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PRX-102 in children and adolescents with Fabry disease

Submission date	Recruitment status	[X] Prospectively registered
09/05/2024	Recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
29/07/2024	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
27/01/2025	Nutritional, Metabolic, Endocrine	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Fabry disease is a genetic disorder in which the body does not properly produce an enzyme required to break down a type of fat called Gb3 (for short). If this enzyme is missing or not working properly, Gb3 builds up in cells, which can lead to serious health problems, such as heart disease, kidney failure and strokes. The drug being tested is called pegunigalsidase alfa or PRX-102 which is approved for sale and has shown to be effective in treating adult patients affected by Fabry disease. It is a type of enzyme replacement therapy, meaning that like the natural enzyme, it acts to break down Gb3. It is given by intravenous infusion (through a needle placed in a vein) every 2 weeks. PRX-102 is an investigational drug in children and adolescents, meaning that it is not approved for sale in these age groups and is being studied to see how well it works and how safe it is.

Who can participate?
Children and adolescents aged from 2 to less than 18 years old with Fabry disease

What does the study involve?
This study is being conducted to learn more about the drug that is designed to prevent or reduce the development of health problems caused by this disease. Since the symptoms of Fabry disease appear at a young age and get worse over time, a treatment that would help to slow or stop the irreversible damage that the disease causes to organs would improve patients' health and quality of life. At this time, not many treatments have been approved for children, so there is an important need to develop new therapies. The goals of this study are to see if this new drug is safe for children and adolescents and to see how well it works. The study is divided into three parts, or "stages": a dose-finding stage (Stage I), to try and determine the best dose for each age group which will last up to 6 months, a confirmatory stage (Stage II), which will last for up to 12 months; and an optional extension stage. The study will take place in six countries globally including at one UK site and approximately 20-22 participants will be enrolled in the study globally.

What are the possible benefits and risks of participating?
As with all studies, drug treatment and other therapies may involve risks that are known or unknown. Based on previous studies and the experience of other people who have received PRX-

102 some side effects may occur.
The most serious possible side effect is an allergic reaction to PRX-102, this has been seen in very few patients receiving PRX-102.
The most commonly reported side effects are:
- Dizziness
- Vertigo
- Asthenia
- Nausea
- Abdominal pain
- Agitation
- Diarrohea
- Vomiting
- Rash
- Erythema
- Pruritus
- Arthralgia
- Musculoskeletal pain
- Chills
- Chest pain
- Generalised pain
- Infusion-related reaction
- Supraventricular extrasystoles (abnormal heartbeat)

Please see protocol/ICF for a full list of side effects.

There may be pain, bleeding, bruising or swelling at the site where the blood samples are taken. The participant may also feel dizzy or faint.
Participants may have to visit the hospital more frequently than normal when taking part in this study.
ECG - During an ECG participants will need to lie still for a few minutes & small electrodes will be attached to their chest with adhesive pads. It may cause slight discomfort when they are being put on / taken off. Male participants may need to have their chest shaved to perform the ECG. Some participants may be sensitive to the adhesive pads resulting in itchy red areas where the patches were placed. This reaction should settle within a few hours.

Where is the study run from?
Chiesi Farmaceutici S.p.A (Italy)

When is the study starting and how long is it expected to run for?
May 2024 to December 2029

Who is funding the study?
Chiesi Farmaceutici S.p.A (Italy)

Who is the main contact?
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Public, Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-503128-29-00/110161

Integrated Research Application System (IRAS)
1010087

ClinicalTrials.gov (NCT)
NCT06328608

Protocol serial number
CLI-06657AA1-01, IRAS 1010087, CPMS 62298

Study information

Scientific Title
Multi-centre, open-label trial to assess the saFety, pharmacodynamics, efficacy and pharmacokinetics of pegunigaLsidase alfa in patients from 2 years to less than 18 years of age with confirmed FabrY disease (FLY)

Acronym
FLY

Study objectives
To assess the safety, pharmacodynamics, efficacy and pharmacokinetics of PRX-102 in three different age cohorts in paediatric patients with confirmed Fabry disease.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 02/07/2024, North of Scotland Research Ethics Committee (Summerfield House, 2 Eday Road, Aberdeen, AB15 6RE, United Kingdom; +44 1224558458; gram.nosres@nhs.scot), ref: 24/NS/0061

Study design
Multi-centre open-label trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Fabry's disease

Interventions
Arms:
Experimental: Single Arm - Pegunigalsidase alfa (PRX-102)
For Cohort C, PXR-102 administered every two weeks at 1.0 mg/kg is believed to be the minimum effective dose.
For Cohorts A and B, the starting dose will be 1.0 mg/kg every two weeks but it may be adjusted on the outcomes of Stage I, with the support of the Data Safety Monitoring Board.

Assigned Interventions:
Drug: PRX-102 1 mg/kg every two weeks
Drug: PRX-102 1 mg/kg every two weeks

Other Names:
• pegunigalsidase alfa
• Recombinant human alpha galactosidase-A

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Pegunigalsidase alfa

Primary outcome(s)

1. Safety Variables will be measured at each study visits, and will be measured using:
1.1. Treatment-emergent adverse events (TEAEs)
1.2. Infusion-related reactions (IRRs)
1.3. Injection site reactions (ISRs)
1.4. Clinical laboratory safety tests
1.5. Physical examination
1.6. Vital signs
1.7. Electrocardiogram (ECG)
1.8. Assessment for the development of anti-drug antibodies (ADA) against PRX-102
1.9. Use of pre-medications to manage infusion-related reactions
1.10. Growth and development (height, weight, and sexual development by Tanner staging)

2. Efficacy Variables will be measured:
2.1.1. For the first patients in Cohorts A and B: at Baseline, Weeks 4, 12, 26 in Stage I, and Weeks 4, 12, 26, 38, 52 in Stage II and quarterly in Stage III
2.1.2. For the first patients in Cohort C: at Baseline, Week 4 in Stage I, Weeks 26, 38 and 52 in Stage II and quarterly in Stage III
2.1.3. For patients entering directly in Stage II: at Baseline, Weeks 26 and 52 in Stage II and quarterly in Stage III
2.2. Efficacy Variables will be measured using:
2.3. Renal function:
2.3.1. eGFR, calculated using the Creatinine-Cystatin C–based
2.3.2. Chronic Kidney Disease in Children (CKiD) (2012).
2.3.3. Albuminuria, as determined by the urine albumin-to-creatinine ratio (uACR) test, and proteinuria, as determined by the urine protein-tocreatinine ratio (UPCR) test.
2.4. Cardiac function:
2.4.1. Echocardiogram
2.4.2. Holter ECG
2.4.3. Cardiac biomarkers:
2.4.3.1. High-sensitivity cardiac troponin T (hs-cTnT)
2.4.3.2. N-terminal pro B-type natriuretic peptide (NTproBNP)
2.5. Fabry disease biomarkers:
2.5.1. Plasma globotriaosylceramide (Gb3) concentration
2.5.2. Plasma globotriaosylsphingosine (lyso-Gb3) concentration
2.5.3. Urine lyso-Gb3 concentration
2.6. Other measures of Fabry disease:
2.6.1. Use of pain medications
2.6.2. Occurrence of Fabry clinical events (FCEs)
2.6.3. Mainz Severity Score Index (MSSI)
2.6.4. Gastrointestinal Symptoms (PedsQL-GI) questionnaire: parent version and age-appropriate subject version
2.6.5. Fabry Specific Pediatric Health and Pain Questionnaire (FPHPQ): age appropriate subject version
2.6.6. PedsQL Pediatric Pain Questionnaire (PedsQL-PPQ): parent version and age- appropriate subject version
2.6.7. EQ-5D-Y questionnaire for assessment of quality of life: parent version and age-appropriate subject version
2.6.8. Measures to be used if a subject reaches the age of 18 years:
2.6.8.1. Gastrointestinal Symptom Rating Scale (GSRS) in place of the PedsQL-GI
2.6.8.2. Brief Pain Inventory - Short Form (BPI-SF) in place of the PedsQL-PPQ
2.6.9. Measures to be used if a subject reaches the age of 18 years:
2.6.9.1. Quality-of-life (EQ-5D-5L) questionnaire in place of the EQ-5D-Y

2.6.9.2. In addition, the FPHPQ will be dropped. The other measures (use of pain medications, occurrence of FCEs, and completion of the MSSI) will remain the same.

3. Pharmacokinetic Assessments will be measured by blood samples at the following time points:
3.1.1. For the first patients in Cohorts A and B: at Baseline, Weeks 2, 4, 12, 26 in Stage I, and Baseline, Weeks 12, 26, 52 in Stage II and every other weeks in Stage III
3.1.2. For the first patients in Cohort C: at Baseline, Weeks 2, 4, 12 in Stage I, Weeks 26 and 52 in Stage II and every other weeks in Stage III
3.1.3. For patients entering directly in Stage II: at Baseline, Weeks 12, 26, 52 in Stage II and every other weeks in Stage III

4. Pharmacodynamic Assessments: Fabry disease is characterised by the progressive accumulation of Globotriaosylceramide (Gb3) and its metabolite Globotriaosylsphingosine (lysoGb3), so concentrations of Gb3 and lyso-Gb3 are biomarkers of the extent of the disease.
4.1. For purposes of determining the dosages of PRX-102 to be used in Stage II for Cohorts A and B, blood samples for measuring the concentration of Gb3 and lyso-Gb3 will be collected in Stage I every 2 weeks from Visits #1 to #9 (baseline to Week 16) and urine samples for measuring lyso-Gb3 will be collected as outlined from Visit #1 to #8 (baseline to Week 12).
4.2. For purpose of assessing efficacy, additional blood samples for the measurement of Gb3 and lyso-Gb3 and urine samples for the measurement of lyso-Gb3 will be collected at specified time points during the study in all cohort.
4.3. PD will be measured at the following time points:
4.3.1. For the first patients in Cohorts A and B: at Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 26 in Stage I, and Weeks 12, 26, 38, 52 in Stage II and quarterly in Stage III
4.3.2. For the first patients in Cohort C: at Baseline, Weeks 2, 4, 12 in Stage I, Weeks 26, 38 and 52 in Stage II and quarterly in Stage III
4.3.3. For patients entering directly in Stage II: at Baseline, Weeks 12, 26, 52 and (54) in Stage II and quarterly in Stage III

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
31/12/2029

Eligibility

Key inclusion criteria
1. Male or female aged 2 to 7 years (Cohort A), 8 to 12 years (Cohort B), or 13 to <18 years (Cohort C)
2. A documented diagnosis of Fabry disease, as determined by the following:
2.1. Males: Plasma and/or leukocyte alpha-galactosidase-A (α-GAL-A) activity (by activity assay) that is ≤ 5% of mean normal laboratory levels, or, if the enzymatic activity is above the 5% limit but still under the normal level, a confirmed disease-causing mutation of the α-GAL-A (GLA)gene.
2.2. Females: Historical genetic test results consistent with Fabry mutations, or, in the case of novel mutations, a first-degree male relative with Fabry disease.
2.3. All subjects: At least one of the following characteristic features of Fabry disease: neuropathic pain, cornea verticillata, and/or clustered angiokeratoma.
3. History of Fabry pain:
3.1. Episodic crises (Fabry crises) characterised by agonizing burning pain originating in the extremities and radiating inwards to the limbs and other parts of the body, OR

3.2. Chronic pain characterised by burning and tingling paraesthesia
4. Clinical condition that, in the opinion of the Investigator, requires treatment with enzyme replacement therapy (ERT).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 years

Upper age limit
17 years

Sex
All

Key exclusion criteria
1. Estimated glomerular filtration rate (eGFR) at screening < 80 mL/min/1.73 m2, calculated using the Creatinine Cystatin C-based Chronic Kidney Disease in Children (CKiD) equation (2012).
2. History of type I hypersensitivity reactions (anaphylactic or anaphylactoid life-threatening reaction) to other ERT treatment for Fabry disease or to any component of the study drug.
3. Initiation of treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), or a change of dose in ongoing treatment, in the 4 weeks prior to screening.
4. Subject with urine protein to creatinine ratio (UPCR) > 0.5 g/g (0.5 mg/mg or 500 mg/g) if not treated with an ACE inhibitor or ARB.
5. Currently taking another investigational drug for any condition.
6. Carry only known non-pathogenic Fabry mutations.
7. History of acute kidney injury in the 12 months prior to screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischaemia, toxic injury); or extrarenal pathology (e.g., prerenal azotaemia, acute postrenal obstructive nephropathy).
8. History of renal dialysis or kidney transplantation.
9. History of or current malignancy requiring treatment.
10. Severe cardiomyopathy or significant unstable cardiac disease within 6 months prior to screening.
11. A positive test for Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) within 3 months prior to screening, using a validated molecular assay or antigen assay.
12. Presence of any medical, emotional, behavioural, or psychological condition that in the judgement of the Investigator could interfere with the subject’s compliance with the requirements of the study.
13. Additional Exclusion Criteria for Subjects Enrolled in Stage I:For subjects enrolled in Stage I (targeting up to 9 subjects total) these specific exclusion criteria, in addition to those above, apply: a) Female b) Non-classic form of Fabry disease c) Receipt of treatment for Fabry disease within 6 months prior to screening d) Positive for anti-PRX-102 antibodies at screening

14. Additional Exclusion Criteria for Subjects in Stage II: a) Unwilling to discontinue current ERT treatment for Fabry disease at least 14 days, or chaperone therapy at least 3 days, before baseline.
15. Additional Exclusion Criteria for Subjects in Stage II: Females: Pregnant or lactating, or of childbearing potential with a fertile male partner and/or unwilling to undergo pregnancy testing as outlined and to use a highly reliable method of contraception from the informed consent signature until 30 days after the last infusion. Note: Before the start of treatment, the Investigator will decide whether or not pregnancy testing and contraception counselling are necessary. Since over the course of the study, pre-pubertal girls may reach menarche and adolescents of either gender may become sexually active, the Investigator must periodically check on the status of these issues and implement pregnancy testing and/or contraception counselling if required. A female subject is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
16. Note: Inclusion and Exclusion criteria will be assessed at the screening visit and verified at the baseline visit.

Date of first enrolment
30/04/2025

Date of final enrolment
29/09/2027

Locations

Countries of recruitment
United Kingdom

England

Austria

France

Norway

Spain

United States of America

Study participating centre
Great Ormond Street Hospital
Great Ormond Street
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Sponsor information

Organisation
Chiesi (Italy)

ROR
https://ror.org/0511bn634

Funder(s)

Funder type
Industry

Funder Name
Chiesi Farmaceutici S.p.A

Alternative Name(s)
Chiesi Pharmaceuticals, CHIESI Farmaceutici S.p.A., CHIESI, CHIESI GROUP

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Italy

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to the Clinical trial transparency policy - Patient-level data will not be shared from rare disease trials since the risk of re-identification is too high and the Sponsor values the privacy rights of its patients.

IPD sharing plan summary
Not expected to be made available