

HEALTH TECHNOLOGY BRIEFING NOVEMBER 2020

Pegunigalsidase alfa for Fabry disease – first-line

NIHRIO ID	12815	NICE ID	10035
Developer/Company	Chiesi Ltd	UKPS ID	648801

Licensing and market availability plans	Currently in phase III clinical trials.
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SUMMARY

Pegunigalsidase alfa is being developed as a first-line, long-term enzyme replacement therapy in adult and paediatric patients (>3 yr) diagnosed with Fabry disease (FD). FD is an inherited disease that is caused by the lack of an enzyme called alpha galactosidase A, which breaks down and removes Gb3, a complex molecule containing sugars and fats. Symptoms include pain that spreads through the body, gastrointestinal complications, headaches, impaired sweating and hearing impairment. FD is a long-term debilitating and life-threatening disease due to recurrent episodes of severe pain not responding to painkillers.

Pegunigalsidase alfa is produced by a method known as 'recombinant DNA technology': it is made by cells into which a gene (DNA) has been introduced, which makes them able to produce the enzyme. The replacement enzyme has also been modified to reduce the rate at which it is removed from the body, allowing it to act for longer. Pegunigalsidase alfa was designed to increase amount of medicine in the blood and reduce the ability of a substance to provoke an immune response, thereby enhancing efficacy compared with available products. If licensed, pegunigalsidase alfa would offer an additional first-line, long-term ERT options for adult and paediatric patients (>3 yr) diagnosed with FD.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

Long-term enzyme replacement therapy in adult and paediatric patients (>3 yr) diagnosed with Fabry disease – first line.^a

TECHNOLOGY

DESCRIPTION

Pegunigalsidase alfa (PRX-102), is a novel enzyme for the therapy of Fabry disease (FD), produced in the ProCellEx® plant cell-based protein expression system and expressed in a BY2 Tobacco cell culture. The enzyme is chemically modified with a homo-bifunctional polyethylene glycol (PEG, 2000 Da) cross-linker attached to the two protein sub-units of the alpha galactosidase A (α -Gal-A) enzyme, resulting in a PEGylated and covalently-bound homodimer.¹ It is expected to replace the human enzyme α -Gal-A, which people with Fabry disease are lacking, helping to break down globotriaosylceramide (Gb3) and stop it from building up in the patient's tissues.²

In the phase III clinical trials, patients were administered either 2 mg/kg of pegunigalsidase alfa IV infusion every 4 weeks for 52 weeks (BRIGHT, NCT03180840) or 1 mg/kg IV infusion every 2 weeks for 12 months (NCT03018730).^{3,4}

INNOVATION AND/OR ADVANTAGES

Although two enzyme replacement therapies (ERTs) are commercially available, they may not effectively restore function or reverse some of the Fabry pathology.¹ Pegunigalsidase alfa was designed to increase plasma half-life and reduce immunogenicity, thereby enhancing efficacy compared with available products.⁵

In *in vitro* testing, pegunigalsidase alfa showed greater stability than agalsidase alfa and agalsidase beta in human plasma at 37°C and under simulated lysosomal-like conditions. In Fabry mice, compared with agalsidase alfa, pegunigalsidase alfa demonstrated prolonged plasma half-life and an enhanced biodistribution, including increased enzymatic activity in the heart and kidney and reduced clearance by the liver.⁵ Topline results from a phase III clinical trial (NCT03018730) indicated that pegunigalsidase alfa was well tolerated, with all adverse events being transient in nature without sequelae.^{3,6}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pegunigalsidase alfa does not currently have Marketing Authorisation in the EU/UK for any indication.

Pegunigalsidase alfa has the following regulatory designations/awards:

- an orphan drug in the EU for the treatment of Fabry disease in December 2017²
- a Fast Track designation by the US FDA in January 2018⁷

^a Information provided by Chiesi Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

FD is a rare, inherited lysosomal storage disease caused by a non-functional or only partially functional enzyme, α -Gal-A. Decreased activity of α -Gal-A in lysosomes results in the accumulation of enzyme substrates (Gb3 and lyso-Gb3) which cause cellular damage in tissues throughout the body.⁸ FD can result from more than 900 mutations in the *GLA* gene.⁵ Fabry disease is classified as a sphingolipidosis which is a type of lysosomal storage disease.⁹

FD is X-linked, therefore men who have only one copy of the defective gene are more likely to develop the disease. Men can have either:¹⁰

- no α -Gal-A activity, in which case symptoms will usually develop during childhood and be quite severe (this is the standard presentation); or
- some α -Gal-A activity, in which case symptoms develop between the ages of 60 and 80 years (this is atypical and these men can remain asymptomatic for many years before being diagnosed with FD)

Because women have two X chromosomes, enzyme activity is extremely variable due to random X-chromosomal activation. Therefore, some women will have no disease activity, while others may have mild, moderate or severe symptoms.¹⁰

Symptoms include pain that spreads through the body (called a Fabry crisis), gastrointestinal complications, headaches, impaired sweating, vertigo and hearing impairment. The age of onset, severity and progression of FD is variable. Accumulation of Gb3 in lysosomes leads to irreversible organ damage, resulting in progressive kidney and heart disease and increased risk of stroke at a relatively young age. FD can have a profound impact on health-related quality of life and can reduce life expectancy.⁸

CLINICAL NEED AND BURDEN OF DISEASE

Globally, annual incidence of FD is reported to be 1 in 80,000 live births but this figure may underestimate disease prevalence. When late-onset variants of the disease are considered, a prevalence of approximately 1 in 3,000 has been suggested.¹¹ The incidence of males with FD is approximately 1 in 40,000.¹² In 2017, FD affected approximately 2.2 in 10,000 people in the EU which is equivalent to a total of around 113,000 people.² The company estimates that there are 855 people with this disease in England.^b

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 769 finished consultant episodes (FCE) for other sphingolipidosis (ICD-10 code: E75.2), resulting in 734 hospital admissions, 1,139 FCE bed days and 549 day cases.¹³

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for FD. ERT (agalsidase alfa and agalsidase beta) are administered to replace the nonfunctioning enzyme and help prevent the development of disease-related symptoms in younger patients, and slow disease progression in people with more advanced disease. For people with severe kidney disease, a kidney transplant may be considered.¹⁰

^b Information provided by Chiesi Ltd on UK PharmaScan

Supportive care to manage the symptoms and complications.⁸ FD and related conditions (labelled as lysosomal storage diseases) are usually managed in specialist centres in England.¹⁰

CURRENT TREATMENT OPTIONS

The current treatment options available for FD are as follows:

- Migalastat (Galafold) is recommended, within its marketing authorisation, as an option for treating FD in people over 16 years of age with an amenable mutation.⁸
- Agalsidase alfa (Replagal) is indicated for long-term ERT in patients with a confirmed diagnosis of FD.¹⁴
- Agalsidase beta (Fabrazyme) is indicated for long-term ERT in patients with a confirmed diagnosis of FD in adults, children and adolescents aged 8 years and older.¹⁵

PLACE OF TECHNOLOGY

If licensed, pegunigalsidase alfa would offer an additional first-line, long-term ERT options for adult and paediatric patients (>3 yr) diagnosed with FD.

CLINICAL TRIAL INFORMATION

Trial	BALANCE ; NCT02795676 ; PB-102-F20 ; 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 Phase III – active, not recruiting Location(s) : EU (incl UK), USA, Canada and other countries Primary completion date : Oct 2021
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N=78 (planned); adult patients with Fabry disease who have impaired renal function; aged 18 to 60 years
Intervention(s)	1 mg/kg of pegunigalsidase alfa IV infusion every 2 weeks
Comparator(s)	1 mg/kg of agalsidase beta every 2 weeks
Outcome(s)	Primary outcome: eGFR Slope [Time frame: every month for 2 years] See trial record for full list of other outcome
Results (efficacy)	-
Results (safety)	-

Trial	NCT03018730 ; PB-102-F30 ; An Open Label Study of the Safety and Efficacy of PRX 102 in Patients With Fabry Disease Currently Treated With REPLAGAL® (Agalsidase Alfa) Phase III – active, not recruiting Location(s) : EU (incl UK), USA, Canada and other countries Primary completion date : Jan 2020	NCT03566017 ; PB-102-F60 ; Open Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegunigalsidase Alfa (PRX-102) in Patients With Fabry Disease Phase III –enrolling by invitation Location(s) : EU (incl UK), USA, Canada and Australia Primary completion date : Sep 2022
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Trial design	Non-randomised, single group assignment, open-label	Non-randomised, single group assignment, open-label, extension
Population	N=22; adult patients with Fabry disease who were treated with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months; aged 18 to 60 years	N=110 (planned); adult Fabry patients who have successfully completed studies PB-102-F20 or PB-102-F30; aged 18 to 60 years
Intervention(s)	Pegunigalsidase alfa 1 mg/kg IV infusion every 2 weeks for 12 months	Pegunigalsidase alfa 1 mg/kg IV infusion every other week
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcome: Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 [Time frame: throughout the 12 months study] See trial record for full list of other outcome	Primary outcome: Evaluation of treatment-related adverse events as assessed by CTCAE v4.03 [Time Frame: through study completion, 4 years] See trial record for full list of other outcome
Results (efficacy)	<p>Topline results of the data generated in the study showed substantial improvement in renal function as measured by mean annualized estimated Glomerular Filtration Rate (eGFR slope) in both male and female patients who were switched from agalsidase alfa to pegunigalsidase alfa:⁶</p> <ul style="list-style-type: none"> • From -5.90 mL/min/1.73m²/year to -1.19 mL/min/1.73m²/year in all patients • From -6.36 mL/min/1.73m²/year to -1.73 mL/min/1.73m²/year in male patients • From -5.03 mL/min/1.73m²/year to -0.21 mL/min/1.73m²/year in female patients <p>While lyso-Gb3 levels remain slightly high, particularly within the male cohort, continuous reduction in lyso-Gb3 levels was observed of 19.55nM (32.35%) in males and 4.57nM (29.81%) in females.⁶</p>	-
Results (safety)	Pegunigalsidase alfa was found to be well tolerated, with all adverse events being transient in nature without sequelae. ⁶	-

Trial	BRIGHT; NCT03180840; PB-102-F50; Phase 3, Open-Label, Switch Over Study to Assess Safety, Efficacy	Bright 51; NCT03614234; PB-102-F51; Open Label Extension Study to Evaluate the Long-term Safety and
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	<p>& PK of Pegunigalsidase Alfa 2 mg/kg Administered Every 4 Weeks for 52 Weeks in Fabry Disease Patients Currently Treated With Enzyme Replacement Therapy: Fabrazyme® (Agalsidase Beta) or Replagal™ (Agalsidase Alfa)</p> <p>Phase III – active, not recruiting</p> <p>Location(s): EU (incl UK), USA, Canada, Taiwan and Turkey</p> <p>Primary completion date: Jul 2020</p>	<p>Efficacy of 2 mg/kg Pegunigalsidase Alfa (PRX-102) Administered by Intravenous Infusion Every 4 Weeks in Adult Patients With Fabry Disease</p> <p>Phase III –enrolling by invitation</p> <p>Location(s): EU (incl UK) and USA</p> <p>Primary completion date: Jan 2023</p>
Trial design	Non-randomised, single group assignment, open-label	Non-randomised, single group assignment, open-label, extension
Population	N=30; Fabry patients previously treated with ERT (agalsidase alfa or agalsidase beta) for at least 3 years; aged 18 to 60 years	N=40; adult Fabry patients who have successfully completed PB-102-F50; aged 18 years and older
Intervention(s)	Pegunigalsidase alfa 2 mg/kg IV infusion every 4 weeks for 52 weeks	Pegunigalsidase alfa 2 mg/kg IV infusion every 4 weeks
Comparator(s)	No comparator	No comparator
Outcome(s)	<p>Primary outcome: Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 [Time frame: throughout the 52-week study]</p> <p>See trial record for full list of other outcome</p>	<p>Primary outcome: Evaluation of treatment-related adverse events as assessed by CTCAE v4.03 [Time frame: throughout the study, 156 weeks]</p> <p>See trial record for full list of other outcome</p>
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The cost of pegunigalsidase alfa was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Migalastat for treating Fabry disease (HTT4). February 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Lysosomal storage disorders service (Children). E06/S(HSS)/c.
- NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children). November 2012.

OTHER GUIDANCE

- Germain DP et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. 2019.¹⁶
- Otiz A et al. Fabry disease revisited: Management and treatment recommendations for adult patients. 2018.¹⁷
- National Society of Genetic Counsellors. Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counsellors. 2013.¹⁸
- American College of Medical Genetics. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. 2006.¹⁹

ADDITIONAL INFORMATION

Protalix has partnered with Chiesi Farmaceutici S.p.A., both in the United States and outside the United States, for the development and commercialization of pegunigalsidase alfa.²⁰

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