A Randomized, Double blind, Active Control Study of the Safety and Efficacy of PRX-102 compared to Agalsidase Beta on Renal Function in Patients with Fabry Disease Previously Treated With Agalsidase Beta

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To evaluate the safety and efficacy of PRX-102 compared to agalsidase beta in Fabry disease patients with impaired renal function.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON45301

Source
ToetsingOnline

Brief title
BALANCE study

Condition

- Metabolic and nutritional disorders congenital

Synonym
Fabry disease, lysosomal storage disease

Research involving
Human

Sponsors and support

Primary sponsor: Protalix Ltd
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Efficacy, Pegunigalsidase alfa, PRX-102, Safety

Outcome measures

Primary outcome

The primary efficacy parameter is the comparison of the mean annualized change (slope) in estimated glomerular filtration rate (eGFRCKD-EPI) between treatment groups.

Secondary outcome

* Left Ventricular Mass Index (g/ m2) by MRI

* Plasma Lyso-Gb3

* Plasma Gb3

* Urine Lyso-Gb3

* Protein/Creatinine ratio spot urine test

* Frequency of pain medication use

* Exercise tolerance (Stress Test)

* Short Form Brief Pain Inventory (BPI)

* Mainz Severity Score Index (MSSI)

* Quality of life EQ-5D-5L

Study description

Background summary

Fabry disease is a progressive lysosomal storage disease that is seriously debilitating and ultimately life-threatening. It is caused by X-linked deficiency of the enzyme alpha galactosidase-A (alpha-GAL-A), and affects both males and females. The disease is characterized by subnormal or absent activity of alpha-GAL-A. Clinical onset of the disease typically occurs during childhood or adolescence (Schaefer et al. 2009) and will progress to end- stage renal disease, cardiac complications and cerebrovascular problems in the fourth or fifth decade of life (Wilcox et al. 2008). Although Fabry disease is a X-linked disorder, females are also affected and develop manifestations of the disease due to lack of cross-correction between cells with normal alpha-GAL-A activity (mutated X chromosome is inactivated) and cells with enzyme deficiency (non-mutated X chromosome is inactivated). The clinical abnormalities in females are more variable, and of later onset compared to males (Schiffmann 2009).
Fabry disease is regarded as a rare disease and it is estimated that 1 in 40,000 males has the disease, whereas the estimated prevalence in the general population is 1 in 117,000 (Meikle et al. 1999).
Protalix has developed PRX-102, a chemically modified recombinant human alpha-GAL-A expressed in plant cell culture. As a result of this modification, PRX-102 exhibits more stabilized homo dimer with active enzyme over longer period, extended circulation residence time and enhanced bioavailability of the enzyme relative to the commercial drug. Therefore, PRX-102 provides continuous presence of enzyme over the 2 week dosing interval.

Study objective

To evaluate the safety and efficacy of PRX-102 compared to agalsidase beta in Fabry disease patients with impaired renal function.

Study design

This is a randomized, double blind, active control study of PRX-102 in Fabry disease patients with impaired renal function. Patients treated for approximately 1 year with agalsidase beta and on a stable dose for at least 6 months will be screened and then randomized to continue treatment with 1 mg/kg agalsidase beta or to treatment with 1 mg/kg of PRX-102. The identity of the enzyme will be blinded to the patient and the investigator. Patients will receive intravenous infusions every two weeks.

Patients will be randomized in a 2:1 ratio of PRX-102 to agalsidase beta. Randomization will be stratified by urine protein to creatinine ratio (UPCR) of < or * 1 g/g by spot urine sample.

At the time of randomization, premedication, if used for the agalsidase beta infusions before study entry will be continued and gradually tapered at the investigator*s discretion during the first 3 months of the study. The first

infusions of blinded agalsidase beta or PRX-102 will be administered under controlled conditions at the investigation site. The patient can receive their infusions at their pre-defined infusion facility or as part of a home setup once the investigator and Sponsor Medical Director agree that it is safe to do so.
An interim analysis will be conducted at 12 months and the final analysis at 24 months of treatment.

Intervention

Pegunigalsidase alfa (PRX-102) 1 mg/kg or agalsidase beta 1 mg/kg, intravenously over 3 hours, every 2 weeks.
After the first 3 months of treatment infusion time may be reduced gradually to 1.5 hours pending patient tolerability, PI evaluation, and Medical Monitor/Director approval.

Study burden and risks

PRX-102 has been given to 16 people for a duration of more than a year, but the specific side effects are not yet well known. The safety profile of PRX-102 however does not seem very different from other enzymes used to treat Fabry disease.
It is possible that the symptoms will not improve during the study or may even worsen. Please see the Investigators Brochure and/or Informed Consent form for an overview of all possible side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Symptomatic adult Fabry disease patients, age 18-60 years
a. Plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than 30% mean normal levels
b. One or more of the described characteristic features of Fabry disease:
i. neuropathic pain,
ii. cornea verticillata,
iii. clustered angiokeratoma
2. Screening eGFR by CKD-EPI equation 40 to 90 mL/min/1.73 m2
3. Linear negative slope of eGFR of * 2 mL/min/1.73 m2 based on at least 3 serum creatinine values over approximately 1 year (range of 9 to 18 months, including the value obtained at the screening visit)
4. Treatment with a dose of 1 mg/kg agalsidase beta per infusion every 2 weeks for at least one year and at least 80% of 13 (10.4) mg/kg total dose over the last 6 months
5. Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically accepted method of contraception, not including the rhythm method.

Exclusion criteria

1. History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase beta
2. History of renal dialysis or transplantation
3. 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, ischemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotemia, and acute postrenal obstructive nephropathy)
4. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
5. Urine protein to creatinine ratio (UPCR) > 0.5 g/g and not treated with an ACE inhibitor or

ARB
6. Cardiovascular event (myocardial infarction, unstable angina) in the 6 month period before randomization
7. Congestive heart failure NYHA Class IV
8. Cerebrovascular event (stroke, transient ischemic attack) in the 6 month period before randomization
9. Known history of hypersensitivity to Gadolinium contrast agent
10. Female subjects who are pregnant, planning to become pregnant during the study, or are breastfeeding
11. Presence of any medical, emotional, behavioral or psychological condition that, in the judgment of the Investigator and/or Medical Director, would interfere with the patient*s compliance with the requirements of the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-10-2017
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fabrazyme
Generic name:	AGALSIDASE BETA
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	NA
Generic name:	Pegunigalsidase alfa

Ethics review

Approved WMO Date:	17-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000378-38-NL
ClinicalTrials.gov	NCT02795676
CCMO	NL59184.018.16