 (15.8%) |
| 48 - 60 months | 21 (70.0%) | 18 (75.0%) | 3 (50.0%) | 8 (80.0%) | 1 (100.0%) | 12 (63.2%) |
| >60 months | 4 (13.3%) | 2 (8.3%) | 2 (33.3%) | 1 (10.0%) | 0 | 3 (15.8%) |

ADA: Anti-drug antibody; BL: Baseline; E2W: every 2 weeks; E4W: every 4 weeks; N: number of patients in group; n (%): number of patients in category, percentage based on N

a. Positive = ADA positive at BL; Negative = ADA negative at BL and all post-BL assessments, Induced = ADA negative at BL and at least 1 ADA positive post-BL. Please note information was not available for all patients and timepoints.

Reference: 2.7.4.1.6; Source: Addendum ISS Table 5.1.1 and Table 5.1.2

All included patients were between 17 and 60 years of age (only one patient was below 18 years at enrolment into Study PB-102-F01 after a waiver had been granted. No exposure analysis by age classification, e.g., adults, elderly was conducted.

General demographics characteristics are provided in Table 6.

**Table 6: Demographics and Baseline Characteristics**

| | | Overall | Gender | |
|---|---|---|---|---|
| **Cohort 1 (1 mg/kg pegunigalsidase alfa EOW)** | | | | |
| | | **N=111** | **Male N=70** | **Female N=41** |
| Gender (n, %) | Male | 70 (63.1%) | 70 (100.0%) | 0 |
| | Female | 41 (36.9%) | 0 | 41 (100.0%) |
| Age (years) | Mean (SD) | 43.4 (11.1) | 42.3 (11.5) | 45.2 (10.0) |
| Age range (years) | | 17; 60 | 17; 60 | 21; 60 |
| Age at diagnosis (years) | Mean (SD) | 29.4 (13.2) | 28.0 (13.6) | 31.9 (12.2) |
| Race (n, %) | Asian | 2 (1.8%) | 2 (2.9%) | 0 |
| | Black or African American | 6 (5.4%) | 5 (7.1%) | 1 (2.4%) |
| | White | 102 (91.9%) | 62 (88.6%) | 40 (97.6%) |
| | Other | 1 (0.9%) | 1 (1.4%) | 0 |
| Previous ERT experience (n, %) | Naïve | 17 (15.3%) | 11 (15.7%) | 6 (14.6%) |
| | Experienced | 94 (84.7%) | 59 (84.3%) | 35 (85.4%) |
| | *Switch from Fabrazyme* [a] | *72 (76.6%)* | *44 (74.6%)* | *28 (80.0%)* |
| | *Switch from Replagal* [a] | *22 (23.4%)* | *15 (25.4%)* | *7 (20.0%)* |
| Last continuous ERT, duration (years)[b] | Mean (SD) | 6.86 (4.07) | 7.75 (4.43) | 5.37 (2.89) |
| ADA status for pegunigal-sidase alfa at baseline (n, %) | Positive | 27 (24.3%) | 26 (37.1%) | 1 (2.4%) |
| | Negative | 84 (75.7%) | 44 (62.9%) | 40 (97.6%) |
| **Cohort 2 (2 mg/kg pegunigalsidase alfa E4W)** | | | | |
| | | **N=30** | **Male N=24** | **Female N=6** |
| Gender (n, %) | Male | 24 (80.0%) | 24 (100.0%) | 0 |
| | Female | 6 (20.0%) | 0 | 6 (100.0%) |
| Age (years) | Mean (SD) | 40.5 (11.3) | 39.3 (12.2) | 45.2 (5.3) |
| Age range (years) | | 19; 58 | 19; 58 | 37; 52 |
| Age at diagnosis (years) | Mean (SD) | 26.3 (15.0) | 24.2 (15.8) | 34.8 (7.1) |
| Race (n, %) | White | 30 (100.0%) | 24 (100.0%) | 6 (100.0%) |

| | | Overall | Gender | |
|---|---|---|---|---|
| Previous ERT experience (n, %) | Naïve | 0 | 0 | 0 |
| | Experienced | 30 (100.0%) | 24 (100.0%) | 6 (100.0%) |
| | *Switch from Fabrazyme* [a] | *23 (76.7%)* | *19 (79.2%)* | *4 (66.7%)* |
| | *Switch from Replagal* [a] | *7 (23.3%)* | *5 (20.8%)* | *2 (33.3%)* |
| Last continuous ERT, duration (years)[b] | Mean (SD) | 8.39 (4.82) | 9.06 (5.01) | 5.72 (2.94) |
| ADA status for pegunigal-sidase alfa at baseline (n, %) | Positive | 10 (33.3%) | 10 (41.7%) | 0 |
| | Negative | 20 (66.7%) | 14 (58.3%) | 6 (100.0%) |

ADA: Anti-drug antibody; BL: Baseline; E2W: Every 2 weeks; E4W: Every 4 weeks; ERT: Enzyme replacement therapy; N: Number of patients in dose group; n (%): Percentage based on N; SD: Standard deviation.

a. Percentages based on number of patients with ERT experience.

b. Duration of last ERT treatment is calculated only for switchers and refers to patients who had several periods of treatment with ERT in the past.

Reference: 2.7.4.2.1; Source Original MAA ISS Table 2.1, and Table 3.1.

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

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

**Patients with a known allergy to Enzyme Replacement Therapy (ERT).**

As with any intravenous protein product, severe allergic-type hypersensitivity reactions are possible. If a severe allergic or anaphylactic-type reaction occurs, immediate discontinuation of treatment is recommended, and current emergency medical standards need to be implemented.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity reactions are included as important risks and, therefore, are discussed and characterized for the purpose of this RMP.

**Pregnancy and lactation.**

There is limited available data on pegunigalsidase alfa use in pregnant women to determine the drug-associated risk. There is no data on the presence of pegunigalsidase alfa in human milk, the effects on the breast fed infant or the effects on milk production. Studies in rats have shown no adverse effect on any of the reproductive parameters and no evidence of teratogenicity at doses up to 10 times the recommended human bi-weekly dosage. Despite that, 2 pregnancies have been reported during the clinical development of pegunigalsidase alfa notwithstanding a requirement for contraception. One pregnancy was terminated for personal reason whereas the other resulted in the birth of a healthy baby at gestational week 40. However, since animal reproductive studies are not always predictive of human responses, pegunigalsidase alfa should be used during pregnancy and lactation only if the potential benefit justifies the potential risk. In addition, the developmental and health benefits of breastfeeding should be evaluated along with the mother's clinical need for pegunigalsidase alfa and any potential adverse effects on the breastfed infant from pegunigalsidase alfa or from the underlying maternal condition.

Is it considered to be included as missing information? Yes

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

A total of 142 patients have been exposed to pegunigalsidase alfa during clinical development as of 31 December 2022. The mean exposure duration for patients receiving pegunigalsidase alfa 1mg/kg E2W was 41,7 months whereas for patients receiving pegunigalsidase alfa 2mg/kg E4W was 51,4 months; 12 % and 14% of patients in the groups, respectively, were treated for more than 60 months. The clinical development programme is limited in terms of the number of exposed patients and relatively limited in terms of exposure time and, thus, unlikely to detect certain types of adverse reactions such as rare adverse reactions.

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

| Type of special population | Exposure |
|---|---|
| Pregnant and breastfeeding women | Pregnancy and breastfeeding were exclusion criteria for all pegunigalsidase alfa clinical trials in the development programme. However, during the development programme 2 pregnancies have been reported despite a requirement for contraception. One was reported in study PB-102-F03. The patient had normal ultrasound findings at week 13 of gestation but decided to terminate the pregnancy at week 14 for personal reasons. Another pregnancy in patient 06-F01-002 in Study PB-102-F60 was reported. The pregnancy occurred after more than 5 years of treatment with pegunigalsidase alfa in studies PB-102-F01/02/03 and PB-102-F60. The pregnancy resulted in the birth of a healthy baby at gestational week 40. |
| Population with relevant different ethnic origin | In the development program of pegunigalsidase alfa the vast majority of patients were White. Specifically, 92% in the group that received pegunigalsidase alfa at a dose of 1mg/kg E2W and 100% in the group that received pegunigalsidase alfa at a dose of 2mg/kg E4W. However, in Fabry disease, there are no reported differences in the disease prevalence, severity, or progression in different ethnic, racial or geographic groups. Therefore, there is no expectation that data collected from patients outside of the Europe will differ from that of the European patient population in terms of the Fabry disease state or safety aspects. |
| Subpopulations carrying relevant genetic polymorphisms | Screening for Fabry disease reveals a high prevalence of individuals with *GLA* genetic variants of unknown significance, therefore such subpopulations were not included in the development plan. |
| Elderly patients (≥65 years) | Safety and efficacy of pegunigalsidase alfa in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients. |
| Paediatric population (0-17 years) | The current indication is targeting adult patients only, therefore paediatric population was not included in the current clinical development program. |

# Part II: Module SV - Post-authorisation experience

Pegunigalsidase alfa received marketing authorization approval with the brand name Elfabrio® in EU, US, UK and Switzerland in 2023, Peru and Israel in 2024.

The product was authorized in EU/EEA on 04 May 2023 through centralized procedure (EU/1/23/1724/001-006) as long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase) at a dosage of 1 mg/kg of body weight administered once E2W (same indication as UK, Switzerland, Peru and Israel). The marketing authorization in US has been granted on 09 May 2023 for the treatment of adults with confirmed Fabry disease at a dosage of 1 mg/kg of body weight administered E2W.

The product has been launched at the DLP in 12 countries worldwide.

## SV.1 Post-authorisation exposure

Elfabrio® received the marketing authorization as long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha galactosidase) at a dosage of 1 mg/kg of body weight administered E2W.

### SV.1.1 Method used to calculate exposure

Due to the peculiarity of the target population for the product and its recent launch on the market, the number of patients under treatment with Elfabrio® in the post-marketing setting can be currently tracked.

### SV.1.2 Exposure

Cumulatively, from IBD 04 May 2023 till 15 July 2024 the patient's post-marketing exposure corresponds to 221 patients worldwide (some patients directly switched to commercial setting from clinical trials and EAPs).

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

## SVI.1 Potential for misuse for illegal purposes

As this drug is intended for a very limited part of the general population affected by this rare disease and also the administration should be carried out under medical supervision, the potential for misuse for illegal purpose is very limited if not completely absent.

# 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

#### SVII.1.1.1 Overdose

In animal studies (mice and monkeys), no evidence of systemic toxicity was reported at any dose up to 40 times the target dose (doses up to 40 mg/kg/dose were administered). There have been no reports of overdose with pegunigalsidase alfa. In clinical trials, patients received doses up to 2.0 mg/kg body weight. The adverse reactions experienced by patients who received treatment with 2.0 mg/kg E2W were similar to the adverse reactions experienced by patients who received the target dose of 1.0 mg/kg E2W.

#### SVII.1.1.2 Withdrawal or rebound

No evidence of withdrawal or rebound was observed.

#### SVII.1.1.3 Potential for off-label use

Pegunigalsidase alfa is intended to replace an enzyme (alpha-galactosidase-A; α-Gal-A) that is missing specifically in patients with Fabry disease. There are no known experimental uses of pegunigalsidase alfa for other indications. There is no information concerning off-label use.

#### SVII.1.1.4 Potential for paediatric off-label use

Based on the clinical trial programme and the agreed Pediatric Investigation Plan (PIP) which is expected to extend the indication to the paediatric population, the potential for paediatric off label use is not applicable for the purpose of this RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable

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

#### SVII.1.2.1. Important Identified Risks

| Important identified risk | Identification and benefit-risk impact |
|---|---|
| | |

| | |
|---|---|
| Hypersensitivity Reactions (infusion related) | Infusion Related Reactions (IRRs) were defined as those related TEAEs which occurred during the infusion or within a limited timeframe after the completion of the infusion and were assessed to be related to study treatment. IRRs do not include injection site reactions (ISRs), which are considered to be related to the procedure rather than the study drug. IRRs were analysed for the time windows during or within 2 hours of infusion. The proportions of patients with severe hypersensitivity reactions were generally similar across the different dosages. Serious reactions (infusion related) were rare in all patients regardless of the posology with a rate of 0.1 events being reported per 100 infusions in all patients. Five (5) severe infusion related reactions were reported over all studies. Four serious IRRs in 4 patients were indicative of Type I hypersensitivity, however, for one (1) patient that experienced chills that was not confirmed as he was not tested for IgEs, however, he was IgG positive throughout treatment. The other IRR refers to an event of bronchospasm that was resolved without sequelae. The management of these reactions should be based on the severity of the reaction, and include slowing the infusion rate, treatment with medicinal products such as antihistamines, antipyretics and/or corticosteroids, for mild to moderate reactions. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required, although infusion-associated related reactions occurred in some patients after receiving pre-treatment. Collectively, the data indicate that infusion related hypersensitivity reactions, although potentially serious and life-threatening, can be adequately prevented and mitigated with administration of antihistamines, corticosteroids, intravenous IV fluids, and/or oxygen. The impact on the patient wellbeing is therefore expected to be low. |

### SVII.1.2.2 Important potential risks

| Important potential risk | Identification and benefit-risk impact |
|---|---|
| Medication errors in the home infusion setting | The experience regarding administration of home infusion of pegunigalsidase alfa is limited. As in all studies where such treatment was foreseen, home infusion was only allowed when the investigator agreed that it was safe to do so for individual |

| | |
|---|---|
| | patients. the high rate of home infusions in the studies underlines the positive safety profile of pegunigalsidase alfa treatment for both posologies and all populations investigated. For the majority of patients, investigators were confident the patients were stable on pegunigalsidase alfa treatment and considered it safe to administer infusions in the less controlled outpatient setting. |

### SVII.1.2.3 Missing information

| Missing information | Identification and benefit-risk impact |
|---|---|
| None | N/A |

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

No new safety concern or re-classification was performed for the submission of updated version.

## 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 Identified Risk**

| **Hypersensitivity Reactions (infusion related)** | |
|---|---|
| MedDRA PT Term (code) | • Anaphylactic reaction (SMQ code: 20000021)<br>• Hypersensitivity (MedDRA code: 10020751) |
| Potential mechanisms | Hypersensitivity reactions are those related TEAEs which occurred during the infusion or within a limited timeframe after the completion of the infusion and were assessed to be related to study treatment. IRRs do not include injection site reactions (ISRs), which are considered to be related to the procedure rather than the study drug. IRRs were analysed for the time windows during or within 2 hours of infusion. The mechanism of sensitisation involves primary stimulation and expansion of drug-specific T lymphocytes. This may affect T cells alone or both T cells and B cells with consequent formation of drug-specific antibodies (mostly IgE). After primary sensitisation to a causative drug, a second exposure |

| | |
|---|---|
| | causes affected T cells and antibodies to enter the elicitation phase, corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I (IgE-mediated) or IV (T-cell mediated) reactions; type II (IgG-mediated) and III (immune-complex deposition) reactions are only encountered infrequently [Schnyder 2009] |
| Evidence source and strength of evidence | Clinical trials included in the development programme. |
| Seriousness/outcomes | Hypersensitivity reactions (infusion related) were all severe in intensity although they were observed in only five (5) patients in the development program in 1 mg/kg E2W cohort and resolved under adequate treatment.<br><br>A higher rate of IRRs was observed with the 2 mg/kg E4W dose regimen, but all were assessed to be non-serious. |
| Frequency | Serious reactions (infusion related) were rare in all patients regardless of the posology with a rate of 0.053 events being reported per 100 infusions in all patients.<br><br>Serious related events of hypersensitivity were reported in 5 (4.5%) patients, all in 1mg/kg E2W, were Bronchospasm, Hypersensitivity, and Chills in 1 patient each, and Type I hypersensitivity in 2 patients.<br><br>One patient in study PB-102-F30 was a 29-year-old white male who presented with a severe (Grade 3), "Type I hypersensitivity" reaction at Visit 1. The event occurred soon after the start of the infusion and was considered as definitely treatment related. Symptoms included: nausea and itchy eyes, vomiting, shortness of breath, throat tightness, facial oedema, blanching rash over trunk, hives, and tachycardia (heart rate of 148-150 bpm). No infusion pre-medication had been given, the study treatment was interrupted after 18 minutes (i.e., 8.7 mg of pegunigalsidase alfa was administered), and the patient received epinephrine (once at 500 µg intramuscularly), cetirizine (once at 10 mg and once at 20 mg, orally), hydrocortisone (once at 100 mg IV), and prednisolone (once a day for 2 days at 50 mg, orally) as per local anaphylaxis protocol and the patient was admitted to the short stay unit for overnight observation. The patient recovered without sequelae. |

| | |
|---|---|
| | Another patient in study PB-102-F30, was a 24-year-old white male who presented with a severe "Type I hypersensitivity" reaction on Visit 1. This event occurred immediately after the start of the infusion and was considered as definitely treatment related. Symptoms included: nausea, headache, agitation, oedema of the hands, periorbital area and tongue, rigor, and chills; blood pressure decreased to 84/45 from 134/81 mmHg. No infusion pre-medication had been given, the study treatment was stopped 5 minutes after the start of infusion (i.e., 2.1 mg of pegunigalsidase alfa were administered), and the patient received methylprednisolone (once at 80 mg, IV), clemastine (once at 2 mg, IV) and sodium chloride (1000 mL once, IV). The patient recovered the same day without sequelae.<br><br>One patient in study PB-102-F20 experienced an allergic reaction at the 1st infusion of study medication. The patient exhibited clinical signs of urticaria, intense pruritus, moderate upper airway obstructions, macroglossia, mild lip oedema, transient low blood pressure. The patient was administered cetirizine 5mg orally, albuterol inhalation, methylprednisolone IV, and oxygen with terbutaline nebuliser solution. The patient was transferred to the intensive care unit for monitoring, with complete resolution of the clinical signs on the same day.<br><br>One patient in study PB-102-F01, was a 52-year-old white male who experienced a Grade 3 bronchospasm (considered serious and treatment related) 40 minutes into his first infusion. The infusion was interrupted, the patient was hospitalised and recovered the following day; the patient discontinued from the study.<br><br>All abovementioned four events led the patients to study withdrawal.<br><br>One patient was originally enrolled in PB-102-F20 and subsequently rolled over to the PB-102-F60 open-label extension study. The patients exhibited "chills" few minutes after the end of the infusion. He was hospitalized and recovered completely while completing the treatment as planned. The patient had not experienced infusion reactions from the study drug infusion previously or afterwards. The event was considered possibly related to study treatment. |

| | |
|---|---|
| | The patient was found to have pre-dosing and post-treatment anti-drug IgG antibodies, with neutralising activity.<br>The abovementioned patient continued in the study programme. |
| Background incidence/prevalence | Not known |
| Risk groups or risk factors | Patients undergoing IV infusion and/or subjects that had previous ERTs (Fabrazyme or Replagal) and/or patients referred to as "switchers" defined as subjects that had the last ERT less than 6 months prior to pegunigalsidase alfa. |
| Preventability | The management of infusion related hypersensitivity reactions should be based on the severity of the reaction and includes slowing the infusion rate, treatment with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. The patient should be kept under observation for during the course of the infusion, and one (1) or two (2) hours longer after the infusion, according to the treating physician's judgement. |
| Impact on the risk-benefit balance of the product: | Infusion related hypersensitivity reactions although serious had a rather low incidence rate (0.1/100 infusions) and can be effectively managed. Provided close monitoring is undertaken, their impact on the risk/benefit balance of the product is expected to be low. |
| Public health impact | Given that Fabry disease is an orphan disease, the public health impact is expected to be low. |

**Important Potential Risk**

| **Medication errors in the home infusion setting** | |
|---|---|
| MedDRA PT Term (code) | Medication errors (SMQ code 20000224) |
| Potential mechanisms | Drug errors may occur at the stage of drug preparation or administration and are typically associated with multistep |

| | |
|---|---|
| | preparations requiring careful preparation for the IV administration. Errors may include preparing the wrong dose or selecting the wrong time of infusion. |
| Evidence source and strength of evidence | Clinical trials included in the development programme. |
| Seriousness/outcomes | All patients in the study PB-102-F01/F02 were treated only at the study site, per protocol. In study PB-102-F03, home infusion could be implemented based on investigators' judgement, and country regulations. In studies PB-102-F20, PB-102-F30, and PB-102-F50, the first infusions of pegunigalsidase alfa were to be administered under controlled conditions at the investigation site. The patients could switch to receive their infusions at a controlled home care setup once the investigator and Sponsor Medical Director agreed that it was safe to do so, and in accordance with country specific regulations. In study PB-102-F60, which collects subjects from different studies including PB-102-F20, the patient was able to return to the previous treatment set up, either home infusion or predefined infusion centre, once the Investigator and Sponsor Medical Director agreed that it was safe to do so. In study PB-102-F51, the subjects could continue the infusions in the same setup they were in the parental study PB-102-F50. Collectively, patients receiving home infusion at home did not develop any serious adverse events that required medical attention. |
| Frequency | The majority, 94 of the 142 patients having received pegunigalsidase alfa at any dose or frequency, had also received at least one infusion at home. As of the cut-off date (December 31, 2022), a total of 142 individual patients have received a total number of 9924 infusions of pegunigalsidase alfa at any dose or posology. Maximum individual exposure was 195 infusions. Most of the infusions were treatment with 1 mg/kg pegunigalsidase alfa E2W (7579 infusions). Exposure to the alternative dose of 2 mg/kg E4W, albeit lower, was still substantial with 1817 infusions. The mean individual numbers of infusions were similar in male and female patients and in ADA positive and negative patients. Patients with induced ADA status, the smallest subgroup, showed higher mean numbers of infusions in subjects taking pegunigalsidase alfa at a dose of 1 mg/kg E2W compared to the other ADA subgroups, while in subjects taking |

| | |
|---|---|
| | pegunigalsidase alfa at a dose of 2 mg/kg E4W no such patient was identified. Most patients received at least one of their infusions in a home setting. In subjects taking pegunigalsidase alfa at a dose of 1 mg/kg E2W, 72 of 111 patients (65% of) received 46% of infusions at home and in subjects taking pegunigalsidase alfa at a dose of 2 mg/kg E4W, 21 of 30 patients (70%) received 43% of infusions at home. When the mean number of infusions in individual patients is considered, the mean numbers of infusions with 1 mg/kg pegunigalsidase alfa E2W received at home was similar to the mean number received on site (48.3 vs. 36.9 infusions). The mean numbers of infusions with 2 mg/kg pegunigalsidase alfa E4W per patient received in a home setting compared to on-site administration were 26.1 vs. 24.1infusions respectively. A substantial proportion of infusions were also administered in a home setting both in Naïve and Non-naïve studies, i.e., regardless of previous ERT. In summary, as in all studies where such treatment was foreseen, home infusion was only allowed when the investigator and the medical monitor agreed that it was safe to do so for individual patients. The high rate of home infusions in the studies underlines the positive safety profile of pegunigalsidase alfa treatment for both posologies and all populations investigated. For the majority of patients, investigators were confident the patients were stable on pegunigalsidase alfa treatment and considered it safe to administer infusions in the less controlled outpatient setting. |
| Background incidence/prevalence | Not Applicable |
| Risk groups or risk factors | Patients receiving pegunigalsidase alfa infusions in the home setting by an HCP |
| Preventability | Routine pharmacovigilance activities and additional risk minimization measures (aRMMs) such as an HCP brochure for the HCP to enable selection of patient eligible for home infusion and to train the Caregiver to administer the product at home and a patient/caregiver/HCP guide to aid in the infusion at home to prevent medication errors. |
| Impact on the risk-benefit balance of the product: | Given the high number of infusions in the home setting and the relatively absence of any relevant serious adverse event, |

| | |
|---|---|
| | the impact on the benefit/risk of pegunigalsidase alfa is expected to be low. |
| Public health impact | The public health impact is expected to be low. |

### SVII.3.2. Presentation of the missing information

None

# Part II: Module SVIII - Summary of the safety concerns

**Summary of safety concerns**

| | |
|---|---|
| **Important identified risks** | • Hypersensitivity Reactions (infusion related) |
| **Important potential risks** | • Medication errors in the home infusion setting |
| **Missing information** | • None |

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

## III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include adverse reactions reporting, signal detection and PSURs.

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities for Elfabrio: None

## III.2 Additional pharmacovigilance activities

None

## III.3 Summary Table of additional Pharmacovigilance activities

Beside routine pharmacovigilance practices, no additional PV activities have been planned for Elfabrio®.

## Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned or ongoing as a conditions of marketing authorisation.

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

Although safety concerns are well addressed through standard pharmacovigilance measures and common risk management measures such as pharmacovigilance monitoring, detection and evaluation of safety signals, appropriate labelling and good communication with regulatory authorities and other stakeholders, the possibility of administering the treatment in the home environment has necessitated the development of additional risk minimisation measures. The HCP brochure and patient/caregiver/HCP guide have been developed to minimize the occurrence of medication errors as well as adverse effects during home infusion therapy.

## V.1. Routine Risk Minimisation Measures

| **Safety concern** | **Routine risk minimisation activities** |
|---|---|
| Hypersensitivity Reactions (infusion related) | Routine risk communication:<br>• SmPC section 4.4.<br>• PL section 2<br>Other routine risk minimisation measures beyond the Product Information:<br>None |
| **Safety concern** | **Routine risk minimisation activities** |
| Medication errors in the home infusion setting | Routine risk communication:<br>• SmPC section 4.2<br>• SmPC section 6<br>Other routine risk minimisation measures beyond the Product Information:<br>None |

## V.2. Additional Risk Minimisation Measures

HCP brochure and patient/caregiver/HCP guide related to home infusion therapy.

Objectives:

The objective is to provide guidance to healthcare professionals (HCPs), patients and caregivers for the management of patients receiving Elfabrio at home.

Rationale for the additional risk minimisation activity:

Patients with Fabry disease may be offered home infusion therapy in order to reduce the burden of bi-weekly administration of infusions in the hospital setting which will increase comfort and flexibility of infusion timing. However, in order to minimize the risk for medication errors in the home setting which may result in severe adverse events, the following educational materials will be provided:

- HCP brochure for the HCP to enable selection of patient eligible for home infusion and to train the Caregiver to administer the product at home
- Patient/caregiver/HCP guide to aid in the infusion at home to prevent medication errors.

Target audience and planned distribution path:

The educational materials will be distributed to treating physicians who, in turn, will train registered nurses, and caregivers.

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

Through routine pharmacovigilance, including preparation of Periodic Safety Update Reports (PSURs) and signal detection and analysis. A low rate of medication errors or no medication errors as well as the number of other ADRs reported especially in setting of home infusion will be key to validate the effectiveness of the intervention will be evaluated in the context of routine PV activities such as Signal detection and PSUR/PBRER preparation.

Removal of additional risk minimisation activities

Not Applicable.

## V.3 Summary of risk minimisation measures

**Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| **Important Identified Risk** | | |
|---|---|---|
| **Safety concern** | **Risk minimisation measures** | **Pharmacovigilance activities** |
| Hypersensitivity Reactions (infusion related) | Routine risk minimisation measures:<br>• SmPC section 4.4.<br>• PL section 2<br>Additional risk minimisation measures:<br>• HCP brochure | Routine pharmacovigilance<br>• Regular review of safety reports<br>• Signal detection activities<br>• Inclusion of discussion in the EU Periodic Safety Update Report (PSUR) |

| Important Identified Risk | | |
|---|---|---|
| **Safety concern** | **Risk minimisation measures** | **Pharmacovigilance activities** |
| | • Patient/caregiver/HCP guide | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |

| Important Potential Risk | | |
|---|---|---|
| **Safety concern** | **Risk minimisation measures** | **Pharmacovigilance activities** |
| Medication errors in the home infusion setting | Routine risk minimisation measures:<br>• SmPC section 4.2<br>• SmPC section 6<br>Additional risk minimisation measures:<br>• HCP brochure<br>• Patient/caregiver/HCP guide | Routine pharmacovigilance<br>• Regular review of reports<br>• Signal detection activities<br>• Inclusion of discussion in the EU Periodic Safety Update Report (PSUR)<br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |

## Part VI: Summary of the risk management plan

# SUMMARY OF THE RISK MANAGEMENT PLAN FOR ELFABRIO® (PEGUNIGALSIDASE ALFA)

This is a summary of the risk management plan (RMP) for Elfabrio 2 mg/mL concentrate for solution for infusion (hereinafter referred to as Elfabrio). The RMP details important risks of Elfabrio, how these risks can be minimised, and how more information will be obtained about Elfabrio's risks and uncertainties (missing information).

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

This summary of the RMP for Elfabrio 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 Elfabrio*'s* RMP.

### I. The medicine and what it is used for

Elfabrio is authorised for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase) (see SmPC for the full indication). It contains pegunigalsidase alfa as its active substance and is given by infusion in hospital or home settings.
Further information about the evaluation of Elfabrio's benefits can be found in Elfabrio 's EPAR, included in its plain-language summary, available on the EMA website, under the medicine's webpage Elfabrio | European Medicines Agency (EMA) (europa.eu).

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

Important risks of Elfabrio, together with measures to minimise such risks and the proposed studies for learning more about Elfabrio' s risks, 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 the case of Elfabrio, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

### II.A List of important risks and missing information

Important risks of Elfabrio 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 Elfabrio. 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).

| **List of important risks and missing information** | |
|---|---|
| **Important identified risks** | Hypersensitivity Reactions (infusion related) |
| **Important potential risks** | Medication errors in the home infusion setting |
| **Missing Information** | None |

### II.B Summary of important risks

| **Important identified risk: Hypersensitivity Reactions (infusion related)** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical trials included in the development programme |
| Risk factors and risk groups | Patients undergoing IV infusion and/or subjects that had previous ERTs (Fabrazyme or Replagal) and/or patients referred to as "switchers" defined as subjects that had |

| | |
|---|---|
| | the last ERT less than 6 months prior to pegunigalsidase alfa. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC section 4.4.<br>• PL section 2<br>Additional risk minimisation measures:<br>• HCP brochure<br>• Patient/caregiver/HCP guide |

| **Important potential risk: Medication errors in the home infusion setting** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical trials included in the development programme |
| Risk factors and risk groups | Patients receiving Elfabrio infusions in the home setting by an HCP |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC section 4.2<br>• SmPC section 6<br>Additional risk minimisation measures:<br>• HCP brochure<br>• Patient/caregiver/HCP guide |

## II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation for Elfabrio.

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

There are no studies required for Elfabrio.

# Part VII: Annexes

## Annex 1 – EudraVigilance Interface

## Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not Applicable

## Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

## Annex 4 - Specific adverse drug reaction follow-up forms

None

## Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

**Annex 6 - Details of proposed additional risk minimisation activities**

Prior to the use of Elfabrio in each Member State in the home setting the 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 MAH shall ensure that in each Member State where Elfabrio is marketed, all Healthcare Professionals (HCP) who are expected to prescribe Elfabrio are provided with the following educational pack which includes:

1. **HCP brochure providing** relevant information for the HCP to train the caregiver to administer the product at home which describe the following key elements:

    - checklist with eligibility criteria for home infusion
    - the need for prescribing medication to treat IRRs and that the patient/caregiver should be able to use them
    - the need for premedication if necessary (with antihistamines and/or corticosteroids) in those patients where symptomatic treatment was required.
    - The training of the person who will infuse pegunigalsidase alfa on how to identify IRRs.
    - The training of the person who will infuse pegunigalsidase alfa about the preparation and administration of the product and the use of the logbook".
    - The need of the logbook and its function in communication with the treating physician
    - Describe the importance of the presence of a caregiver in case emergency medical care is needed

2. **Patient/ caregiver/ HCP guide for the administration at home** which describe the following key elements:

    - Step by step instructions on the preparation and administration technique including proper aseptic technique
    - The dosing and infusion rate will be determined by the treating physician.
    - Signs and symptoms of IRRs and how to treat or manage them
    - the importance of the presence of a caregiver to monitor the patient in case emergency medical care is needed.
    - medication prescribed by the treating physician for IRRs or pre-medication should be available at home and should be used accordingly

- the logbook should be used to record the infusion and any IRR and taken to the treating physician visits.

**Annex 7 - Other supporting data (including referenced material)**

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## Annex 8 – Summary of changes to the risk management plan over time

| Version | Approval date<br>Procedure | Change |
|---|---|---|
| 0.1 | Approval date:<br>Not Applicable<br>Procedure number: Not Applicable | Safety concerns<br>Not Applicable<br>Pharmacovigilance Plan<br>Not Applicable<br>Post-authorisation efficacy plan<br>Not Applicable<br>Risk minimisation measures<br>Not Applicable<br>Annexes<br>Not Applicable |
| 0.2 | Approval date:<br>Not Applicable<br>Procedure number:<br>EMEA/H/C/005618 | Safety concerns<br>Important identified risks<br>• As per PRAC Rapporteur's comment, "Infusion related reactions (IRR)" safety concern was renamed and focused on the most severe events such as hypersensitivity reactions.<br>Missing information<br>• As per PRAC Rapporteur's comments the missing information "Elderly" and "Paediatrics population" and "Pregnant and/or breastfeeding women" have been removed from the list of missing information.<br>Risk minimisation measures<br>• The proposed manual for treating physicians to train registered nurses, was modified and amended to comply with the comments by the PRAC Rapporteur<br>• Additional risk minimisation measures were included for the safety issue hypersensitivity reactions (infusion related) in the home setting as per PRAC Rapporteur's comments<br>Annexes<br>• As per the PRAC Rapporteur's comments, the full HCP brochure has been deleted from the Annex 6 of the RMP and only key features have been reported. A statement that the details will be assessed at national level has been included as well. Annex IID of the SmPC was updated accordingly.<br>Other<br>Part VI "Summary of activities in the risk management plan by medicinal product", was updated in line with the issues raised in other parts of the RMP |

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| 0.3 | Approval date:<br>Not Applicable<br>Procedure number:<br>EMEA/H/C/005618 | <u>Annexes</u><br>• As per the PRAC Rapporteur's comments (D180), the full HCP brochure has been removed from Annex 6 of the RMP and only key elements of two separate educational materials have been included<br>1. The HCP brochure for the HCP<br>2. Patient/caregiver/HCP guide,<br>• The full content and format, and distribution modalities of the 2 materials will be agreed, subsequently to the initial MAA procedure, at the national level by NCAs, and after authorisation Annex IID of the SmPC was updated accordingly. |
| 0.4 | Approval date:<br>04 May 2023<br>Procedure number:<br>EMEA/H/C/005618 | <u>Safety Concerns</u><br>• The safety concern "Immunogenicity" was removed from the RMP as per the Rapporteur's request.<br><u>Annexes</u><br>• The following HCP brochure key elements were re worded in the Annex IID of the PI and Annex 6 of the PRX-102 RMP:<br>1. 'training on how to identify IRRs' was reworded into "training of the person who will infuse pegunigalsidase alfa on how to identify IRRs".<br>2. 'training about the preparation and administration of the product and the use of the logbook' was reworded into "training of the person who will infuse pegunigalsidase alfa about the preparation and administration of the product and the use of the logbook".<br>• The HCP brochure key element 'the logbook is an important communication tool' was removed in the Annex IID of the PI and Annex 6 of the PRX-102 RMP.<br>• The following patient/ caregiver/ HCP guide for the administration at home key elements were reworded in the Annex IID of the PI and Annex 6 of the PRX-102 RMP:<br>1. 'the importance of the dosing and infusion rate' was reworded into "the dosing and infusion rate will be determined by the treating physician".<br>2. 'the importance of the presence of a caregiver in case emergency medical care is needed' was reworded into "the importance of the presence of a caregiver to monitor the patient in case emergency medical care is needed".<br>3. 'the logbook should be used to record the infusion and any IRR' was reworded into "the logbook should be used to record the infusion and any IRR, and taken to the treating physician visits". |

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| | | Other<br>Removal of self-administration as a treatment option in all relevant RMP sections. |
| 1.0 | Approval date:<br>04 May 2023<br>Procedure number:<br>EMEA/H/C/005618 | Updated of post approval version number as per Guidelines - GVP Module V Rev.2 |
| 1.1 | Approval date:<br>Not applicable<br><br>Procedure number:<br>EMEA/H/C/005618/II/0007 | • Part I – addition of proposed posology and update of ATC<br>• Part II- Minor changes in Epidemiology of the indication section<br>• Module SIII – updates related to clinical trial exposure<br>• Module SV - addition of post-authorisation experience data<br>• Module SVII.3 – update on risks presentation<br>• Part VI – Updates as per GVP Module V Rev.2 guidelines<br>• Trade name and active substance update in RMP<br>• Safety concerns – no changes |
| 1.2 | Approval date:<br>Not applicable<br><br>Procedure number:<br>EMEA/H/C/005618/II/0007 | Minor changes as per PRAC Rapporteur's comments in:<br>• Part II: SIII – update information on Cohort 3<br>• Part II: SVII.3, Part VI - harmonization of the text according to the Guidelines - GVP Module V Rev.2 |
| 1.3 | Approval date:<br>Not applicable<br><br>Procedure number:<br>EMEA/H/C/005618/II/0007 | Minor changes to the wording of the proposed dosing for every four weeks administration.<br>Updates according to the guidelines - Anonymisation of personal data and assessment of commercially confidential information (EMA/63692/2025 Rev. 3):<br>• SV.1.2 – removal of country-specific data.<br>SVII.3.1 – removal of individual patient information. |
| 1.4 | Approval date:<br>Not applicable<br><br>Procedure number:<br>EMEA/H/C/005618/II/0007 | Minor changes to the wording of the proposed dosing for every four weeks administration. |
| 1.5 | Approval date:<br>Not applicable<br><br>Procedure number:<br>EMEA/H/C/005618/II/0007 | Minor changes related the wording of the proposed dosing for every four weeks administration. |