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OBSERVATIONAL STUDY PROTOCOL

STUDY CODE No.: CLI-06657AA1-06

Maternal and Postnatal Outcomes Study (MOS)

A worldwide decentralized observational registry to evaluate the safety in women with Fabry disease and their infants exposed to Elfabrio® (pegunigalsidase alfa-iwxj/pegunigalsidase alfa) during pregnancy and/or lactation

Version No.: 3.0
Version Date: 21 October 2024

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
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GENERAL INFORMATION

SPONSOR:	Chiesi Farmaceutici S.p.A.* Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
SPONSOR MEDICAL EXPERT (Clinical Research Physician)	[redacted] Readily available in case of medical questions

VERSION HISTORY

Version	Date	Change History
1.0	13 November 2023	Initial protocol
2.0	31 May 2024	FDA General Advice Implementation
3.0	21 October 2024	FDA General Advice Implementation

PROTOCOL OUTLINE

Study title	**Maternal and Postnatal Outcomes Study (MOS)** **A worldwide decentralized observational registry to evaluate the safety in women with Fabry disease and their infants after exposure to Elfabrio® (pegunigalsidase alfa-iwxj/pegunigalsidase alfa) during pregnancy and/or lactation**
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Medicinal Product	Elfabrio® (pegunigalsidase alfa-iwxj/pegunigalsidase alfa)
Centres	This registry will be run as a fully decentralized study.
Indication	Fabry disease
Study design	This is a worldwide, decentralized, single arm, prospective and retrospective, observational registry in women with Fabry disease exposed to pegunigalsidase alfa during pregnancy (within 30 days prior to the date of conception and/or during pregnancy) and/or lactation, and their infants. An outreach campaign using a variety of online and print methods will be implemented to increase awareness of the registry among both patients and physicians. The registry will allow physicians to enrol eligible patients and will also allow eligible patients to self-enrol. Patient enrolment and data collection will be coordinated through a centralized web-based platform. The web-based platform will include information about the registry and will allow the patient or the physician to create an online account to participate in the registry and independently and remotely record patient's data. Patients who pass eligibility per a pre-screening form (or their parents/legal guardian for minor patients) will be asked to review and sign an informed consent form (ICF) to confirm their agreement to participate in the registry. In addition, patients (or their parents/legal guardian) will be asked to complete and sign a contact form authorizing the Sponsor designee (contract research organization) to contact them and their primary care/other attending physician during their participation in the registry. The patient (or their parents/legal guardian) will also be asked to complete and sign a medical information release form authorizing the physician to release patient's medical information. Minor patients will be asked to review and sign an assent form indicating their consent to participate in the registry. Minor patients who reach the age of consent during the registry period will be asked to sign an ICF to confirm their consent to participate in the registry. After enrolment in the registry, pregnancy and clinical outcomes will be collected throughout pregnancy and up to the infant's 12 months of age. Congenital malformations will be described according to established criteria (e.g., Metropolitan Atlanta Congenital Defects Program [MACDP] criteria, European Surveillance of Congenital Anomalies [EUROCAT] criteria).

	Reported congenital malformations will be adjudicated by an independent Scientific Advisory Committee. The registry is observational and will not change the patient/physician relationship, nor influence the physician's drug prescription or therapeutic management of the patient.
Objectives	To evaluate pregnancy and clinical outcomes in women with Fabry disease and their infants after exposure to pegunigalsidase alfa at any time during pregnancy and/or lactation.
Observational period	The registry is planned to enrol over a period of 10 years. Pregnancy and maternal health information will be collected until delivery or within 42 days of termination of pregnancy. Infants will be followed up to 12 months of age.
Number of subjects	10 pregnant and/or breastfeeding women are expected to be enrolled into the registry.
Study population	Pregnant and/or breastfeeding women with Fabry disease and their infants, after exposure to at least 1 dose of pegunigalsidase alfa during pregnancy and/or during lactation.
Inclusion/exclusion criteria	Inclusion Criteria: • Female patients with Fabry disease who have been exposed to at least 1 dose of pegunigalsidase alfa at any time during pregnancy (defined as having received pegunigalsidase alfa within 30 days prior to the date of conception and/or during pregnancy) and/or during lactation, and their infants. • Patient or parent/legally authorized representative must be able to understand and provide consent through an Institutional Review Board / Independent Ethics Committee (IRB/IEC) approved Informed Consent Form. Exclusion Criteria: None.
Study plan	Information on pregnancy, birth, post-pregnancy health, breastfeeding, and infant's health will be obtained directly from the patient and/or from the physician. Patients can be enrolled in the registry at any time (during pregnancy or after the end of pregnancy). Depending on when the patient will enrol in the registry, patient and infant data will be collected retrospectively and/or prospectively. Data on infants will be collected when the infant is 3, 6, 9, and 12 months of age, as applicable.
Primary Outcome Measures	• Pregnancy outcome: o Number of live births [time frame: at the delivery, after an average of 40 weeks of pregnancy] o Number of preterm birth [time frame: at delivery, prior to 37 weeks of gestation]

	○ Number of pregnancy losses (number of spontaneous abortions [time frame: up to 20 weeks of pregnancy], number of pregnancy terminations [time frame: through the pregnancy], number of foetal deaths or stillbirths [time frame: greater than 20 weeks of pregnancy and through the pregnancy, average of 40 weeks])
Secondary Outcome Measures	• Number of neonates/infants with major congenital malformations (MCM) [time frame: through the pregnancy, an average of 40 weeks and up to 12 months of infant age] • Number of ectopic or molar pregnancies [time frame: through the pregnancy, an average of 40 weeks] • Number of women with obstetric and delivery complications [time frame: at the delivery, an average of 40 weeks of pregnancy] • Number of women with complications of preeclampsia or eclampsia [time frame: through the pregnancy, an average of 40 weeks] • Number of women with complications of preterm prelabour rupture of membrane [time frame: before the onset of labour and prior to 37 weeks of gestation] • Number of neonates/infants with minor congenital malformations [time frame: through the pregnancy, an average of 40 weeks and up to 12 months of infant age] [time frame: through the pregnancy, an average of 40 weeks and up to 12 months of infant age] • Number of infants with developmental deficiency [time frame: up to 12 months of infant age] • Number of hospitalisations in infants [time frame: up to 12 months of infant age] • Mortality in infants, including neonatal death and infant death [time frame: up to 12 months of infant age] • Head circumference in infants (cm) [time frame: up to 12 months of infant age] • Weight in infants (kilograms) [time frame: up to 12 months of infant age] • Length in infants (cm) [time frame: up to 12 months of infant age] • Number of infants born as small for gestational age [time frame: up to 12 months of infant age] • Number of infants with postnatal growth deficiency or failure to thrive [time frame: up to 12 months of infant age] • Duration of breastfeeding, number of exclusively breastfeeding women and number of breastfeeding women supplemented with formula [timeframe: up to 12 months of infant age] • Number of adverse events in infants exposed to pegunigalsidase alfa during breastfeeding
Sample size calculation	As Fabry disease is a rare disease with X-linked inheritance, heterozygous female subjects show a variable expression with a broad range of disease severity, ranging from asymptomatic to classical phenotype, which in turn influences the timing of treatment initiation, often postponed compared to male patients. Moreover, there are currently different therapies approved for

	Fabry disease, including enzyme replacement treatments (Fabrazyme and Elfabrio in the United States [US], with the addition of Replagal in the European Union [EU]), and the oral chaperone Galafold. Therefore, the number of pregnant women with Fabry disease treated with pegunigalsidase alfa cannot be accurately estimated. It is anticipated that very few pregnant women will be exposed to pegunigalsidase alfa every year; therefore, a sample size of 10 pregnant and/or breastfeeding women is expected for the approximate 10-year duration of this study. Additionally, reports of pregnancy and congenital malformations from any past or ongoing pegunigalsidase alfa clinical studies, post-marketing setting, and published literature will be included in the study as supportive data.
Statistical methods	Analyses will be descriptive, with data listings, frequency tabulations, and summary statistics as appropriate. Descriptive statistics will comprise of the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and n and percent for categorical variables. The 95% confidence intervals will also be presented for selected pregnancy outcomes variables. Analyses will be conducted for prospective and retrospective reports separately and pooled together, if the data are available. If external reports, such as those from ongoing clinical studies, literature, and post-marketing surveillance are available, these will be presented.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACOG	American College of Obstetricians and Gynecologists
ADA	Antidrug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CA	Competent authority
CCPA	California Consumer Privacy Act
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract research organization
CSR	Clinical study report
DCT	Decentralized Clinical Trial
DOC	Date of conception
DPO	Data Protection Officer
DSUR	Development safety update report
EDD	Estimated date of delivery
E2W	Every 2 weeks
E4W	Every 4 weeks
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOW	Every other week
ERT	Enzyme replacement therapy
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FAS	Full analysis set
FDA	Food and Drug Administration
FTT	Failure to thrive
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GDPR	European General Data Protection Regulation
α-GAL-A	Alpha-galactosidase-A
GPP	Good Pharmacoepidemiology Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
LLT	Lowest level term
LMP	Last menstrual period
MedDRA	Medical Dictionary for Regulatory Activities
MACDP	Metropolitan Atlanta Congenital Defects Program

MCM	Major congenital malformation
MOS	Maternal and Postnatal Outcomes Study
MRHD	Maximum recommended human dose
PMR	Post-marketing requirement
PT	Preferred term
PTC	Peritubular capillaries
SAE	Serious adverse event
SD	Standard deviation
SGA	Small for gestational age
SOC	System organ class
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment emergent adverse event
UK	United Kingdom
US	United States
USPI	United States prescribing information
WHO	World Health Organization

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1 INTRODUCTION

1.1 Background Information

Fabry disease is an X-linked lysosomal storage disorder caused by alterations in the gene that encodes the lysosomal enzyme alpha-galactosidase-A (α-GAL-A) 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 had the disease, whereas the estimated prevalence in the general population was 1 in 117,000 (Tuttolomondo, 2021). However, newer studies suggest that Fabry disease has a much higher prevalence following the development of better diagnostic tools including peri-natal screening and increasing awareness (Rocchetti, 2022). 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 among studies covering different periods and/or different geographic areas. 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 not be identified (Mehta, 2004; Eng, 2007).

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 Gb3 and its degradation product, lyso-Gb3 in tissues and plasma, which both correlate with organ damage (Boutin, 2014; Ouyang, 2017; Kramer, 2018; Tuttolomondo, 2021). Progressive accumulation of Gb3, lyso-Gb3, and related lipids, leads to impaired tissue and organ function, particularly in the kidney, heart, and cerebrovascular system (Tuttolomondo, 2021). In addition, involvement of the central, peripheral, and autonomic nervous systems results in episodes of pain and impaired peripheral sensation.

Phenotypic expression is variable in female patients with Fabry disease due to variations in residual α-Gal-A activity and X-chromosome inactivation patterns in tissues. This can vary from nearly asymptomatic to the severe phenotype classically observed in male patients (Wilcox, 2008; Echevarria, 2016; Arends, 2017). More than half of women with Fabry disease suffer from disease symptoms, including hypertension prior to onset of worsening renal disease, severe abdominal cramping, hypohidrosis, central nervous system involvement with premature stroke, and psychological issues (Deegan, 2006; Wang, 2007; Wilcox, 2008; Bouwman et al. 2012).

Specific concerns associated with females with Fabry disease during pregnancy include microvascular disease that could increase the risk for clotting and worsening kidney function (MacDermot, 2001; Eng, 2006). The results of a retrospective study showed a worsening of several Fabry-related symptoms (e.g., gastrointestinal symptoms, acroparesthesias, proteinuria) in pregnant untreated female patients (Holmes, 2015). In addition, Gb3 accumulation has been found in maternal- and foetal-derived placental tissues, which heightens the risk of constriction of the placental blood vessels (Bouwman, 2010; Politei, 2012).

Current treatment options for Fabry disease include recombinant enzyme replacement therapy (ERT), gene therapy and chaperone therapy (Lenders, 2021). No randomized clinical trials have been specifically conducted in pregnant patients with Fabry disease, and the efficacy and safety of ERT on pregnancy and foetal development have not been established. ERT use in pregnant patients with Fabry disease has been reported through various case reports and in a sub-registry of pregnant patients with Fabry disease treated with ERT. Available information is summarised

in Appendix 1, Table 2. Overall, no ERT-associated risks for the mother and the children were observed.

Elfabrio® (pegunigalsidase alfa-iwxj), an ERT, is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme. It is a PEGylated homodimeric, covalently cross-linked recombinant human α-Gal-A enzyme expressed in plant cells. The PEGylation of pegunigalsidase alfa results in a substantial improvement of availability of active enzyme in the circulation throughout the dosing interval and may induce immune tolerance in patients who develop treatment-induced antidrug antibodies (ADAs) (Schiffmann, 2019); both parameters have been shown to be limitations of existing ERT treatments (Wang, 2008; Benichou, 2009; Rombach, 2012; Smid, 2013).

The clinical development program of Elfabrio in Fabry disease investigated doses of either 1 mg/kg every other week (EOW) or 2 mg/kg every 4 weeks (E4W), and included two Phase 1/2 studies, 3 completed Phase 3 studies, 2 ongoing open-label extension Phase 3 studies, and 1 ongoing Phase 2/3 study in Japan.

A randomized, double-blind, active-control Phase 3 study (PB-102-F20) aimed to compare the effect of pegunigalsidase alfa to Fabrazyme on renal function in Fabry disease patients, with impaired kidney function, previously treated with Fabrazyme. This study demonstrated an improvement, from baseline, in estimated glomerular filtration rate (eGFR) slope (annualised change in estimated eGFR) after 24 months of treatment, indicating long-term ERT efficacy. This study also demonstrated a comparable annualised eGFR slope between patients randomised to pegunigalsidase alfa treatment (1 mg/kg every EOW) or Fabrazyme treatment after two years of exposure. Other studies showed a reduction from baseline in renal Gb3 inclusions in the peritubular capillaries (PTC) (Phase 1/2 studies; PB-102-F01/F02), and a reduction from baseline in plasma lyso-Gb3 (from the open-label studies in ERT-naïve patients: Phase 1/2; PB-102-F01/F02 and in the ERT-switchover Fabry population: Phase 3 study, PB-102-F030). The most common adverse reactions associated with Elfabrio use were infusion-related reactions (IRRs) and hypersensitivity reactions, which are expected and frequently reported in patients who are treated with ERTs. Based on an analysis of integrated, pooled safety data, serious treatment emergent adverse events (TEAEs) were reported in 32.4% of patients dosed at 1 mg/kg EOW and related serious adverse events (SAEs) were very rare with <2 events in 100 patient-years in patients dosed at 1 mg/kg EOW and none in patients dosed at 2 mg/kg E4W. A total of 4 deaths were reported and none were related to study treatment.

The potential adverse effects of pegunigalsidase alfa on fertility and development were assessed in both rats and rabbits. No adverse effects on embryofoetal development were observed in pregnant rats intravenously administered pegunigalsidase alfa twice per week at exposures up to [redacted] times that of the maximum recommended human dose (MRHD; based on area under the concentration time curve). Maternal toxicity was observed in pregnant rabbits intravenously administered pegunigalsidase alfa twice per week at doses that were [redacted] times the MRHD (based on human equivalent dose).

Three pregnancy cases in 3 patients were reported in the ongoing and completed clinical studies as of 15 July 2023 (Development Safety Update Report [DSUR] date). One pregnancy resulted in live, healthy birth (the patient was treated with pegunigalsidase alfa for more than 5 years in total, at the initial dose of [redacted] in the PB-102-F01/F02 studies and later at dose of [redacted] E2W - dose used up to the diagnosis of pregnancy that occurred after 1 month after her last period and when pegunigalsidase alfa administration was stopped); there was one pregnancy termination (the patient had been treated with pegunigalsidase alfa [redacted] EOW for a total

of [redacted] and stopped in occasion of the diagnosis of pregnancy that occurred [redacted] after [redacted] and was based on positive urine and serum pregnancy tests and an ultrasound that revealed a [redacted] week embryo; a subsequent ultrasound showed one intrauterine foetus of [redacted] weeks with no abnormal findings. The patient decided to terminate the pregnancy); and one spontaneous abortion in a patient treated with pegunigalsidase alfa [redacted] every 2 weeks (E2W) from [redacted] and who continued treatment after being diagnosed with pregnancy on [redacted], the patient sustained an acute ischemic stroke while pregnant, had other comorbidities and was taking other medications contraindicated during pregnancy due to their potential for complications (such as increased risk of spontaneous abortion and foetal injury/death).

1.2 Study Rationale

Elfabrio received approval in 2023 in the European Union (EU), in the United States (US), in the United Kingdom (UK) and in Switzerland. Elfabrio is indicated for the treatment of adults with confirmed Fabry disease and the recommended dosage of Elfabrio is 1 mg/kg EOW administered by intravenous (IV) infusion (Elfabrio USPI, 2023; Elfabrio SmPC, 2023).

There are limited available data on pegunigalsidase alfa use in pregnant females to evaluate a drug-associated risk of major birth defects, miscarriage or other adverse maternal or foetal outcomes (Elfabrio USPI, 2023, Elfabrio SmPC, 2023).

This pregnancy registry is being conducted by Chiesi as a Post-Marketing Requirement (PMR) to the US Food and Drug Administration (FDA). The Elfabrio United States Prescribing Information (USPI) indicates that physicians should advise patients exposed to Elfabrio during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes and encourage patients to report the pregnancy to Chiesi (Elfabrio USPI, 2023).

The purpose of the registry is to collect prospective and retrospective data in women and their infants after exposure to pegunigalsidase alfa during pregnancy and/or lactation to assess pregnancy and clinical outcomes, adverse effects on the developing foetus and neonate, and adverse effects on the infant.

1.3 Compliance Statement

This registry will be conducted in compliance with the Declaration of Helsinki (1964 and amendments), Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA), Guide on Methodological Standards in Pharmacoepidemiology, the 2019 FDA Guidance for Post-Approval Pregnancy Safety Studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), and with local regulation for observational studies conduct.

Moreover, the registry will be managed according to the principles of the current International Council for Harmonisation (ICH) E6 GCP.

Participating physicians will conduct the study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the registry and in accordance with currently standard clinical practice.

2 STUDY OBJECTIVES

The objective of this registry is to evaluate pregnancy and clinical outcomes in women with Fabry disease and their infants after exposure to pegunigalsidase alfa at any time during pregnancy and/or lactation.

3 STUDY DESIGN

This is a worldwide, decentralized, single arm, prospective and retrospective, observational registry in women with Fabry disease exposed to pegunigalsidase alfa during pregnancy (within 30 days prior to the date of conception [DOC] and/or during pregnancy) and/or lactation, and their infants.

The registry is planned to enrol over a period of 10 years.

The registry will allow physicians to enrol eligible patients and will also allow eligible patients to self-enrol, in accordance with local regulations. Patient enrolment and data collection will be coordinated through a centralized web-based platform. The web-based platform will include information about the registry and will allow the patient or the physician to create an online account to participate in the registry and independently and remotely record patient's data through electronic case report forms (eCRFs).

On the web-based platform, the physician or the patient will complete and submit a pre-screening form to determine patient's eligibility for participation in the registry. If the patient passes the pre-screening, the physician or the patient will be asked to create a user account.

The patient (or their parents/legal guardian if the patient is minor) will be asked to review and provide informed consent to confirm their agreement to participate in the registry. In addition, the patient (or their parents/legal guardian) will be asked to complete and sign a contact form authorizing the Sponsor designee (contract research organization [CRO]) to contact them and their primary care/other attending physician during their participation in the registry. In the contact form, along with the primary contact, alternative contacts will be collected to assist in reaching the patient or healthcare provider. The patient (or their parents/legal guardian) will also be asked to complete and sign a medical information release form authorizing the physician to release patient's medical information.

Minor patients will be asked to review and sign an assent form indicating their consent to participate in the registry. Minor patients who reach the age of consent during the registry period will be asked to sign an ICF to confirm their consent to participate in the registry.

After enrolment in the registry, pregnancy and clinical outcomes will be collected throughout pregnancy and up to the infant's 12 months of age. Pregnancy information will be collected until delivery or within 42 days of termination of pregnancy (11th revision of the International Classification of Disease, ICD-11).

Congenital malformations will be described according to established criteria (e.g., Metropolitan Atlanta Congenital Defects Program [MACDP] criteria, European Surveillance of Congenital Anomalies [EUROCAT] criteria).

Reported congenital malformations will be adjudicated by an independent Scientific Advisory Committee (see Section 16).

Patients can be enrolled in the registry at any time (during pregnancy or after the end of pregnancy). Depending on when the patient will enrol in the registry, patient and infant data

will be collected retrospectively and/or prospectively via the web-based platform. Patient and infant data will be collected either by the physicians or provided directly by the patients (for self-enrolled patients). Information on pregnancy and infant outcomes provided by self-enrolled patients will be confirmed with their primary care or other attending physician by the CRO.

While participating in the registry, patients and/or physicians may receive registry newsletters or other communications regarding the registry or Fabry disease (e.g., status of the registry, educational materials about Fabry disease).

The registry is observational and will not change the patient/physician relationship, nor influence the physician's drug prescription or therapeutic management of the patient.

3.1 Limitations of the Study

Potential sources of biases are described below:

- Since participation in the registry will be voluntary, the included patients may not be representative of the overall pregnant women population.
- As reporting of pregnancies is voluntary, it is possible that even among prospectively reported pregnancies there could be bias in type of pregnancies which are reported. For example, high-risk pregnancies may be more likely to be reported.
- In case of pregnancy termination, pregnancy and birth outcome will be unknown which may introduce a bias.
- Those pregnancies that have reached the estimated delivery date, but for which outcome information is unobtainable will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes.

4 SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

An outreach program will be implemented to increase awareness of the registry among both patients and physicians.

The awareness campaign may include the following elements in each participating country:

- The registry web-based platform will be designed in local language with a section for patients and a section for physicians and will provide information about the registry and describe the process for participation for physicians and patients. The registry web-based platform will be developed in collaboration with patient advisory groups and patient experts.
- Targeted educational material describing the purpose of the registry purpose will be provided to physicians who are known to manage Fabry disease patients.
- Advertising and scientific presentations to physician professional societies at national meetings.
- Partnering with patient communities.
- Search engine.
- Persistent awareness activities incorporating a variety of other online approaches such as:

- FDA listing of pregnancy registries on *www.fda.gov*
- *www.clinicaltrials.gov*
- Society for Maternal-Fetal Medicine listing of registries
- Chiesi website
- Elfabrio website

In addition, to encourage the participation and retention of pregnant women in the registry, appropriate and adequate incentives will be included according to local regulations. Incentives may include both engagement strategies such as sharing study results through newsletters or the web-based platform or financial incentives such as cash, vouchers, or gifts.

All recruitment and retention strategies (including financial incentives) will be reviewed and/or approved by the appropriate bodies as per local regulations.

Overall, 10 pregnant and/or breastfeeding women with Fabry disease who have been exposed to at least 1 dose of pegunigalsidase alfa during pregnancy and/or during lactation are expected to participate in the registry.

Prior to data collection, informed consent must be obtained from the eligible patient. The decision of patients to participate in this registry must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. The prescription of treatments during the study period is at the discretion of the patient's doctor and independent from the inclusion in the registry.

4.2 Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrolment into the registry:

- Female patients with Fabry disease who have been exposed to at least 1 dose of pegunigalsidase alfa at any time during pregnancy (defined as having received pegunigalsidase alfa within 30 days prior to the DOC and/or during pregnancy) and/or during lactation, and their infants.
  - DOC, defined as $2^{0/7}$ gestational weeks, will be calculated from last menstrual period [LMP] or ultrasound
- Patient or parent/legally authorized representative must be able to understand and provide consent through an Institutional Review Board / Independent Ethics Committee (IRB/IEC) approved Informed Consent Form.

4.3 Exclusion Criteria

None.

4.4 Patient Withdrawals

Participation in this registry is voluntary and patients are free to withdraw from the registry at any time and for any reason without prejudice to their drug prescriptions or therapeutic management. Missing data at one or more time points will not be considered as criteria for patient withdrawal.

The patients are also free to withdraw their consent to being contacted by the CRO without justification or prejudice.

Patients must be withdrawn from the registry for any one of the following reasons:

- The patient withdraws consent to participate in the registry.
- The patient withdraws her medical release form.
- For self-enrolled patients, the patient withdraws consent to being contacted by the CRO.
- The patient is lost to follow-up before the last follow-up collection point.
- The patient requests discontinuation from the registry for any reason.
- The patient's physician withdraws the patient from the registry for medical reasons based on their own clinical decision making.

If a patient prematurely withdraws from the registry, regardless of cause, the date and the reason for registry withdrawal will be documented in the registry completion form of the eCRF, if this information is available. Every effort should be made to obtain this information on patients who discontinue participation in the registry. Patients who withdraw from the registry will be informed that their data collected up to that point will be used in the statistical analyses, but after withdrawal no further data will be collected for them.

No specific procedures after patient withdrawal from the registry are required per registry protocol. Patients who withdraw from the registry will not be replaced. Physician continuation of patient care should continue as per standard of care.

5 STUDY PLAN

5.1 Study Schedule

Patient data will be collected via the registry web-based platform by the physician and/or the patient at registry enrolment (after informed consent has been signed) and throughout the follow-up period. No additional monitoring or diagnostic procedures will be required by this protocol. Only information available as per routine clinical practice will be collected. Data collected are summarised in Table 1.

Table 1 Data Collected

Data	Enrolment	During pregnancy - End of first trimester (~13 weeks), second trimester (~27 weeks), third trimester (~40 weeks)	End of pregnancy	3, 6, 9, and 12 months after end of pregnancy	Registry discontinuation / Registry completion
Pre-screening form (inclusion/exclusion criteria)	X				
Informed consent[1]	X				
Demographic data[2]	X				
Fabry disease and treatment history	X				
Other relevant medical history	X				
Obstetric history[3]	X				
Family history	X				
Pregnancy information[4]	X	X			
Pegunigalsidase alfa treatment	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Obstetric complications	X[5]	X	X		
Occurrence of preeclampsia or eclampsia	X[5]	X	X		
Occurrence of preterm prelabour rupture of membrane	X[5]	X	X		
Pregnancy outcome[6]	X[5]	X	X		
Information on breastfeeding	X[5]		X	X	
Major and minor congenital malformations	X[5]	X	X	X	
Infant date of birth	X[5]		X		
Infant sex, race/ethnicity	X[5]		X		
Infant weight, length, head circumference	X[5]		X	X	
Infant development and postnatal growth	X[5]			X	
Infant hospitalisations	X[5]			X	
Infant mortality	X[5]			X	
Safety information[7]	X	X	X	X	X
Registry completion form					X
Reason for premature registry discontinuation					X

1 Informed consent must be obtained prior to any registry-related data collection.
2 Age, race/ethnicity, height, weight
3 Number of previous pregnancies and outcome

4 Date of last menstrual period, date of conception, estimated date of delivery, method of pregnancy confirmation, gestational weeks, prenatal testing
5 For women who enrol after the end of pregnancy or during lactation, patient data will be collected retrospectively at enrolment.
6 Live birth, premature delivery (prior to 37 completed weeks of gestation), spontaneous abortion (<20 weeks gestation), pregnancy termination, foetal death or stillbirth (≥20 weeks gestation), ectopic or molar pregnancy.
7 Safety information will be reported to the Sponsor by the contract research organization (see Section 8).

5.2 Patient Enrolment

Eligible patients will be enrolled by a physician or will self-enrol via the registry web-based platform. Patients can be enrolled in the registry at any time (during pregnancy or after the end of pregnancy).

5.2.1 Pre-screening

All patients will be pre-screened online for eligibility. Female patients with Fabry disease exposed to at least 1 dose of pegunigalsidase alfa at any time during pregnancy (within 30 days prior to the DOC and/or during pregnancy), and/or during lactation will be eligible.

Patients who are not eligible will be informed online that they cannot participate in the registry.

5.2.2 Enrolment

If the patient is eligible, the physician or the patient will be asked to create a unique user account on the registry web-based platform.

The patients (or their parents/legal guardian for minor patients) will be asked to provide informed consent. Minor patients will be asked to review and sign an assent form.

The patients (or their parents/legal guardian) will also be asked to complete and sign a contact form (patient contact information, contact schedule including preferred days and hours, and preferred communication channels [phone, email, text message, etc.], and contact information of their primary care or other attending physician). In the contact form, primary and alternative contacts outside of the patient's household will be collected to assist in reaching the patient or healthcare provider. The patient's identifiable information including the primary and the alternative contacts will be available only to the CRO and not the Sponsor. The patient (or their parents/legal guardian) will also be asked to complete and sign a medical information release form authorizing the physician to release patient's medical information.

Eligible patients who pass the pre-screening but do not provide consent will not be enrolled and their pre-screening data (selection criteria) will be destroyed.

5.3 Follow-up

Pregnancy information will be collected until delivery or within 42 days of termination of pregnancy. Infant information will be collected up to 12 months of age.

If the patient is enrolled by a physician, the patient and infant will be followed in accordance with standard of care, and patient and infant data will be collected by the physician in the registry web-based platform. The CRO will support the physician by contacting other healthcare professionals (e.g., obstetrician/gynaecologist, paediatrician) to obtain follow-up information or medical confirmation of pregnancy or clinical outcomes.

For self-enrolled patients, patient and infant data will be collected directly by the patients via the registry web-based platform. Medical information provided by self-enrolled patients (e.g., pregnancy outcome, congenital malformations) will be confirmed with their primary care or other attending physician by the CRO. The information provided by their primary care or other attending physician will be recorded in the registry by the CRO.

The CRO will report any relevant safety information to the Sponsor's pharmacovigilance department (see Section 8).

For women who enrol during pregnancy, patient data will be collected retrospectively at enrolment, and prospectively once per trimester and at the end of pregnancy.

For women who enrol after the end of pregnancy or during lactation, patient data will be collected retrospectively at enrolment.

Data on infants will be collected when the infant is 3, 6, 9, and 12 months of age, as applicable.

Patients and physicians will be contacted by the CRO after enrolment and during follow-up to review the registry process, answer any questions they may have, check data collection status (self-enrolled patients), and document the reason for registry discontinuation.

The CRO will make a minimum of 3 attempts to collect data at each timepoint. If there is no response from the physician, the CRO will contact the patient for outcome or follow-up information, if consistent with local regulations. Enrolled pregnancies for which outcome or follow-up information is unobtainable following the above attempts will be considered lost to follow-up.

5.4 Patient Contact

The CRO will record the patients' contact details in a contact tracker during the registry. There will be no information about patient's condition, health state or treatment either on the contact forms or in the contact tracker.

The CRO will not substitute as the physicians or interfere with the patients' usual healthcare management. The CRO staff will consistently advise patients to contact their physician for any question related to their treatment or their health status.

The patients' personal information collected by the CRO will only be used by the CRO and its subcontractors for the purpose of this registry, they will not be shared with the Sponsor. They will be securely stored by the CRO throughout the registry, separately from registry information/forms.

Patients' personal information will be destroyed at the end of the registry (or earlier upon patient's request).

The patients' health data and contact details (personal identifiable data) will be kept strictly separated from each other (i.e., in different files or databases). Health data (e.g., safety data) collected by the CRO will only be collected and/or transferred to the Sponsor using the patient's study identification number.

6 STUDY ACTIVITIES AND MEASUREMENTS

6.1 Demographic Data

Demographic data (including age, race/ethnicity, height, weight) will be collected at enrolment.

6.2 Fabry Disease and Treatment History

Fabry disease history will be collected at enrolment (date of diagnosis, how the diagnosis was made, and major clinical events).

Fabry disease treatment history will be collected at enrolment (e.g., enzyme replacement therapy other than pegunigalsidase alfa).

6.3 Other Relevant Medical History

Relevant medical history other than Fabry disease (including smoking status and alcohol consumption) will be collected at enrolment.

6.4 Obstetric History

Obstetric history (number of previous pregnancies and outcome) will be collected at enrolment.

6.5 Family History

Family history of congenital malformations will be collected at enrolment.

6.6 Pregnancy Information

Pregnancy information (date of last menstrual period, DOC, estimated date of delivery (EDD), method of pregnancy confirmation, prenatal testing) will be collected at enrolment.

The registry will follow the American College of Obstetricians and Gynecologists (ACOG) recommendations for the determination of the DOC and the EDD, representing the best obstetric estimate.

The DOC, defined as $2^{0/7}$ gestational weeks, will be calculated from LMP or ultrasound.

The calculation of the EDD will be performed by the obstetric healthcare, when available, and information whether LMP, and/or ultrasound, or assisted reproductive technology data were used for the calculation will be reported.

In relation to the EDD calculation, the following are defined:

- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP, as following:
    - Gestational weeks $2^{0/7}$ to $13^{6/7}$ will be considered the first trimester
    - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
    - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester

In case information from an obstetric healthcare is not available, data from the patient will be collected.

6.7 Pegunigalsidase Alfa Treatment

Information about pegunigalsidase alfa treatment (administration dates, dosing information) will be collected, including exposure to pegunigalsidase alfa treatment while enrolled in a clinical trial. Reasons for any change in dose or interruption to treatment will be collected.

If the pegunigalsidase alfa treatment is discontinued, the date of pegunigalsidase alfa discontinuation and the reason for discontinuation will be collected.

This registry is non-interventional, therefore any decision on whether to continue or not pegunigalsidase alfa treatment is independent from registry participation and is at the discretion of the patient's doctor.

6.8 Concomitant Medications

Concomitant medications taken at enrolment and during follow-up will be collected.

6.9 Obstetric and Delivery Complications

Information on obstetric complications (e.g., preeclampsia, eclampsia, preterm labour) will be collected at enrolment (retrospective data) and throughout pregnancy. Information on delivery complications will be also collected.

Information on maternal mortality will be collected.

Preeclampsia is defined as a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria (ACOG). Or, in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

o Thrombocytopenia: Platelet count less than 100,000 × 10^9/L

o Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

o Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration

o Pulmonary oedema

o New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Eclampsia is defined as the convulsive manifestation of the hypertensive disorders of pregnancy and is among the more severe manifestations of the disease. Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions, such as epilepsy, cerebral arterial ischemia and infarction, intracranial haemorrhage, or drug use (ACOG).

Preterm Prelabour Rupture of Membrane is defined as membrane rupture before labour that occurs before 37 weeks of gestation (ACOG).

6.10 Pregnancy Outcomes

Pregnancy outcomes as defined below will be collected:

- Live birth: Birth of a living foetus at ≥ 20 gestational weeks or, if gestational age is unknown, a foetus weighing ≥ 350 g.
- Premature delivery: A live birth delivered prior to 37 completed weeks of gestation. Gestational age is based on the obstetric estimate of gestation.
- Pregnancy loss
    - Spontaneous abortion (<20 weeks gestation): Any loss of a foetus due to natural causes less than 20 weeks gestation as a spontaneous abortion. If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural defects.
    - Pregnancy termination: The termination of pregnancy through medical or surgical procedures. If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural defects.
    - Foetal death or stillbirth (≥20 weeks gestation): Foetal death or stillbirth refers to foetuses born dead at ≥ 20 weeks gestation or weighing ≥ 350 grams. Foetal death occurring > 20 weeks but less than 28 weeks gestation is considered an early foetal loss. Foetal death occurring > 28 weeks is considered a late foetal loss (ACOG). If gestational age is unknown, stillbirth refers to a foetus weighing ≥ 350 g. If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural defects. Foetal death or stillbirth is included as perinatal death which is defined to include stillbirth or neonatal death.
- Ectopic or molar pregnancy

6.11 Congenital Malformations

Information on major and minor congenital malformations will be collected throughout pregnancy and up to the infant's 12 months of age.

Major congenital malformations (MCM) are defined as structural changes that have significant medical, social, or cosmetic consequences for the affected individual, and typically require medical intervention (US Centers for Disease Control and Prevention (CDC)).

The CDC guidelines disqualify the following as MCM: (1) those findings that are present in infants with outcomes at < 36 weeks gestational age or if gestational age is unavailable, weighing < 2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus, patent foramen ovale, and inguinal hernias; and (2) infants with only transient or infectious conditions, or biochemical abnormalities, who are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized MCM.

Classification of reported congenital malformations will be adjudicated by an independent Scientific Advisory Committee (see Section 16).

6.12 Breastfeeding

Information on breastfeeding patterns, including its duration, the proportion of women who exclusively breastfeed compared to women who supplement with formula, will be collected after the end of pregnancy and up to the infant's 12 months of age.

6.13 Infant Characteristics

The date of birth, sex and race/ethnicity of the infant will be collected.

The infant weight, length, and head circumference will be collected at birth and up to the infant's 12 months of age.

The infant will be identified to experience the following, if applicable, based on the definitions:

Small for gestational age (SGA): Weight at birth is < 10th percentile for sex and gestational age using standard growth charts for full and preterm liveborn infants. For the determination of SGA, the study will use the sex-specific international growth reference standards from the International Foetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks. The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multi-ethnic, diverse population, and have been specifically developed for modern research.

Postnatal growth will be evaluated at 3, 6, 9, and 12 months of infant age. For the determination of postnatal growth, the study will utilize the sex-specific international growth reference standards from the World Health Organization for children ages 0 to 24 months. The World Health Organization growth standards are recommended for use in the US for infants and children 0 to 2 years of age.

Postnatal growth deficiency or failure to thrive (FTT): Weight is < 10^{th} percentile for sex and chronological age on standard growth charts.

6.14 Infant development

Infant development will be evaluated at 3, 6, 9, and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and

movement/physical development) separately. Infant developmental deficiency is defined as failure to achieve the developmental milestones for chronological age, as defined by the CDC.

Information on infant development will be collected up to 12 months of age.

6.15 Infant Hospitalisations

Information on infant hospitalisations will be collected up to 12 months of age.

6.16 Infant Mortality

Information on infant mortality will be collected up to 12 months of age. The following definitions apply:

• Neonatal death: death of a live-born infant within 28 days of life. Neonatal death is included as perinatal death. which is defined to include stillbirth or neonatal death.

• Infant death: death of a live-born infant within 1 year of life.

6.17 Safety Information

Patient and infant information will be reviewed by the CRO to identify all possible adverse events. Serious adverse events (SAEs) and adverse drug reactions (ADRs) to report to the Sponsor's pharmacovigilance department. These events will be confirmed/followed with patient-provided healthcare professional.

6.18 Registry Completion / Registry Discontinuation

The date of registry completion will be recorded. In the event of premature withdrawal from the registry, the date and the reason for withdrawal will be documented.

7 ASSESSMENTS

7.1 Primary Outcome Measures

The primary outcome measures of the registry are as follows:

- Pregnancy outcome:
  - Number of live births [time frame: at the delivery, after an average of 40 weeks of pregnancy]
  - Number of preterm birth [time frame: at delivery, prior to 37 weeks of gestation]
  - Number of pregnancy losses (number of spontaneous abortions [time frame: up to 20 weeks of pregnancy], number of pregnancy terminations [time frame: through the pregnancy], number of foetal deaths or stillbirths [time frame: greater than 20 weeks of pregnancy and through the pregnancy, average of 40 weeks])

7.2 Secondary Outcome Measures

The secondary outcome measures for the registry are as follows:

- Number of neonates/infants with MCMs [time frame: through the pregnancy, an average of 40 weeks and up to 12 months of infant age]
- Number of ectopic or molar pregnancies [time frame: through the pregnancy, an average of 40 weeks]
- Number of women with obstetric and delivery complications [time frame: at the delivery, an average of 40 weeks of pregnancy]

- Number of women with complications of preeclampsia or eclampsia [time frame: through the pregnancy, an average of 40 weeks]
- Number of women with complications of preterm prelabour rupture of membrane [time frame: at delivery, prior to 37 weeks of gestation]
- Number of neonates/infants with minor congenital malformations [time frame: through the pregnancy, an average of 40 weeks and up to 12 months of infant age]
- Number of infants with developmental deficiency [time frame: up to 12 months of infant age]
- Number of hospitalisations in infants [time frame: up to 12 months of infant age]
- Mortality in infants, including neonatal death and infant death [time frame: up to 12 months of infant age]
- Head circumference in infants (cm) [time frame: up to 12 months of infant age]
- Weight in infants (kilograms) [time frame: up to 12 months of infant age]
- Length in infants (cm) [time frame: up to 12 months of infant age]
- Number of infants born as SGA [time frame: up to 12 months of infant age]
- Number of infants with postnatal growth deficiency or FTT [time frame: up to 12 months of infant age]
- Duration of breastfeeding, number of exclusively breastfeeding women and number of breastfeeding women supplemented with formula [time frame: up to 12 months of infant age]
- Number of adverse events in infants exposed to pegunigalsidase alfa during breastfeeding

8 COLLECTION, RECORDING AND REPORTING OF SAFETY DATA

8.1 Definitions

Adverse Event (AE). Any untoward medical occurrence in a subject 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 (including laboratory abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered as related to the investigational medicinal product.

Adverse Drug Reaction (ADR). 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 adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Special situations. This term includes:

- Product overdose, abuse, misuse, medication errors, off-label use, occupational exposure and/or falsified product.
- Interactions (i.e., drug/drug, drug/food, drug/device and drug/alcohol interactions).
- Lack of therapeutic efficacy/Modification of effect.
- Cases of suspected transmission of infectious agent via the product.

- Pregnancy and breast-feeding exposure of an embryo/foetus or an infant to the product (maternal or paternal exposure).

Serious Adverse Event (SAE) / Serious ADR. A SAE is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

Death is not an adverse event but an outcome. It is the cause of death that should be regarded as the adverse event. The only exception to this rule is "sudden death" where no cause has been established; in this latter instance, "sudden death" should be regarded as the adverse event and "fatal" as its reason for being serious.

- **Is life-threatening**

Life-threatening refers to an event in which the subject was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it was more severe.

- **Requires hospitalisation or prolongation of existing in subjects' hospitalisation**

Hospitalisation refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for the purpose of investigating and/or treating the AE. Hospitalisation for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis should not necessarily be regarded as a SAE.

- **Results in persistent or significant disability or incapacity**

The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the subject's physical or psychological well-being to the extent that the subject is unable to function normally.

- **Is a congenital anomaly or birth defect**
- **Is medically significant**

This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardize the subject's health or may require intervention to prevent one of the above outcomes.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; development of drug dependency or drug abuse.

Any **suspected transmission via a medicinal product of an infectious agent** is also considered a serious adverse reaction.

Non-Serious AE/Non-Serious ADR. An AE or ADR that does not meet the criteria listed above for a serious AE/serious ADR.

8.2 Reporting of SAEs/ADRs to Chiesi

Patient and infant information collected via the registry web-based platform will be reviewed by the CRO to identify all possible SAEs and ADRs (e.g., mortality, hospitalisation, adverse pregnancy outcome, adverse infant outcome).

The CRO must report all possible SAEs and ADRs to the Sponsor within 24 hours of awareness, using the Adverse Event Form, which should be sent by e-mail:

Safety Contact Information:

Chiesi Pharmacovigilance Department

Email: [redacted]

The collected safety report should be as complete as possible. Safety information to be collected includes an identifiable reporter (the reporter can be identified by either name or initials, or address or qualification), an identifiable subject (at least one among subject initials, subject number, date of birth or age or age group, gestation period), a description of the event, start and stop dates, seriousness criteria, causality, severity, action taken, and outcome. All possible SAEs should be reported even if not all information is yet available.

8.3 Reporting to Competent Authorities/Ethic Committees

CRO must report all possible SAEs to Chiesi, as described in Section 8.2, that will process them and report to the relevant Competent Authority (CA) as required.

In particular, all case reports will be reported by Chiesi supported by the CRO, to the applicable CAs/IRBs/IECs based on the applicable pharmacovigilance requirements.

Should any event be separately reported by the physician to the authorities (e.g., using the Spontaneous reporting system), the physician will be asked to inform Chiesi by copying it [redacted] to the relevant correspondence.

The physician will be reminded to report to the concerned CA, in accordance with the applicable laws in the country, ADRs with other suspect drugs other than pegunigalsidase alfa administered to the patients during the study period.

9 DATA MANAGEMENT

All data collected in the context of this registry will be stored and evaluated in accordance with regulatory and local requirements and applicable guidance for electronic records. Specific processes used to manage the data throughout the registry and ensure the accuracy and completeness of the data collected will be documented in the Data Management Plan.

Patient data will be collected in the electronic data capture (EDC) system via the registry web-based platform by the physician and/or the patient. Patient information provided by the self-enrolled patient's primary care or other attending physician will be captured in the EDC by the CRO.

Only authorized personnel will have access to the EDC system. Patients will be identified by use of the identification number assigned to them when they enrol in the study.

Programmed automated edit checks (e.g., value range, units, internal consistency) will be implemented in the EDC system to provide controls for data entry accuracy. Supplemental validation performed via regular reviews of the data will be implemented to identify data inconsistencies that are not detected by automated edit checks. In case of inconsistent, erroneous, or missing data, queries may be generated electronically and sent to the physician for correction. Self-enrolled patients may be contacted by the CRO to address the queries. An audit trail within the system will track all changes made to the data.

Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary. Concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary.

10 STATISTICAL METHODS

10.1 Sample Size

As Fabry disease is a rare disease with X-linked inheritance, heterozygous female patients show a variable expression with a broad range of disease severity, ranging from asymptomatic to classical phenotype, which in turn influences the timing of treatment initiation, often postponed compared to male patients. Moreover, there are currently different therapies approved for Fabry disease, including enzyme replacement treatments (Fabrazyme and Elfabrio in US, with the addition of Replagal in EU), and the oral chaperone Galafold.

Therefore, the number of pregnant women with Fabry disease treated with pegunigalsidase alfa cannot be accurately estimated. It is anticipated that very few pregnant women will be exposed to pegunigalsidase alfa every year; therefore, a sample size of 10 pregnant and/or breastfeeding women is expected for the approximate 10-year duration of this study.

Additionally, reports of pregnancy and congenital malformations from any past or ongoing pegunigalsidase alfa clinical studies, post-marketing setting, and published literature will be included in the study as supportive data.

10.2 Populations for Analysis

The full analysis set (FAS) will include all eligible patients (patients meeting all inclusion/exclusion criteria). All analysis will be based on the FAS.

Analyses will be conducted for prospective and retrospective reports separately and pooled together, if the data are available.

Reports will be considered prospective if the pregnancy outcome is unknown at enrolment (e.g., before the conduct of any prenatal tests that could provide knowledge of the pregnancy outcome). If the pregnancy outcome is known at enrolment (e.g., assessed through prenatal testing [e.g., targeted ultrasound, amniocentesis]), such reports will be considered retrospective.

If external reports, such as those from ongoing clinical studies, literature, and post-marketing surveillance are available, these will be presented.

10.3 Statistical Analysis

Details about the planned statistical analysis will be described in the Statistical Analysis Plan. The plan will be finalised before database lock.

Analyses will be descriptive, with data listings, frequency tabulations, and summary statistics as appropriate. No formal hypothesis testing will be performed.

10.3.1 Descriptive Statistics

Descriptive statistics will comprise of the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and n and percent for categorical variables. The 95% confidence intervals will also be presented for selected pregnancy outcomes variables.

10.3.2 Missing data

There will be no imputation for missing data.

10.3.3 Demographics and other clinical characteristics

Demographic and other clinical characteristics will be summarised descriptively.

10.3.4 Primary Analyses

The number and proportions with their 95% confidence intervals will be reported for each of the pregnancy outcomes including live births, preterm births, and pregnancy losses (i.e., spontaneous abortions, pregnancy terminations, and foetal deaths or stillbirths).

10.3.5 Secondary Analyses

The number and proportion of patients/infants with the following birth and pregnancy outcomes will be calculated and reported.

- Major and minor congenital malformations
- Ectopic or molar pregnancies
- Obstetric and delivery complications
- Preeclampsia or eclampsia
- Preterm prelabour rupture of membrane
- SGA
- Postnatal growth deficiency or FTT
- Infant developmental deficiency

The number and proportion of infant hospitalisations and infant mortality, including neonatal death and infant death will be reported.

Infant head circumference, weight and length at birth and during follow-up will be summarised descriptively.

Breastfeeding patterns will be summarized, including the duration of breastfeeding, number of women exclusively breastfeeding and number of women who supplemented with formula.

The number and rate of adverse events in infants exposed to pegunigalsidase alfa during breastfeeding will be summarized.

In addition, maternal deaths will be reported.

10.3.6 Comparative Analyses

The reporting rate of each pregnancy outcome from the Registry will be compared to publicly available information on pregnancies from previous Fabry disease observational studies and case series to identify any signals of potential adverse effect of pegunigalsidase alfa during pregnancy.

10.3.7 Interim analysis

Interim analyses may be conducted to provide results to the health authorities based on agreed schedule.

11 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The final protocol and the final versions of the ICF, assent form, the contact form, and the medical information release form (clearly identifying the study number, study title and version of the document) must be approved or given a favourable opinion in writing by the IRB/ IEC.

Patient's enrolment will not start before the approval of the IEC/IRB, if applicable per local requirement.

The IEC/IRB must also approve any additional patient material and any substantial amendment to the Protocol according to local regulations, if applicable.

A copy of all communications with the IEC/IRB will be provided to the Sponsor.

12 REGULATORY REQUIREMENTS

The registry will be notified to the Health Authorities (or authorized by) according to the legal requirements in each participating country.

Enrolment of the patients will not start before the approval of the IRB/IEC has been obtained and the registry notified to Health Authorities, if applicable.

13 INFORMED CONSENT

For both self-enrolled patients and patients enrolled by the physicians, the ICF approved by the IRB/IEC must be signed electronically within the registry web-based platform or on paper before any protocol-specified procedures are carried out, according to local requirements. When applicable, minor patients will be given an assent form and will be asked to sign it to confirm their agreement to participate. A copy of the signed ICF must be provided to the patient and/or their parent/legal guardian.

As an additional option, a verbal consent procedure will be allowed, provided it is documented appropriately and permitted by local regulations. This process will involve providing a detailed explanation of the study to the participant, followed by an audio recording or a written note of the consent, including the date, time, and names of the participant and the person obtaining the consent. This approach ensures that participants receive comprehensive information about the study and provide informed consent in a manner that complies with regulatory and ethical standards.

Before enrolment in the registry, the patient and/or their parent/legal guardian will be asked to review the information provided in the ICF, which will detail the nature, purpose, possible risk and benefit of the registry. Patients will also be informed that they are free to withdraw their consent at any time.

The ICF will also explain that participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care they will receive.

14 SOURCE DOCUMENTS/DATA

Patient data will be collected by the physician or directly by the patient at enrolment and throughout the follow-up period. Registry data of interest will be entered into the EDC system

via the registry web-based platform by the physician and/or the patient. Patient information provided by the self-enrolled patient's primary care or other attending physician will be captured in the EDC by the CRO.

15 STUDY MONITORING

As this registry does not include any study sites, no site monitoring and no source data verification are planned. The Sponsor of this registry has the ultimate responsibility for ensuring the proper conduct of the registry in regard to protocol adherence and validity of the data recorded in the digital forms.

16 SCIENTIFIC ADVISORY COMMITTEE

An independent Scientific Advisory Committee will review cumulative study data over the course of the registry, including review and classification of reported congenital malformations. The Scientific Advisory Committee will comprise relevant expert(s) (e.g., obstetrics, embryology, teratology, epidemiology, paediatrics, clinical genetics). The member(s) of Scientific Advisory Committee will not be actively involved in the study design and study conduct, and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision making.

The roles, responsibilities, procedures and decision criteria of the Scientific Advisory Committee will be defined in a charter.

17 QUALITY ASSURANCE

The Sponsor will implement processes to manage quality and oversight throughout all stages and activities of the study based on data and processes identified as critical for the patients' rights and safety as well as data reliability and robustness.

Quality management will include system tools, and procedures for data collection and processing, as well as the collection of information essential to decision making.

The quality management system will use a risk-based approach as described in ICH E6 with:

- Critical Process and Data Identification;
- Risk Identification/Evaluation/Control/Communication and Review;
- Risk Reporting.

The R&D Quality Assurance Department of Chiesi may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the registry is being conducted in agreement with Good Clinical Practices and the currently approved protocol.

18 CONFIDENTIALITY

All registry documents are provided by the Sponsor in confidence to the physician and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the registry without written permission from Chiesi.

The physician must assure the patient's anonymity will be maintained. The physician will keep a separate list with at least the initials, the patient's study numbers, names, and addresses and telephone numbers. The physician will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

19 PERSONAL DATA AND DATA SECURITY

As an EU-based Sponsor, Chiesi will collect and process patient's data in accordance with the European General Data Protection Regulation ("GDPR"), and any applicable data protection laws and regulations, including but not limited to: (a) the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Rules, 45 C.F.R. Parts 160-164; (b) any other U.S. state or federal laws or regulations governing the privacy or security of personal data; (c) the California Consumer Privacy Act of 2018, Cal. Civ. Code § 1798.100 et seq. ("CCPA"). The personal data involved in the study will be processed in a pseudonymized form, in compliance with both the Good Clinical Practice ("GCP") and the data protection laws and regulations.

Chiesi is committed to abiding by all the data protection requirements foreseen by the applicable data protection laws and regulations, including processing patient's data in compliance with the data minimization, transparency, purpose limitation principles and by implementing adequate technical and organizational safeguards, to ensure data security as provided under Article 32 of the GDPR. More specifically, all the Sponsor's employees are bound to confidentiality obligations set out in their employment contracts and the specific data processing instructions and trainings programs provided by the Sponsor. Therefore, the Sponsor's employees will not disclose or permit the disclosure of any of the information, including the patient's data and any other confidential, non-public, or proprietary information related to the study protocol.

The access to the patient's data will be granted to the Sponsor's appointed employees through their personal credentials, solely for the purposes herein described and, on a need-to-know basis in compliance with the purpose limitation and data minimization principles. All the registry information, including personal data, will be processed and stored in an encrypted form to prevent their identification by non-authorized persons.

The Sponsor has implemented adequate cybersecurity measures, including best practices, software, hardware, and physical means to protect the patient's data and prevent any unexpected disclosure or threat that may affect the data. Chiesi will also conduct periodical cybersecurity assessments, such as penetration tests, to ensure its systems in line with the required security standards.

In compliance with the GDPR, Chiesi has in place a dedicated data breach management process to detect, mitigate, and, where applicable, notify a data security breach affecting the patient's data to the competent data protection authority. The process is coordinated by the Sponsor's data protection functions, including the appointed data protection officer (the "DPO Office"), which must be notified as soon a data incident has been detected. After being notified, the DPO Office convenes the working group together with the cybersecurity function as well as with the business functions potentially affected by the incident. The working group, coordinated by the DPO office, is responsible for assessing the impact of the incident and carries out the activities necessary to mitigate the adverse effects eventually occurred. Based on the result of the evaluation of risks of the breach the working group will determine whether it is necessary to notify the data protection authority and will proceed in compliance with the legal term provided under Article 33 of the GDPR. In any case, the DPO Office keeps track of all the notified data incidents in a dedicated register.

The data breach management process described above will be initiated by the Sponsor upon notification by any parties involved in the study, for example CROs, with whom Chiesi has entered into specific data processing agreements.

20 PREMATURE TERMINATION OF THE STUDY

The IRB/IEC/CA in each country will be notified about the end of the registry (date of termination of the study, last patient out date, number of patients observed) or early termination of the observation accordingly.

Both the Sponsor and the physician reserve the right to prematurely terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

The Sponsor should submit a written notification to the Regulatory Authority concerned and IEC/IRB providing the justification of premature ending or of the temporary halt.

21 CLINICAL STUDY REPORT

The interim and final clinical study reports (CSRs), including the statistical and clinical evaluations, shall be prepared and sent for agreement and signature to the Study Investigator, when applicable.

The distribution of interim and final CSRs or CSR synopses to all IECs/IRBs, to the CA will follow local regulations.

At the end of the study, the CSR synopsis will be provided to physicians, when applicable.

22 RECORD RETENTION

As this registry does not include any study sites and Investigators, the registry documents and patient records are collected and retained by only the Sponsor. The Sponsor will maintain the data collected and documents for at least 7 years after the end of the registry.

23 DISSEMINATION OF CLINICAL STUDY DATA

In accordance with local legislative and applicable requirements on clinical studies (if any), Chiesi will disclose protocol- and registry-related information of this registry in public registries.

In accordance with Chiesi commitments on Clinical Trial Transparency, registry information will be also publicly disclosed on a voluntary basis. The Chiesi website www.chiesi.com contains the commitments on Clinical Trial Transparency and all the registry information publicly disclosed.

Results should be published or otherwise made publicly available according to the relevant regulatory requirements, if any.

24 PUBLICATION POLICY

Chiesi is entitled to publish and/or present any results of this registry at scientific meetings; Chiesi furthermore reserves the right to use such data for industrial purposes.

During the registry, only the Sponsor may make registry information available to physicians or to regulatory agencies, except as required by law or regulation. Any public disclosure (including publicly accessible websites) related to the protocol or registry results, other than study recruitment materials, is the sole responsibility of the Sponsor.

In the absence of a Study Steering Committee, physicians should inform Chiesi before using the results of the study for publication or presentation and agree to provide the Sponsor with a

copy of the proposed presentation. This allows the Sponsor, respectfully of the rights relating to the ownership of the data collected, to provide with comments based on information from other studies that may not yet be available to the physician.

Data from physicians shall not be published separately without the previous consent of Chiesi.

25 REFERENCES

11th revision of the International Classification of Disease, ICD-11 available at https://icd.who.int.

ACOG, The American College of Obstetricians and Gynecologists, Obstetric Care Consensus No. 10, 2020

Aerts JM, Groener J, Kuiper S, et al. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(8):2812-7.

Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. J Am Soc Nephrol. 2017;28(5):1631-1641.

Benichou B, Goyal S, Sung C, Norfleet AM, O'Brien F. A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease. Mol Genet Metab. 2009;96(1):4-12.

Boutin M, Auray-Blais C. Multiplex Tandem Mass Spectrometry Analysis of Novel Plasma Lyso-Gb3-Related Analogues in Fabry Disease. ACS Publica. 2014;86(7):3476-83.

Bouwman MG, Hollak CEM, et al. Analysis of placental tissue in Fabry disease with and without enzyme replacement therapy. Placenta. 2010;31:344–346.

Bouwman MG, Rombach SM, et al. Prevalence of symptoms in female Fabry disease patients: a case–control survey. J Inherit Metab Dis. 2012;35(5):891–898.

Deegan PB, Baehner AF, et al. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet. 2006;43(4):347–352.

Echevarria L, Benistan K, Toussaint A, et al. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016;89(1):44-54.

Elfabrio USPI, Chiesi Farmaceutici S.p.A., May 2023

Elfabrio SmPC, Chiesi Farmaceutici S.p.A., May 2023

Eng CM, Germain DP, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med. 2006;8(9):539–548.

Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis. 2007;30:184-92.

European Medicines Agency (EMA). (2023) Guideline on computerised systems and electronic data in clinical trials. Amsterdam. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

Food and Drug Administration (FDA). (2019) Guidance for industry: Establishing Pregnancy Exposure Registries. Rockville, MD. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdf.

Holmes A, Laney D. A Retrospective Survey Studying the Impact of Fabry Disease on Pregnancy. JIMD Rep. 2015;21:57-63.

Kramer J, Weidemann F. Biomarkers for Diagnosing and Staging of Fabry Disease. Curr Med Chem. 2018;25(13):1530-1537.

Lenders M, Brand E. Fabry Disease: The Current Treatment Landscape. Drugs. 2021 Apr;81(6):635-645.

MacDermot KD, Holmes A, et al. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38(11):769–775.

Mehta A, Ricci R, Dehout F. et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Euro J Clin Investigation. 2004;34(3):236-42.

Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999 Jan 20;281(3):249-54.

Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, Hopkin RJ, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018 Apr;123(4):416-427.

Ouyang Y, Chen B, Pan X, et al. Clinical significance of plasma globotriaosylsphingosine levels in Chinese patients with Fabry disease. Experi and Thera Medi. 2017 December;(15):3733-42.

Politei JM, Thurberg BL. Histologic abnormalities of placental tissues in Fabry disease: a case report and review of the literature. Hum Pathol. 2012;43:610-614.

Rocchetti MT, Spadaccino F, Catalano V, Zaza G, Stallone G, Fiocco D, Netti GS, Ranieri E. Metabolic Fingerprinting of Fabry Disease: Diagnostic and Prognostic Aspects. Metabolites. 2022 Jul 28;12(8):703.

Rombach SM, Aerts JMFG, Poorhuis BJHM, et al. Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome. PLOS One. 2012;7(10):e47805.

Schiffmann R, Goker Alpan O, Holida M, et al. Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year Phase 1/2 clinical trial. J Inherit Metab Dis. 2019;42:534–44.

Schiffmann R. Fabry disease. Pharmacol Ther. 2009;122(1):65-77.

Smid BE, Hoogendijk SL, Wijburg FA, et al. A revised home treatment algorithm for Fabry disease: influence of antibody formation. Molecular Genetics and Metabolism. 2013;108:132-7.

Tuttolomondo A, Simonetta I, Riolo R, Todaro F, Di Chiara T, Miceli S, Pinto A. Pathogenesis and Molecular Mechanisms of Anderson-Fabry Disease and Possible New Molecular Addressed Therapeutic Strategies. Int J Mol Sci. 2021 Sep 18;22(18):10088.

Wang RY, Lelis A, et al. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007;9(1):34–45.

Wang J, Lozier J, Johnson G, et al. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention, and treatment. Nat Biotechnol. 2008;26(8):901-8.

Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, Sims K, Waldek S, Pastores GM, Lee P, Eng CM, Marodi L, Stanford KE, Breunig F, Wanner C, Warnock DG, Lemay RM, Germain DP. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab. 2008;93(2):112–128.

APPENDIX 1 - ERT USE IN PREGNANT PATIENTS WITH FABRY DISEASE

Table 2 ERT Use in Pregnant Patients with Fabry Disease

Publication reference	Study type	Number of patients	Exposure to Fabry treatment	Pregnancy outcomes	Neonatal outcomes	Infant outcomes
Laney, 2021	Registry	29	Agalsidase beta	Pregnancy outcomes (33 pregnancies): • Live births in 66.7% • Spontaneous abortion in 3.0% • Unavailable in 30.3% Pregnancy complications in 34.4% Labour/delivery complications in 9.4%	Neonatal complications included ventricular septal defect (n=1); prematurity and respiratory distress (n=1); gallstones (n=1); feeding difficulties and temperature instability (n=1).	No agalsidase beta-associated risks of major birth defects, miscarriages, adverse maternal or offspring outcomes were identified.
Wendt, 2005	Case Report	1	Agalsidase alfa 0.2 mg/kg every 2 weeks throughout pregnancy	All evaluations according to the standardised follow-up of pregnancy in Germany were performed and revealed no abnormalities	• Molecular and biochemical analysis of α-galactosidase in amniotic cells showed a normal male karyotype and normal enzyme activity. • The foetus was therefore not expected to be affected by Fabry disease.	
Ramaswami, 2009	Case Report	1	Pregnancy #2: agalsidase alfa Pregnancy # 3: agalsidase beta	No complications during pregnancy #2 or #3	• Pregnancy #2: delivered a healthy infant • Pregnancy #3: delivered healthy twins	
Bouwman, 2010	Case Report	1	Agalsidase beta 1.0 mg/kg/14 days throughout pregnancy	Uneventful pregnancy	Gave birth to a girl in whom the same mutation was detected.	
Germain, 2010	Case Report	1	Agalsidase beta (Fabrazyme) at 1 mg/kg/14 days throughout pregnancy	• Ultrasound examination at 22 weeks of gestation showed no signs of foetal malformation. • The patient delivered at 38 weeks gestational age via normal vaginal delivery.	• A healthy boy was delivered without congenital abnormalities. • Birth weight was 3.120 kg, length 48 cm, head circumference 35 cm, and the Apgar score at 1 min was 10. • The boy had normal a-galactosidase A activity and the familial	

Publication reference	Study type	Number of patients	Exposure to Fabry treatment	Pregnancy outcomes	Neonatal outcomes	Infant outcomes
					p.Cys52Arg (c.154T > C) mutation was absent.	
Parent, 2010	Case Report	1	Agalsidase beta (Fabrazyme) at 1 mg/kg intravenously every 2 weeks, but discontinued by the patient at 4 weeks' gestation	• Foetal growth was sonographically assessed every 4 weeks beginning at 20 weeks' gestation and remained normal. • The patient entered spontaneous labour at 38 4/7 weeks delivering vaginally.	A healthy 2885 g female infant with 1- and 5-min Apgar scores of 2 and 9, respectively was delivered.	
Politei, 2010	Case Report	1	Agalsidase beta 1 mg/kg every 15 days throughout pregnancy	• Haematological and urine tests did not show any significant changes with respect to prior normal values. • The patient had no ventricular hypertrophy on echocardiogram. • The patient presented with slight anaemia, without any clinical repercussion.	• At week 38, the patient gave birth to a healthy boy via a normal delivery. • Birth length and weight were 46 cm and 3300 g, respectively. • Head circumference was 35 cm and Apgar scores were 9/10/10.	The child demonstrated normal psychomotor development and no malformations and the genetic test for the boy showed the same mutation.
Senocak Tasci, 2015	Case Report	1	Agalsidase beta 1 mg/kg every 2 weeks starting at 8-weeks of pregnancy	• No complications reported. • There were no pathologic findings on electromyography. • At week 40, the patient gave birth to a healthy girl.	• Body length of 45 cm and weight of 3100 g. • The child had no malformation.	
Senocak Tasci, 2015	Case Report	1	Agalsidase beta 1 mg/kg every 2 weeks throughout pregnancy	• No complications reported. • At week 40, she gave birth to a healthy girl	Body length of 51 cm and weight of 3400 g.	
Pisani, 2016	Case Report	1	Agalsidase alfa 0.2 mg/kg every 2 weeks throughout pregnancy	• Infusions were well tolerated and no abnormalities were noted. • Patient delivered via vaginal delivery at a gestational age of 39 weeks.	• The patient gave birth to a healthy boy. • Birth weight 3250 g, length 48 cm, head circumference 33 cm and Apgar score 9/10/10.	

Publication reference	Study type	Number of patients	Exposure to Fabry treatment	Pregnancy outcomes	Neonatal outcomes	Infant outcomes
Iwafuchi, 2017	Case Report	1	• Agalsidase alfa (Replagal) 0.2 mg/kg infused every other week at 8 weeks of gestation. • The dose and frequency of the intravenous enzyme substitution remained unchanged during the pregnancy.	• ERT during pregnancy seemed to be well-tolerated, with no negative effects, including infusion-related reactions, on the mother or child. • At 40 weeks of gestation and an uneventful pregnancy, the patient delivered a healthy girl.	• The infant's length and weight at birth were 49 cm and 2,734 g, respectively. • APGAR scores were 8/9. A mutation analysis of the baby's *GLA* gene was performed, and a diagnosis of Fabry disease was made. • ERT continued for approximately 6 years after her delivery.	
Fernandez, 2019	Case Series	6	• All six women had started ERT prior to their pregnancies and received intravenous infusions of agalsidase alfa at a dose of 0.2 mg/kg every 14 days. • In patients 1, 2, and 3, ERT was discontinued during the first trimester. Given the recurrence of severe	Pregnancy outcomes (7 pregnancies) • No drug-related adverse effects were reported. • End of pregnancy occurred between Weeks 36 and 39 of gestational age by means of five vaginal deliveries and two caesarean sections (C-section). • Patient number 3 had developed eclampsia at Week 36 during her first pregnancy. The patient had proteinuria, a hypertensive crisis, and seizures, which led to an emergency C-section, without further complications.	The median new-borns' birth weight was 2,890 g (range: 2,370-3,800 g), and the median birth length was 50 cm (range: 46-51 cm).	• No infant had their weight or size below the tenth percentile for their gestational age. • The first child of patient number 3 (eclampsia and emergency C-section) had a first-minute Apgar score of less than 8 but recovered spontaneously without any resuscitation manoeuvres. This was the only non-breastfed child. • Three babies were exclusively breastfed for 6 months and continued breastfeeding during the first year. • Babies 1, 5, and 6 were partially breastfed for 5, 12, and 10 months, respectively.

Publication reference	Study type	Number of patients	Exposure to Fabry treatment	Pregnancy outcomes	Neonatal outcomes	Infant outcomes
			untreatable pain crises ERT was resumed.			• One female child experienced five episodes of recurrent uncomplicated urinary tract infections in her first 2 years of age. • Another child had controlled asthma. • Fabry disease was diagnosed only in newborn 3a and ruled out in the remaining six babies by enzyme activity dosage in males and molecular methods in females. • At the time of publication, there were no health issues potentially associated with the use of ERT during pregnancy and breastfeeding have been reported in these children (ages 1-5 years)
Haninger-Vacariu, 2019	Case Report	1	Migalastat HCl 150 mg QOD through 18 + 0 weeks gestation	• 29 weeks' gestation, MRI indicated normal foetal development. • The pregnancy was uneventful. • After delivery, ERT therapy (agalsidase alfa, home infusion) was restarted.	• A healthy female infant (45 cm, 2.29 kg, *GLA* WT) was delivered via caesarean section at 37+ weeks of gestation. • Birth weight (2.29 kg) that met criteria for being low for gestational age.	There was no significant negative effect on the child.
Madsen, 2019	Case Report	1	Agalsidase beta 1 mg/kg every other week throughout pregnancy	• In the third trimester, blood pressure and albuminuria increased while renal function decreased, consistent with moderate-to-severe pre-eclampsia. • The condition was successfully managed by methyldopa.	• A healthy boy was delivered without Fabry disease. • Weight, length and head circumference at birth were 2,675 g, 47 cm and 34 cm, respectively. • Apgar score was 10/1, 10/5 and 10/10.	

Publication reference	Study type	Number of patients	Exposure to Fabry treatment	Pregnancy outcomes	Neonatal outcomes	Infant outcomes
				• Eclampsia did not develop. • Mild haemolysis, slightly elevated liver enzymes and platelets low in the normal range were observed. • Planned Caesarean section without complications was performed at gestational age week 38 + 6	• Placental examination showed no sign of Gb3 accumulation.	
Internal data	Clinical study	3	Pegunigalsidase alfa	• 1 live, healthy birth; • 1 pregnancy termination • 1 spontaneous abortion in a patient with other comorbidities and taking other medications contraindicated during pregnancy due to their potential for complications (such as increased risk of spontaneous abortion and foetal injury/death)		

1. Bouwman MG, Hollak CE, van den Bergh Weerman MA, Wijburg FA, Linthorst GE. Analysis of placental tissue in Fabry disease with and without enzyme replacement therapy. Placenta. 2010 Apr;31(4):344-6.
2. Fernández P, Fernández SO, Gonzalez JGM, Fernández T, Fernández CC, Fernández SP. Enzyme Replacement Therapy in Pregnant Women with Fabry Disease: A Case Series. JIMD Rep. 2019;45:77-81.
3. Germain DP, Bruneval P, Tran TC, Balouet P, Richalet B, Benistan K. Uneventful pregnancy outcome after enzyme replacement therapy with agalsidase beta in a heterozygous female with Fabry disease: A case report. Eur J Med Genet. 2010 Mar-Apr;53(2):111-2.
4. Haninger-Vacariu N, El-Hadi S, Pauler U, Foretnik M, Kain R, Prohászka Z, Schmidt A, Skuban N, Barth JA, Sunder-Plassmann G. Pregnancy Outcome after Exposure to Migalastat for Fabry Disease: A Clinical Report. Case Rep Obstet Gynecol. 2019 Dec 21;2019:1030259.
5. Iwafuchi Y, Maruyama H, Morioka T, Noda S, Nagata H, Oyama Y, Narita I. Enzyme replacement therapy in a patient of heterozygous Fabry disease: clinical and pathological evaluations by repeat kidney biopsy and a successful pregnancy. CEN Case Rep. 2017 Nov;6(2):210-214.
6. Laney A, Ponce E, Yang M, Gudivada B, Carloni L, Lee J, Rasmussen U. Pregnancy outcomes in agalsidase beta treated and untreated females with Fabry disease and their offspring: A Fabry pregnancy sub-registry and pharmacovigilance database 15-year retrospective study. World Symposium. 2021.
7. Madsen CV, Christensen EI, Nielsen R, Mogensen H, Rasmussen ÅK, Feldt-Rasmussen U. Enzyme Replacement Therapy During Pregnancy in Fabry Patients: Review of Published Cases of Live Births and a New Case of a Severely Affected Female with Fabry Disease and Pre-eclampsia Complicating Pregnancy. JIMD Rep. 2019;44:93-101.
8. Parent E, Wax JR, Smith W, Blaszyk H, Pinette MG, Cartin A, Blackstone J. Fabry disease complicating pregnancy. J Matern Fetal Neonatal Med. 2010 Oct;23(10):1253-6.
9. Pisani A, Bifulco G, Di Spiezio Sardo A, Riccio E. Treatment with Agalsidase Alfa during Pregnancy in a Heterozygous Female with Fabry Disease. J Genet Disor Genet Rep 2016;5(4).
10. Politei JM. Treatment with agalsidase beta during pregnancy in Fabry disease. J Obstet Gynaecol Res. 2010 Apr;36(2):428-9.
11. Ramaswami U. Treatment of children and pregnant women with Fabry disease. Clinical Therapeutics. 2009;31(1):S19-S21
12. Senocak Tasci E, Bicik Z. Safe and Successful Treatment With Agalsidase Beta During Pregnancy in Fabry Disease. Iran J Kidney Dis. 2015 Sep;9(5):406-8.
13. Wendt S, Whybra C, Kampmann C, Teichmann E, Beck M. Successful pregnancy outcome in a patient with Fabry disease receiving enzyme replacement therapy with agalsidase alfa. J Inherit Metab Dis. 2005;28(5):787-8.