Medicinrådet

Bilag til Medicinrådets anbefaling vedr. pegunigalsidase alfa til behandling af Fabrys sygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. pegunigalsidase alfa
2. Forhandlingsnotat fra Amgros vedr. pegunigalsidase alfa
3. Ansøgers endelige ansøgning vedr. pegunigalsidase alfa

Chiesi Pharma AB
Klara Norra kyrkogata 34, 5 tr.
SE-111 22 Stockholm
Tel: +46 8 753 3520
E-mail: infonordic@chiesi.com

Dear members of the Medicine Council,

Chiesi have reviewed the assessment report that the expert committee and secretariat has prepared for the Elfabrio application and would like to take this opportunity to highlight that Elfabrio is deemed cost saving in the cost-minimization model and the budget impact model versus agalsidase beta using the pharmacy purchasing price.

There are currently three Fabry treatments available on the Danish market, of which agalsidase alfa and agalsidase beta (both enzyme-replacement therapies) has been on the market since early 2000s and migalastat (chaperone therapy for patients with amenable mutations) since 2016. All these treatments therefore naturally predate the Medicine Council´s process for assessing new medicines and none of the products have been evaluated in any previous processes either. Despite this, Danish Fabry patients have had access to treatment when needed since the Danish regions over the past two decades have accepted the costs of treating this rare disease.

Chiesi were asked, in agreement with current application guidelines, to submit two analyses: one cost-minimization analysis vs. standard of care and one additional analysis vs. no treatment. Chiesi would like to point out that the comparison against no treatment is not aligned with Danish clinical practice dating back the past 20 years and is strictly hypothetical. In our application, we stated that the analysis against no treatments is very difficult to perform since there is no available comparator data. All patients that are eligible for treatment are treated. Untreated patients with the same baseline characteristics as the patients in the BALANCE-trial is extremely difficult to find and would not be relevant in a Danish clinical practice setting. Chiesi therefore ask the Council member to be careful to use this complementary analysis as a basis for their decision-making, since the analysis vs. no treatment in itself is irrelevant to Danish clinical practice.

In the assessment report, the medicine council secretariat and expert group found that Elfabrio and agalsidase beta have comparable efficacy and safety and concluded that there on group level are no clinically relevant differences between the treatments. The cost-minimization approach was deemed the main analysis by the secretariat in the assessment report. In the Chiesi base case, treatment with Elfabrio is found cost saving. This is also confirmed in the budget impact analysis where treatment with Elfabrio would reduce health expenditure compared to agalsidase beta. These analyses were performed with the current pharmacy purchasing price. Using the recently offered Amgros-price, the savings in the cost-minimization and budget impacts analyses are even greater, also when considering that the 5 mg [redacted] Given these outcomes, Elfabrio should be recommended for treatment for Fabry disease in Denmark.

Sincerely,

Patrick Svarvar
Head of Rare Diseases, Nordics
Chiesi Pharma AB

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

22.12.2023

CAF/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.01.2024
Leverandør	Cheisi
Lægemiddel	Elfabrio (pegunigalsidase alfa)
Ansøgt indikation	Elfabrio er indiceret til langvarig enzymsubstitutionsbehandling hos voksne patienter med en bekræftet diagnose på Fabrys sygdom (mangel på alfa-galactosidase).
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Elfabrio (pegunigalsidase alfa):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Elfabrio	2 mg/ml	5x10 ml	61.146,29	[redacted]	[redacted]
Elfabrio	2 mg/ml	10 ml	12.229,26	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har ved forhandling fået ovenstående pris fra leverandøren. Prisen er ikke betinget af Medicinrådets anbefaling af Elfabrio til den ansøgte indikation. Amgros har publiceret et udbud den 08.12.2023 med tilbudsfrist den 31.01.2024. Originalleverandøren byder ind i udbuddet med prisen fra tabel 1.

Aftalen starter den 01.04.2024 og løber til den 31.03.2025 med mulighed for prælevering og forlængelse på 2x6 måneder.

Konkurrencesituationen

Følgende lægemidler anvendes i dag til behandling af Fabrys sygdoms i dansk klinisk praksis: Replagal (agalsidase alfa), Fabrazyme (agalsidase beta) og Galafold (migalastat). De indgår alle tre i udbud, der løber til den 31.03.2025. Fælles for udbuddene er, at de har offentlige priser.

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler fra Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Elfabrio	2 mg/ml	10 ml	1 mg/kg hver 2. uge (IV)	[redacted]	[redacted]
Fabryzyme	35 mg	1 htgl.	1 mg/kg hver 2. uge (IV)	[redacted]	[redacted]
Replagal	1 mg/ml	3,5 ml	0,2 mg/kg (IV)	[redacted]	[redacted]
Galafold	123 mg	14 stk.	123 mg hver 2. dag. (PO)	[redacted]	[redacted]

*Gennemsnits vægt 79 kg jf. Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
Sverige	Under vurdering	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Elfabrio (pegunigalsidase alfa) for the treatment of adult patients with Fabry disease in Denmark

Contents

1. Basic introduction

Table 1: Contact information

Contact information	
Name	Malin Gregorsson Edh
Title	Value and Access Manager
Phone number	+46 706 596 568
E-mail	m.gregorsson-edh@chiesi.com

Table 2: Overview of the pharmaceutical

Contact information	
Proprietary name	Elfabrio
Generic name	Pegunigalsidase alfa
Marketing authorization holder in Denmark	Chiesi Pharma AB
ATC code	A16AB20
Pharmacotherapeutic group	Other alimentary tract and metabolism products, enzymes
Active substance(s)	Pegunigalsidase alfa
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Pegunigalsidase alfa is a pegylated recombinant form of human α-galactosidase-A. The amino acid sequence of the recombinant form is similar to the naturally occurring human enzyme. Pegunigalsidase alfa supplements or replaces α-galactosidase-A, the enzyme that catalyses the hydrolysis of the terminal α-galactosyl moieties of oligosaccharides and polysaccharides in the lysosome, reducing the amount of accumulation of globotriaosylceramide (Gb_3) and globotriaosylsphingosine (Lyso-Gb_3).
Dosage regimen	The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once every two weeks by intravenous infusion.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Pegunigalsidase alfa is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Infusion of pegunigalsidase alfa at home may be considered for patients who are tolerating their infusions well. The infusion can be self-administered by the patient in presence of a

	responsible adult or by the patient's caregiver or administered by a nurse. The decision to have a patient move to home infusion and/or self-administration should be made after evaluation and recommendation by the treating physician.
Combination therapy and/or co-medication	N/A
Packaging – types, sizes/number of units, and concentrations	Pegunigalsidase alfa is available in two different pack sizes, containing one and five vials per carton. One vial contains 20 mg of pegunigalsidase alfa in 10 ml (2 mg/ml). In addition, a 5 mg vial will become available [redacted].
Orphan drug designation	No.

2. Abbreviations

Table 3: list of abbreviations

Abbreviation	Definition
ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BLISS	Barisoni Lipid Inclusion Scoring System
BPI	Brief Pain Inventory
CEFD	Clinically evident Fabry disease
CI	Confidence interval
CKD	Chronic Kidney Disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
E2W	Every two weeks
E4W	Every four weeks
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOW	Every other week
EQ-5D	EuroQoL-5 Dimension Questionnaire™
ERT	Enzyme replacement therapy
ESRD	End-stage renal disease
FD	Fabry Disease
FDA	Food and Drug Administration
FOS	Fabry Outcome Survey
Gb_3	Globotriaocylceramide
GSA	Gastrointestinal symptoms assessment
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G

IRR	Infusion-related reaction
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KDIGO	Kidney disease: improving global outcomes
LLN	Lower limit of normal
LSD	Lysosomal storage disorder
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
Lyso-Gb_3	Globotriaosylsphingosine
MRI	Magnetic resonance imaging
MSSI	Mainz severity score index
NA	Not applicable
nAb	Neutralizing antibody
NCT	National clinical trial
NICE	National Institute for Health and Care Excellence
NNRM	Nonlinear nonparametric regression model
NR	Not reported
NYHA	New York heart association
PEG	Polyethylene glycol
PK	Pharmacokinetic
PPE	Per protocol efficacy
PT	Prothrombin time
PTT	Partial thromboplastin time
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TEAE	Treatment-emergent adverse events
TIA	Transient ischaemic attack
UL	Upper limit
UPCR	Urine protein/creatinine ratio
VAS	Visual analogue scale
VUS	Variant of unclear significance

3. Table and Figures

4. Summary

Fabry disease is a rare, progressive, X-linked lysosomal storage disorder where a mutation in the galactosidase alpha (*GLA*) gene results in a deficiency of the lysosomal enzyme α-galactosidase A . The deficiency leads to progressive accumulation of glycolipids (mainly globotriaosylceramide [Gb_3] and globotriaosylsphingosine [lyso-Gb_3]) in the lysosomes of a wide range of cells.

Disease manifestations

Patients with Fabry disease can experience a wide range of symptoms, including neuropathic pain, gastrointestinal symptoms, fatigue, chest pain and angiokeratoma. Serious complications, including cardiovascular, renal, and cerebrovascular events (such as myocardial fibrosis, kidney failure and strokes) are also common, affecting 34% of males and 15% of females with the condition. As a result of the high symptomatic burden, patients with Fabry disease experience a poorer function and QoL compared with the general population, which reduces further with increasing age and disease severity.

Renal dysfunction, cardiac complications and cerebrovascular events are associated with increased mortality. If untreated, patients with Fabry disease have a shorter life expectancy compared with the general population, which is more pronounced for males than females . The cause of death in patients with Fabry disease varies, with the most common cause being cardiovascular events. Deaths from renal complications and cerebrovascular events are also commonly reported.

The severity of Fabry disease can vary depending on the extent of the α-galactosidase A deficiency. The classic form, involves early symptoms manifesting in childhood in multiple organs while later-onset non-classic form, is associated with slower progression, delayed symptom onset, and more limited organ involvement. As the *GLA* gene is located on the X chromosome, all males carrying the mutation (i.e., hemizygous males) are affected. Females may carry the mutation on both X chromosomes (homozygous) and may be affected, or they may carry it on only one X chromosome (heterozygous) and range from being completely asymptomatic to experiencing severe symptoms, depending on the level of X-chromosome inactivation. Because of the X-linked nature of Fabry disease, the classic phenotype tends to be present more often in males than in females. The management of Fabry disease incurs a substantial economic burden, largely driven by hospital costs, indirect costs in untreated patients, and by treatment costs in treated patients.

Epidemiology

The epidemiology of Fabry disease varies between studies and across geographies. Incidence from new-born screening programmes has been reported to range from one in ~3,300 to one in 80,000 births. The overall prevalence is between one and five in 10,000. In Denmark there are currently approximately 110 patients diagnosed with Fabry disease, of which 57 are treated.

Current treatment options

Currently, there are three commercialized products indicated in Fabry disease, two ERTs (agalsidase alfa and agalsidase beta) and an oral chaperone therapy (migalastat) available in Denmark. According to current treatment guidelines, ERTs, administered by intravenous (IV) infusion, represent the gold standard for the treatment of Fabry disease. Agalsidase alfa and agalsidase beta have regulatory approval in the EU. International and European guidelines, which are followed also in Denmark, recommend that males with classic Fabry disease receive ERT, and females and non-classic Fabry patients receive ERT if they have signs of major organ involvement (kidney, heart and/or central nervous system). Agalsidase beta constitutes the gold standard and is the most commonly used treatment of Fabry disease in Denmark and globally.

Migalastat, a small-molecule chaperone therapy, is an oral option, specifically for patients with amenable *GLA* mutations. There are over 1,000 known *GLA* mutations, and Fabry patients with amenable mutations are estimated to account for 35% to 50% of the global Fabry population. Migalastat received EU regulatory approval in 2016. In Denmark, few patients with Fabry disease are currently treated with migalastat.

Unmet need

While there is no cure for patients with Fabry disease, current treatment options can prevent further cell deterioration. Patients with Fabry may still experience symptoms and long-term complications of their disease due to insufficient enzyme levels in between infusions and for example anti-drug antibodies that may impact efficacy. Further, tolerability issues, production contaminations as well as patient preference indicate that additional treatment options for Danish Fabry patients are needed. To summarize, there is a clear unmet need for a new treatment for patients with Fabry disease that provides an improved and sustained enzyme replacement efficacy while limiting the production of ADAs and occurrence of IRRs, is produced in a less vulnerable cell line, and which gives patients an additional choice of treatment.

Pegunigalsidase alfa

Pegunigalsidase alfa is a next generation PEGylated ERT indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease. It is purposely designed to improve stability, provide a longer half-life, improve biodistribution and reduce the risk of immunogenicity with the two PEGylations. One PEG moiety which cross-link the two enzyme subunits and one additional PEG moiety which is believed to mask the antibody binding sites.

The recommended dose for pegunigalsidase alfa is 1 mg/kg of body weight administered E2W by IV infusion. Infusion of pegunigalsidase alfa at home and administration by the patient in presence of a responsible adult or administration by the patient's caregiver (self-administration) may be considered for patients who are tolerating their infusions well after evaluation or recommendation by the treating physician.

The expected population relevant for treatment with pegunigalsidase alfa are treatment naïve Fabry patients as well as patients currently or previously treated with existing treatments (agalisdase alfa, agalsidase beta or migalastat).

Clinical trial programme

Pegunigalsidase alfa has been investigated in a comprehensive clinical trial program including 142 adult patients with Fabry disease, in one randomized, active-controlled Phase III study (BALANCE), two switch-over Phase III trials (BRIDGE and BRIGHT), two Phase I/II trials (PB-102-F01 and PB-102-F02), a 5-year long-term follow-up Phase I/II extension study (PB-102-F03), and it is currently being studied in two Phase III long-term extensions (PB-102-F51 and PB-102-F60).

The Phase III trials allow for the evaluation of pegunigalsidase alfa in ERT-experienced patients (1 mg/kg E2W- 2 mg/kg E4W), targeting different patient groups and sub-groups.

An open-label, dose-ranging Phase I/II study has also been conducted in 18 treatment-naïve patients or patients who had not received an ERT for the last 6 months and were administered pegunigalsidase alfa E2W for 12 months, followed by an open-label extension of five years.

Efficacy of pegunigalsidase alfa

The efficacy of pegunigalsidase alfa has been evaluated in 142 patients of which 112 received pegunigalsidase alfa according to the recommended posology of 1 mg/kg E2W. In the BRIGHT study, the posology was 2 mg/kg E4W, [redacted].

In the BALANCE study, patients previously treated with agalsidase beta were randomized in a 2:1 ratio to either receive pegunigalsidase alfa (1.0 mg/kg E2W) or continue treatment with agalsidase beta (1.0 mg/kg E2W) for 24 months. Non-inferiority of pegunigalsidase alfa to agalsidase beta in annualized estimated glomerular filtration rate (eGFR) slope was demonstrated, which was the primary endpoint of the study.

In the BRIDGE study, patients experienced significant improvements in renal function (i.e., slowing the decline in kidney function) after switching to pegunigalsidase alfa (1 mg/kg E2W for 12 months) following at least 2 years of treatment with agalsidase alfa. Specifically, the proportion of patients with stable kidney disease increased from 35.0% to 60.0%, while the percentage with fast progressive kidney disease decreased from 45.0% to 25.0%.

In the BRIGHT study, patients switched to pegunigalsidase alfa (2 mg/kg E4W for 12 months) following at least 3 years of treatment with agalsidase alfa or agalsidase beta. The mean annualized eGFR slope changed from -1.8 to -2.9 mL/min/1.73 m2/year, suggesting a relative stability in kidney function (stabilization of function is achieved if a patient has a GFR slope of ≤1–3 mL/min/1.73 m2/year, as a loss of up to 1 mL/min/1.73 m2/year is considered normal for individuals over the age of 40 years).

Safety of pegunigalsidase alfa

The safety of pegunigalsidase alfa has been evaluated in 141 patients with Fabry disease in 8 clinical trials following the posology of either 1 mg/kg E2W or 2 mg/kg E4W for a minimum of 1 infusion up to 6 years. Pegunigalsidase alfa has demonstrated a positive safety and tolerability profile as summarised below.

In BALANCE, no major safety concerns were observed, and the findings were in line with findings of previous studies. Two patients (3.8%) in the pegunigalsidase alfa arm withdrew from the study due to AEs, one of which was considered related to the treatment (hypersensitivity reaction), and one not related to treatment (end stage renal disease). The rate of treatment-related AEs was ~4-fold lower for pegunigalsidase alfa compared to agalsidase beta (42.9 vs. 152.9 events per 100 patient-years of exposure in the pegunigalsidase alfa arm and agalsidase beta arm, respectively). For treatment related serious adverse events (SAEs), there was only one event in the pegunigalsidase alfa arm (a hypersensitivity reaction leading to withdrawal; exposure-adjusted rate: 1.02) and no event in the agalsidase beta arm.

Data from the BRIDGE study showed that almost all (96.9%) TEAEs were mild or moderate in severity, and only 10.2% of these were considered related to pegunigalsidase alfa.

In the BRIGHT study, patients switched to pegunigalsidase alfa (2 mg/kg E4W for 12 months) following at least three years of treatment with agalsidase alfa or agalsidase beta. The majority of TEAEs (90.0%) were mild or moderate in severity, and 30.0% of these were considered treatment-related. Ten of the 30 patients (33.0%) were ADA positive to pegunigalsidase alfa at baseline, of which six remained ADA positive until the end of the study, and two became ADA negative. One was ADA negative at all subsequent timepoints after the baseline visit, and one withdrew consent after the baseline visit. Only patients with pre-existing IgG ADAs were positive during the study; no patients developed ADAs de novo after switching to pegunigalsidase alfa. Five (16.7%) of the patients had non-serious, mild, or moderate IRRs.

Economic value

A health economic model was developed to estimate the incremental costs of pegunigalsidase alfa compared to the most relevant comparator, agalsidase beta, in adult patients diagnosed with Fabry disease. A cost-minimization approach was taken based on the Phase III BALANCE trial results which demonstrated non-inferiority to agalsidase beta. The model used a 2-year time horizon where costs are estimated separately for the first and second year of treatment. Costs following the second year

of treatment are assumed to be the same as in the second year. The analysis was conducted from the Danish limited societal perspective (without productivity related costs). A discount rate of 4% per annum was applied for costs.

Cost outcomes were captured for drug acquisition costs and administration costs. The drug acquisition costs were calculated based on the mean patient weight of 75 kg. Based on clinical expert input no vial sharing was assumed. For pegunigalsidase alfa it was assumed that three 20 mg and three 5mg vials were needed. For agalsidase beta it was assumed that two 35 mg vials and one 5 mg vials were needed. [redacted] of pegunigalsidase alfa have the same PPP per mg as agalsidase beta (35 mg). The agalsidase beta 5 mg is priced slightly higher per mg. A compliance rate of 90% was assumed for all drugs. Although home infusions occur, treatment administration costs were based on a simplified approach where all patients were assumed to receive their infusion in the clinic while being assisted by a nurse for the full infusion time, based on clinical expert input. In addition, the treatment-related costs of patients, such as time consumption and transport costs were included in the model and calculated as part of the treatment administration costs.

The cost model results showed that pegunigalsidase alfa was the least costly therapy for the treatment of patients with Fabry disease. Compared to current gold standard; agalsidase beta, pegunigalsidase alfa leads to an incremental cost saving of 20 227 DKK in the first year of treatment and 10 213 DKK in the following years of treatment.

The Medicines Council has in addition requested a health economic analysis of pegunigalsidase alfa in comparison with no treatment. Due to limitations in data availability, a simplified analysis was made based on a hypothetical scenario in which pegunigalsidase treatment is initiated in male patients with Fabry disease, prior to the manifestation of symptoms and irreversible organ damage, as these patients can be assumed to have a near normal life expectancy and quality of life. The comparator was no treatment in addition to best supportive care, defined as treatment of Fabry disease related symptoms (e.g., pain) and complications (end stage renal disease, cerebrovascular events, and heart failure). Historical mortality and quality of life data of untreated patients was used to model the cost-effectiveness of pegunigalsidase alfa. The base case results of the analysis show that the ICER of pegunigalsidase alfa vs no treatment is approximately [redacted] DKK/QALY. Compared with no treatment, pegunigalsidase also led to a substantial life year gain (62.18 vs 31.05 undiscounted life years for pegunigalsidase alfa and no treatment, respectively).

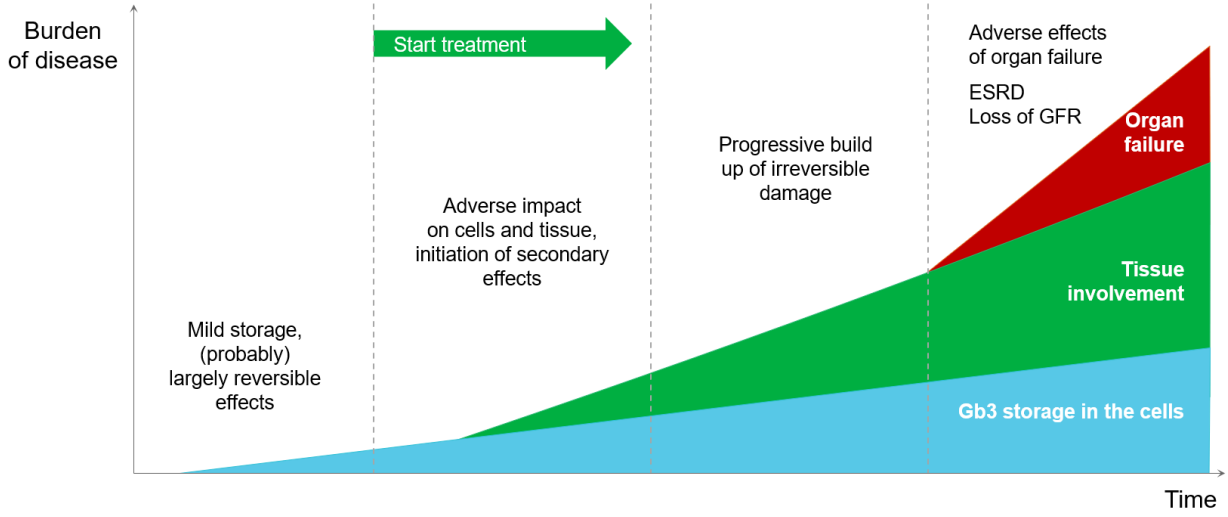
For the budget impact calculations results of the cost model were used. As the cost-model included only cost estimates for pegunigalsidase alfa and the comparator agalsidase beta, the costs of agalsidase alfa and migalastat had to be considered too to estimate the real budget impact. The cost of annual and total budget impact was estimated over five years comparing two scenarios: if pegunigalsidase alfa is introduced to the market vs if pegunigalsidase alfa is NOT introduced to the market. Introducing pegunigalsidase alfa to the market led to budget savings of [redacted] DKK, [redacted] DKK, [redacted] DKK, [redacted] DKK, [redacted] DKK in year 1, year 2, year 3, year 4 and year 5 of the analysis, respectively. When considering the results from the cost-comparison and the budget impact model together, introducing pegunigalsidase alfa can be considered cost-saving.

5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

Fabry disease (Orphanet: ORPHA:324, ICD-10: E75.2, OMIM: 301500) (Orphanet 2022) is a rare, progressive, X-linked lysosomal storage disorder (LSD) where a mutation in the galactosidase alpha (*GLA*) gene results in a deficiency of the lysosomal enzyme α-galactosidase A. This deficiency leads to progressive accumulation of glycolipids, primarily globotriaosylceramide (Gb_3) and its deacylated form, globotriaosylsphingosine (lyso-Gb_3), in the lysosomes of a wide range of cells throughout the body (Laney et al. 2013, Biegstraaten et al. 2015, Ortiz et al. 2018, Wanner et al. 2018). This abnormal storage leads to the dysfunction of basic metabolic processes and subsequent cellular death, secondary (inflammatory) processes, and progressive dysfunction of vital organs (Figure 1) (Eng et al. 2007, Chiesi 2018).

Figure 1: Progression of Fabry disease



Key: ESRD, end-stage renal disease; Gb3, globotriaosylceramide; GFR, glomerular filtration rate

Source: Adapted from (Eng et al. 2007)

Patients with Fabry disease experience progressive kidney damage (renal glomerular and tubular epithelial cells) and damage to the heart (myocardial cells and valvular fibrocytes), nervous system (neurons of the dorsal root ganglia and autonomic nervous system) and circulatory system (endothelial, perithelial, and smooth muscle cells) (Laney et al. 2013, Wanner et al. 2018, MacDermot et al. 2001b, Vedder et al. 2007). The extent of the α-galactosidase A deficiency determines the age at which patients experience the onset of their symptoms, the extent of organ involvement, and prognosis for patients with Fabry disease.

Fabry disease is classified into two types based on α-galactosidase A activity: classic and non-classic Fabry disease. Classic Fabry disease is characterized by the lack of or severely reduced (<1% of mean normal) residual α-galactosidase activity, while non-classic (or 'late-onset') disease has residual α-galactosidase activity that may vary between 2% and 10% of normal levels (El-Abassi et al. 2014, Ortiz et al. 2018). Hence, patients with the classic Fabry disease type have a more severe disease with early

symptoms manifesting during childhood and adolescence, including neuropathic pain, autonomic dysfunction, gastrointestinal disturbances (bloating, diarrhoea, abdominal pain), skin abnormalities (angiokeratomas), hypohidrosis and asymptomatic corneal opacity (cornea verticillata) (Ortiz et al. 2018, Wanner et al. 2018). In particular renal dysfunction occurs early in life in a significant proportion of children (20%) (Sunder-Plassmann G. 2006), in many females (38%) (Fabry Institute 2021) and in the majority of male patients (59%) (Fabry Institute 2021). Renal dysfunction manifests as reduced glomerular filtration rate (GFR) and proteinuria, leading to Chronic Kidney Disease (CKD) and progression to end-stage renal disease (ESRD). Other common organ complications often emerge in young adult patients, including, cardiac manifestations (left ventricular hypertrophy [LVH], myocardial fibrosis, arrhythmias), auditory loss, transient ischaemic attacks (TIAs), strokes, and eventually premature death. Lung manifestations such as dyspnoea, wheezing and dry cough have also been reported (Ortiz et al. 2018).

Patients with the late-onset, non-classic phenotype often have a milder disease, slower progression and delayed onset of symptoms, usually exhibiting symptoms between the ages of 30 and 70 years, and are often confined to a single non-specific symptom, such as CKD or cardiac involvement (Biegstraaten et al. 2015, El-Abassi et al. 2014, Ortiz et al. 2018).

Table 4 presents a summary of the symptoms experienced by patients with Fabry disease.

Table 4: Clinical manifestations of Fabry disease and age at onset

Organ system	Characteristics	Age at onset (decade)
Peripheral nervous system	Neuropathic pain (formerly called 'acroparaesthesia'), pain crises, atypical (for pain characteristics and localization) chronic or episodic pain; heat and/or cold intolerance; impaired sweat function (hypohidrosis)	1st
	Hearing loss, tinnitus; dizziness, vertigo	Begins during 3rd and progresses with age
Gastrointestinal	Nausea, vomiting, intermittent diarrhoea and constipation, abdominal pain and/or bloating, difficulty gaining weight in childhood	1st
Ophthalmological	Cornea verticillata; conjunctival and retinal vasculopathy, cataract, central retinal artery occlusion (rarely), reduced tear secretion	1st/2nd (usually present from birth)
Dermatological	Angiokeratomas	1st/2nd
Renal	Pathological albuminuria/proteinuria	1st/2nd
	Decreased glomerular filtration rate progressing to kidney failure	Mean age at kidney failure: 40 years
Skeletal	Osteopenia, osteoporosis	2nd and 3rd
Cerebrovascular	TIA, ischaemic stroke and (less frequently) haemorrhagic stroke, cerebral venous thrombosis, cervical carotid dissection	3rd and 4th
Neuro-psychological	Common: depression, anxiety, panic attacks, social adaptive function difficulties. Rarely: cognitive decline and dementia	3rd and 4th
Lymphatic	Lymphoedema in all or part of a limb (also below the eyes), pitting oedema	4th
Cardiac	Cardiomyopathy (particularly hypertrophic cardiomyopathy with concentric hypertrophy and minimal/absent outflow obstruction), reduced exercise tolerance, syncope, cardiac fibrosis, heart failure (mostly with preserved ejection fraction). Bradycardia – chronotropic incompetence, atrial fibrillation, ventricular tachycardia, sudden cardiac death	4th/5th (usually asymptomatic until well into adulthood)
Vascular	Aortic stiffness	Unknown

Pulmonary	Dyspnoea, wheezing; dry cough, sleep-disordered breathing	Unknown
Other	Mild facial dysmorphism	Unknown

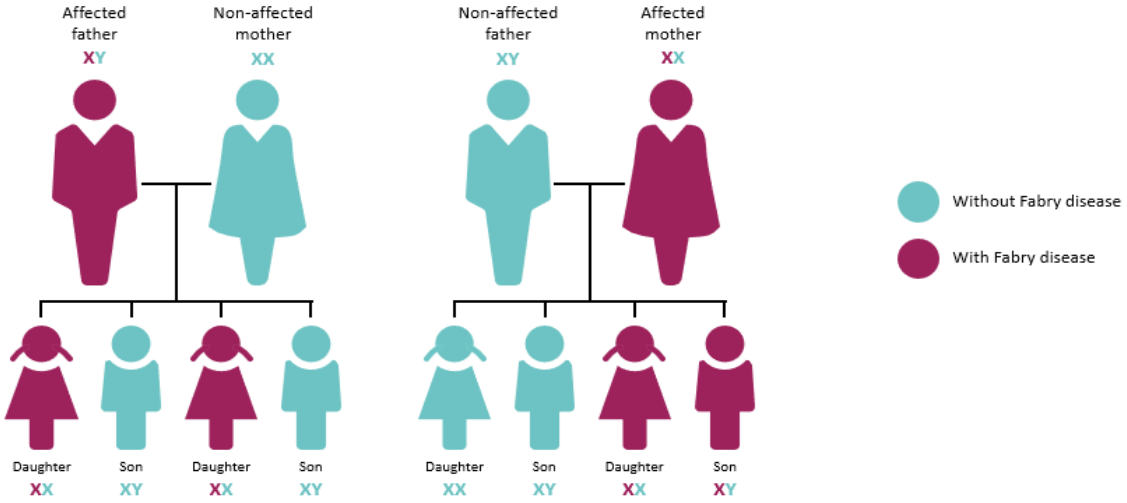
Key: TIA, transient ischaemic attack

Source: (Ortiz et al. 2018)

5.1.1 Fabry disease genetics

The *GLA* gene is located on the X chromosome. Hence, all males carrying the mutation (i.e., homozygous males) are affected by Fabry disease. Females who are homozygotic for the *GLA* mutation (i.e., carry a mutant allele in both X chromosomes) are also affected by Fabry disease, whereas females who are heterozygotic for the *GLA* mutation (i.e., carry the *GLA* mutation in only one X chromosome) range from being completely asymptomatic to experiencing severe symptoms of the disease (Ortiz et al. 2018). Because of the X-linked nature of the disease, the classic phenotype is more common in males than in females (El-Abassi et al. 2014, Laney et al. 2013, Ortiz et al. 2018). Figure 2 describes the inheritance of Fabry disease. In cases where the father carries a *GLA* mutation for Fabry disease and the mother does not carry the mutation, the daughters will be heterozygotic (i.e., carry one copy) for the *GLA* mutation but the sons will be unaffected. Where a mother is heterozygous and a father is unaffected, both their sons and daughters will have a 50% chance of inheriting the mutation. If a mother is homozygous for the *GLA* mutation, all her children will inherit the mutation.

Figure 2: Inheritance of Fabry disease



Source: Marketing data on file. PRX-102 (pegunigalsidase alfa) in Fabry disease (slide 8) (Chiesi 2022b)

Currently more than 1000 different GLA mutations in the coding regions of the GLA gene have been described. Most of the mutations are family-specific and there is no clear genotype–phenotype correlation. Some mutations are classified as variants of unclear significance (VUS) (Amodio et al. 2022, Lenders and Brand 2021, Ortiz et al. 2018).

5.1.2 Fabry disease biomarkers and diagnosis

A diagnosis can be challenging due to the wide range of symptoms experienced by patients with Fabry disease. Table 5 provides a summary of the diagnosis of Fabry disease in males and females.

Table 5: Diagnostic criteria for a definite diagnosis of Fabry disease

Males	Females
GLA mutation previously documented as causing Fabry disease	GLA mutation previously documented as causing Fabry disease
Severely decreased or absent α-galactosidase activity in leukocytes (≤5% of mean reference level)	α-galactosidase activity in leukocytes is normal or deficient
At least one of the following: ≥1 characteristic sign/symptom of Fabry disease Acroparaesthesias (neuropathic pain of the hands and feet) Angiokeratoma Cornea verticillata Increased plasma lyso-Gb3 or Gb3 Affected family member with a definite diagnosis according to the above criteria	
For an unconfirmed diagnosis: For patients with an uncertain diagnosis, a GLA VUS and a non-specific Fabry sign (e.g., LVH, stroke at a young age, proteinuria), further evaluations are needed. Fabry disease can be confirmed by the demonstration of characteristic storage in the affected organ (e.g., heart, kidney) by electron microscopy, according to an expert pathologist, in the absence of medication that can lead to storage.	

Key: Gb_3, globotriaosylceramide; LVH, left ventricular hypertrophy; lyso-Gb_3, globotriaosylsphingosine; VUS, variant of unclear significance.

Source: (Biegstraaten et al. 2015)

For a definite diagnosis of Fabry disease, both genetic testing and an assay for α-galactosidase A activity are required according to European clinical practice, which is followed in Denmark (Biegstraaten et al. 2015, Chiesi 2023b). Levels of α-galactosidase A can be tested in plasma, leukocytes or dried blood spots; this assay alone is a diagnosis for male patients if found to be ≤5% of mean reference level in leukocytes, while in females, the enzyme activity may be within a normal range (Biegstraaten et al. 2015). Thus, confirmation of a disease-causing mutation in the *GLA* gene is required in females. Confirmation of a disease-causing mutation can also be useful in males to help establish the disease phenotype, rule out benign polymorphisms that cause reduced levels of α-galactosidase A activity, and permit testing of at-risk family members (Ortiz et al. 2018).

While increased plasma and/or urinary Gb_3, or plasma lyso-Gb_3 can provide additional diagnostic information, the role of such biomarkers still requires validation (Ortiz et al. 2018). More recently, plasma lyso-Gb_3 has been widely accepted as the most accurate and reliable predictor of clinically relevant disease and, as such, may help improve diagnoses and monitoring of treatment response, although long-term data on clinical outcomes in patients who achieve reductions in lyso-Gb_3 reduction are not yet available (Cairns et al. 2018).

Based on 2007 data from the Fabry Outcomes Survey (FOS), the mean (SD) age at diagnosis is earlier in males (26.3 [15.5]) than in females (32.1 [17.6]) (Fabry Institute 2021).

According to clinical experts, patients are typically referred by cardiologists, based on symptoms and variations in the *GLA* gene. However, many are falsely suspected to have Fabry disease and are later shown to be carrying non-disease causing variants of the gene (Chiesi 2023b).

5.1.3 Burden of disease

As described above, patients with Fabry disease experience a wide range of symptoms, including neuropathic pain, gastrointestinal symptoms, fatigue, chest pain and angiokeratoma. Serious complications, including cardiovascular, renal, and cerebrovascular events are also common, affecting 34% of males and 15% of females with the condition (MacDermot et al. 2001a, MacDermot et al. 2001b). Neuropathic pain is often the first symptom to manifest in patients with Fabry disease, in males most patients are affected (present in 77%) already in childhood (MacDermot et al. 2001b). Although the quality of life (QoL) impairment is more evident and present in males, female carriers of Fabry disease, although experiencing a lower frequency and narrower range of symptoms than males, still experience a debilitating symptomatic burden that should not be dismissed, and an associated reduced QoL (Bouwman et al. 2012, Barba-Romero et al. 2019). As a result of the high symptomatic burden, patients with Fabry disease experience a poorer function and QoL compared with the general population, which reduces further with increasing age and disease severity (Arends et al. 2015, Arends et al. 2018). As a further consequence of the high symptomatic burden, Fabry disease frequently limits a patient's ability to perform normal everyday activities, while also reducing employability and productivity (Ivleva et al. 2018, MacDermot et al. 2001b). While caregiver burden is expected to be substantial for patients with Fabry disease, evidence is currently limited and further research is required.

If untreated, patients with Fabry disease have a shorter life expectancy at birth compared with the general population, which is more pronounced for males than females (MacDermot et al. 2001b, MacDermot et al. 2001a, Waldek et al. 2009). In a range of multinational studies, the mortality rate ranged between 2.7% and 5.1%, with an average age at death of 50.3 years (Waldek et al. 2009, Schiffmann et al. 2009, Mehta et al. 2009), although the rate is consistently greater in males than females. This represents an approximate reduction of 20 years from that of the general population (MacDermot et al. 2001b). For reference, the death rate of the general population in Denmark is approximately 1% (Macrotrends 2023). This finding is unsurprising given the tendency for males to have greater α-galactosidase deficiency and more severe disease. The cause of death in patients with Fabry disease varies, with the most common cause being cardiovascular. Deaths from renal complications and cerebrovascular events are also reported (Waldek et al. 2009, Mehta et al. 2009). Quality of life can be expected to be drastically reduced in the years prior to death due to the accumulation of serious complications (Wyatt et al. 2012).

The management of Fabry disease incurs a substantial economic burden, largely driven by hospital costs, indirect costs in untreated patients, and by treatment costs in treated patients (Rombach et al. 2013a, Wyatt et al. 2012). Indirect costs associated with productivity loss in untreated patients account for almost two-thirds of the overall economic burden (Rombach et al. 2013b). The cost of hospitalization is the main driver of direct medical costs in untreated patients, accounting for approximately 70% of direct medical costs associated with Fabry disease (Rombach et al. 2013a, Wyatt et al. 2012). The economic burden increases with the symptomatic burden of Fabry disease, particularly in terms of increasing indirect costs; patients with multiple complications incur a burden almost three times that of patients with a single complication (Rombach et al. 2013b). In patients who are treated with ERT, the cost of ERT is substantial, accounting for 97% to 98% of the managements costs, which is consistent across markets (Rombach et al. 2013b, Wyatt et al. 2012, CADTH 2018, Moore et al. 2007, Guest et al. 2010).

5.1.4 Epidemiology

Incidence

Incidence based on new-born screening programs has been reported to range from approximately one in 3,300 (Hopkins et al. 2017) to one in 80,000 live births on the Orphanet website (Germain 2012).

In European studies, incidence rates ranged from one male case in ~6,600 in Austria to one in 90,000 births in Sweden (Hult et al. 2014) In Denmark, incidence rates are currently not known as no Danish studies describing the epidemiology of Fabry disease were identified.

Several data from new-born screening programmes suggest that the incidence of Fabry disease may be higher than previously estimated and that the incidence may be underestimated (Fabry Institute 2021).

One international review suggested the overall prevalence of Fabry disease is between one and five in 10,000, but when later-onset variants of Fabry disease are considered, prevalence increases to approximately one in 3,000 (Germain 2012).

In Europe, prevalence was reported as one in 333,333 by the European Medicines Agency (EMA) (European Medicines Agency (EMA). 2014). However, when single European country studies were considered, the prevalence of Fabry disease ranged from one in 366,000 in the UK (MacDermot et al. 2001b) to one in 7,575 males in Spain (Colon et al. 2017).

Epidemiology in Denmark

In Denmark approximately 110 patients have been diagnosed with either classic or non-classic Fabry disease whereof 57 (51.8%) are currently receiving treatment (Chiesi 2023b).

Table 6: Incidence and prevalence in the past 5 years (Denmark)

Year	Year 2018	Year 2019	Year 2020	Year 2021	Year 2022
Incidence in Denmark	2-10	2-10	2-10	2-10	2-10
Prevalence in Denmark	100	104	106	108	110

Table 7: Estimated number of patients eligible for treatment (Denmark)

Year	Year 2023	Year 2024	Year 2025	Year 2026	Year 2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	55	57	59	60	61

5.1.5 Patient populations relevant for this application

Pegunigalsidase alfa is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase) (Elfabrio SmPC 2022).

Pegunigalsidase alfa is anticipated to be used in ERT-naïve Fabry patients and in those currently or previously treated by the commercially available Fabry therapies (agalsidase alfa, agalsidase beta and

migalastat), which is aligned with current clinical practice (further described in section 5.2.1). The number of patients eligible for treatment is not expected to increase with the introduction of pegunigalsidase alfa.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Currently, there are three commercialized products indicated in Fabry disease, two ERTs (agalsidase alfa and agalsidase beta) and an oral chaperone therapy (migalastat) available in Denmark.

In general, ERTs are viewed as the gold standard in Fabry disease. The European clinical guidelines which are followed in Denmark outline that ERT should be considered for all classic Fabry male patients aged 16 years or over are recommended to start ERT, even in the absence of symptoms, while all classic female and non-classic male patients are recommended to be treated as soon as there are signs of organ involvement characteristic of Fabry disease (i.e. kidney, heart and/or CNS signs) (Biegstraaten et al. 2015). For female patients with non-classic Fabry disease, the European Fabry Working Group recommends that ERT initiation should be considered where early clinical signs are consistent with Fabry disease. The working group also provided guidance on when to stop and when not to start ERT, which included non-compliance, patient request, infusion reactions, severe Fabry disease, severe comorbidities, cognitive decline, and a lack of response (Biegstraaten et al. 2015). These recommendations were similar to the international expert panel recommendations published in 2018 (Ortiz et al. 2018). The key conclusions of the 2018 European expert panel were as follows:

- ERT is effective in all patient populations, resulting in improved organ function, delayed disease progression, and potentially enhanced QoL
- ERT is most effective when treatment is started before the development of organ damage and when the dosing regimen is optimized to the patient's response
- Multidisciplinary input is vital at all stages of managing Fabry disease
- Organ-specific adjunctive therapies in addition to ERT are necessary to prevent or treat the effects of organ damage on QoL and long-term prognosis
- Medical care plans for Fabry disease should include appropriate, individualized patient therapeutic goals, based on a comprehensive assessment of affected organs, and regular monitoring

The chaperone therapy, indicated only for patients with amenable mutations which means they still have some enzyme activity, is currently only included in clinical guidelines in some countries. In Denmark it is primarily offered as a first line treatment for patients that have an amenable mutation. These patients can often choose between ERT and migalastat after they have been informed about the

advantages and disadvantages of each treatment. In Denmark, to start migalastat it is required that the patient would qualify for ERT treatment related to disease progression and health status.

Table 8 presents a summary of the currently available treatments for Fabry disease: the ERTs, agalsidase alfa and agalsidase beta, and the chaperone therapy, migalastat.

Table 8: Summary of currently available treatments for Fabry disease

	Agalsidase alfa (Replagal®)	Agalsidase beta (Fabrazyme®)	Migalastat (Galafold®)
Indication	Agalsidase alfa is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency)	Agalsidase beta is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).	Migalastat is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.
Approval date	03 August 2001	03 August 2001	26 May 2016
Chemical/ biological entity	Recombinant human α-galactosidase A (source: cultured human skin fibroblasts)	Recombinant human α-galactosidase A (source: Chinese Hamster Ovary cell system)	Small (chaperone) molecule that enhances α-galactosidase A activity
Route of administration and posology	IV infusion – 0,2 mg/kg, once E2W (infusion time: 40 minutes)	IV infusion – 1 mg/kg, once E2W (infusion time: initial infusion rate should be no more than 0.25 mg/minute[a])	Oral capsule (123 mg per capsule) once every other day
Mechanism of action	Catalyses the hydrolysis of Gb_3, cleaving a terminal galactose residue from the molecule	Catalyses the hydrolysis of glycosphingolipids (including Gb_3) in the lysosomes of multiple cell types and tissues	Binds to and stabilizes endogenous alpha-galactosidase A with an amenable mutation, restoring its function

Key: Gb_3, globotriaosylceramide; IV, intravenous.
Notes: [a], once a patient's tolerance is established, the infusion rate may be increased gradually with subsequent infusions.

Source: Fabrazyme, Replagal and Galafold SmPCs (Genzyme Corporation 2001, Shire 2001, Amicus Therapeutics Europe Limited. 2019)

Unmet needs with current treatment options

While there is no cure for patients with Fabry disease, current treatment option can prevent further cell deterioration. Patients with Fabry may still experience symptoms and long-term complications of their disease due to insufficient enzyme levels in between infusions and anti-drug antibodies that may impact efficacy. Further, tolerability issues, production contaminations as well as patient preference indicate that additional treatment options for Danish Fabry patients are needed. To summarize, there is a clear unmet need for a new treatment for patients with Fabry disease that provides an improved and sustained enzyme replacement while limiting the production of ADAs and occurrence of IRRs, is produced in a less vulnerable cell line, and which gives patients an additional choice of treatment.

Unmet need in ERTs

The short half-life of current ERTs seem to be insufficient in preventing the accumulation of lyso-Gb_3 (Schiffmann et al. 2019). Other contributing factors include administration of sub-optimal doses.

Increasing the dose has been shown to improve the efficacy of ERTs, although this is associated with increased levels of ADAs and tolerability issues (Lenders et al. 2018) and ERT cost per patient.

Infusion with current ERTs requires the use of premedication and prolongation of infusion times to reduce the occurrences of infusion-related reactions (IRR), which in some instances can cause the patient to stop treatment. Moreover, most patients acknowledge they still experience signs and symptoms of Fabry disease despite being on treatment, especially on the days before the next infusion (Chiesi 2022a).

In clinical trials, 68% to 73% (Banikazemi et al. 2007, Wilcox et al. 2012) of adults (both sexes and males, respectively) treated with agalsidase beta, and 24% to 56% of male adults treated with agalsidase alfa developed ADAs (Replagal® SmPC 2020, Schiffmann et al. 2006), with a high incidence of neutralizing antibodies (Lenders and Brand 2018).

The induction of ADAs is a significant influencing factor on the treatment outcome for current ERTs (Hollak and Linthorst 2009). Emergence of antibodies with in vivo neutralizing capacities is frequently encountered in Fabry disease patients treated with ERT. Regardless of the ERT administered, ADAs are more likely to develop in the severe classic Fabry phenotype (Mauhin et al. 2018).

Evidence suggests that ADAs develop early in a patient's clinical journey, with studies reporting that 25% to 88% of patients develop ADA IgG antibodies within the first 6 months of treatment (Schiffmann et al. 2006, Eng et al. 2001a, Eng et al. 2001b). Furthermore, α-galactosidase A antibodies exhibit cross-reactivity, suggesting that switching from one of the existing recombinant ERTs to another is unlikely to prevent the immune response and related effects (Linthorst et al. 2004, Hollak and Linthorst 2009). Currently, administration of higher doses of ERTs can result in saturation of ADAs, which may overcome the negative effect of the neutralizing antibodies (nAbs), but this is not considered a long-term solution as it can lead to increased ADA levels over time (Lenders et al. 2018), thereby reducing the overall treatment effect (Kizhner et al. 2015).

Impact of ADAs on the efficacy

ADAs can have an impact on the treatment efficacy and are associated with increased levels of Fabry disease biomarkers and other clinical responses, as described by several groups:

- ADAs result in inhibition of enzyme activity and adversely affect Gb_3 clearance from plasma, urine, and tissue (Linthorst et al. 2004, Vedder et al. 2008, Bénichou et al. 2009, Hollak and Linthorst 2009)
- In a longitudinal retrospective cohort study involving 39 male patients with classical Fabry disease, ADAs were strongly negatively correlated to a decrease of lyso-Gb_3, a Fabry disease biomarker. It was also observed that ADAs with high titers led to a lower reduction of the biomarker. ADAs also resulted in an accelerated decline of renal function of 1.2 mL/min/1.73 m^2/year compared to ADA-negative patients. Although the observed effect was on average modest, it is clinically highly relevant as a more rapid loss of renal function implies an earlier need for dialyses or renal transplantation (van der Veen et al. 2019)

- This finding is consistent with Rombach and colleagues, who also demonstrated that patients with ADAs suffered from higher lyso-Gb_3 levels in plasma and from a more prominent loss of renal function (Rombach et al. 2012)
- Lenders et al. also reported that patients who develop ADAs have higher lyso-Gb_3 levels, increased left ventricular mass (LVM) ($p = 0.02$) and progressive loss of renal function (difference in estimated glomerular filtration rate (eGFR) of about –30 mL/min per 1.73 m^2; $p = 0.04$), which was confirmed by a longitudinal 5-year retrospective analysis, compared to those with no ADAs (Lenders et al. 2016)
- ADAs have been suggested to worsen the prognosis by inhibiting the ERT (Mauhin et al. 2018)
- The presence of neutralizing ADAs has also been associated with clinical responses, such as severely impaired cardiac and renal disease, and worse severity score values (Lenders and Brand 2018)

Impact of ADAs on the safety

In addition, patients with antibodies against agalsidase beta have a greater potential to experience IRRs (Fabrazyme SmPC 2020).

In a retrospective RWE study involving 79 patients, 85% of which received home infusion, 89% and 26% of ADA-positive and ADA-negative patients, respectively, developed infusion-associated reactions ($p < 0.01$). Of 15 patients that had a serious IRR, 93% had presence of ADA compared to only 6.7% in 26 patients not experiencing a serious IRR ($p<0.01$) (Smid et al. 2013).

Global shortage of ERTs due to contamination of production site

The ERTs currently on the market are produced from mammalian cell lines (agalsidase alfa is produced in a human cell line, whereas agalsidase beta is produced using a mammalian Chinese Hamster Ovary cell line). The mammalian nature of the cell lines makes the production vulnerable to contamination with certain viruses. In 2009, a calicivirus contamination led to the shutting down of the production facility for agalsidase beta for a sanitization of the bioreactors, which led to a global shortage of agalsidase beta (European Medicines Agency 2009b). A result of this shortage was rationing, involuntary dose reductions or switches to agalsidase alfa. In a study on adult Dutch Fabry patients it was concluded that the shortage led to increases in lysoGb3 that suggest recurrence of disease activity (Smid et al. 2011).

Unmet need in chaperone treatment

The pharmacological chaperone migalastat provides an additional treatment option to ERTs but is only efficacious in patients with migalastat-amenable mutations, which constitute 35% to 50% of the global Fabry population (Hughes et al. 2017). Therefore, at least 50% of Fabry patients are deemed ineligible for treatment with migalastat. The activity of migalastat can also vary significantly between amenable genotypes; therefore, the response to migalastat can differ according to the specific amenable mutation (CADTH 2018). In fact, the use of migalastat in patients with non-amenable mutations may result in a net loss of α-galactosidase A activity, thereby potentially exacerbating the disease (Amicus

Therapeutics Europe Limited. 2017). In addition, it is still unclear whether all mutations currently categorised as amenable in vitro do, in fact, show a positive response to migalastat therapy in vivo (Muntze et al. 2019). Thus far, migalastat has demonstrated similar efficacy to the two commercially available ERTs, and a tolerable safety profile in patients switching from ERT to migalastat (Muntze et al. 2019, Hughes et al. 2019). Furthermore, migalastat did not change the renal function decline induced by Fabry disease in the observation period covered by several published studies (Chimenti et al. 2020), for which ERT long-term use has shown clinical effectiveness (Kim et al. 2016). Migalastat is administered orally; however, food must not be consumed at least 2 hours before and 2 hours after taking the product to give a minimum 4 hours' fast (Amicus Therapeutics Europe Limited. 2017). According to Nordic clinical experts some patients with migalastat amenable mutations still prefer ERT treatment due to the long period of fasting associated with migalastat administration (Chiesi 2023b).

5.2.2 Choice of comparator(s)

In Denmark, agalsidase beta (Fabrazyme) is the gold standard for treating patients with Fabry disease and the majority of Danish patients are currently treated with the product (n= 39, 68 %) (Chiesi 2023b).

Clinical experts have discussed that while agalsidase alfa (Replagal) have less safety issues it is also considered to be less effective compared to agalsidase beta, probably due to the lower dose (0.2 mg/kg vs 1.0 mg/kg) (Chiesi 2023b). Agalsidase alfa is only used for the treatment of 6 (11%) Danish patients with Fabry.

Migalastat (Galafold) has a narrower indication than the ERTS (Elfabrio included). Only patients with amenable mutations, estimated 35-50 % of the Fabry population, are eligible for treatment and in Denmark only 12 (21 %) are currently treated with migalastat. Given that agalsidase beta is the considered the gold standard in Denmark, in combination with the more limited use of agalsidase alfa as well as the narrower indication for migalastat makes agalsidase beta the most relevant comparator for pegunigalsidase alfa in Danish clinical practice. The world-wide preference for agalsidase beta, combined with similarities in posology and mechanism of action was also the reason for agalsidase beta to be selected as the comparator in the BALANCE trial, and why switches form agalsidase beta was considered in the BRIGHT studies in the pegunigalsidase alfa clinical program.

As the ERTs on the market predate the formation of the Medicines Council and therefore have never been assessed, the Medicines Council has in addition requested a health economic analysis of pegunigalsidase alfa in comparison with no treatment. A comparison with no treatment is strictly hypothetical and not in any way aligned with clinical practice, as all patients in Denmark eligible for treatment are already on treatment with ERTs or migalastat and withholding effective treatment to this vulnerable population would be considered highly unethical and the reason why a comparator arm against placebo was not included in the pegunigalsidase alfa clinical program.

In addition, there is limited data to support such a comparison as there are few prospective long-term trials carried out in Fabry disease prior to the introduction of ERTs (2001), and a health economic analysis will therefore need to rely to a high degree on assumptions.

5.2.3 Description of the comparator(s)

Table 9: Overview of the comparator

Proprietary name	Fabrazyme

Generic name	Agalsidase beta
Marketing authorization holder in Denmark	Sanofi
ATC code	A16AB04
Pharmacotherapeutic group	Other alimentary tract and metabolism products, enzymes
Active substance(s)	Agalsidase beta
Pharmaceutical form(s)	Powder for concentrate for solution for infusion
Mechanism of action	The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to clear the accumulating substrate in the organ tissues; thereby, preventing, stabilizing, or reversing the progressive decline in function of these organs before irreversible damage has occurred.
Dosage regimen	The recommended dose of agalsidase beta is 1 mg/kg body weight administered once every 2 weeks (E2W) as an intravenous infusion.
Therapeutic indication (as defined by the European Medicines Agency, EMA)	Agalsidase beta is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). Agalsidase beta is indicated in adults, children and adolescents aged 8 years and older.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Infusion of agalsidase beta at home may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion should be made after evaluation and recommendation by the treating physician. Patients experiencing adverse events during the home infusion need to immediately stop the infusion process and seek the attention of a healthcare professional. Subsequent infusions may need to occur in a clinical setting. Dose and infusion rate should remain constant while at home, and not be changed without supervision of a healthcare professional.
Combination therapy and/or co-medication	N/A
Need for diagnostics or other tests	Diagnosis of Fabry disease
Necessary monitoring (during administration and during treatment period)	Agalsidase beta treatment should be supervised by a physician experienced in the management of patients with Fabry disease or other inherited metabolic diseases.
Treatment duration / criteria for end of treatment	Treatment expected to be life-long
Packaging – types, sizes/number of units, and concentrations	Agalsidase beta 35 mg powder for concentrate for solution for infusion. Agalsidase beta 35 mg is supplied in clear Type I glass 20 ml vials. The closure consists of a siliconized butyl stopper and an aluminium seal with a plastic flip-off cap. Agalsidase beta 5 mg powder for concentrate for solution for infusion. Agalsidase beta 5 mg is supplied in clear Type I glass 5

	ml vials. The closure consists of a siliconized butyl stopper and an aluminium seal with a plastic flip-off cap.

Source: (Fabrazyme SmPC 2020)

In the comparison with no treatment, patients in the comparator group do not receive any disease modifying treatment. Instead, they are expected to receive best supportive care in the form of treatment for Fabry disease related symptoms and complications, including pain medication, treatment for end stage renal disease, heart failure and cerebrovascular disorders (stroke, transient ischemic attacks) (Chiesi 2023b).

5.3 The intervention

Pegunigalsidase alfa (ATC: A16AB20) is a novel, PEGylated, chemically modified form of the enzyme α-galactosidase A, developed as an ERT for the treatment of Fabry disease. It is a next generation ERT that is designed to have improved safety and tolerability vs other ERTs on the market while maintaining (and potentially in the long-term improving) efficacy. In a 24 month head-to-head clinical trial it was shown to be non-inferior to agalsidase beta (Chiesi 2017e).

5.3.1 Therapeutic indication and positioning

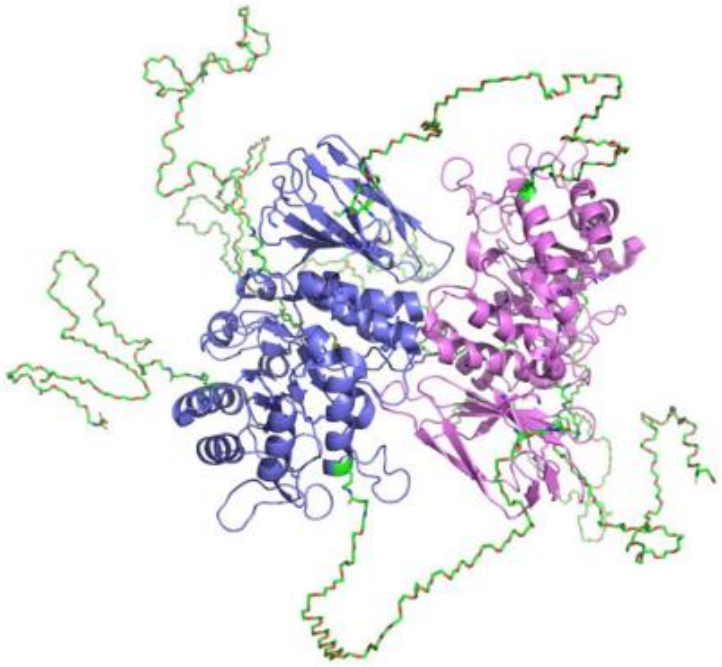
The expected indication of pegunigalsidase alfa is for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

The expected population relevant for treatment with pegunigalsidase alfa are treatment naïve Fabry patients as well as patients currently or previously treated with existing treatments (agalisdase alfa, agalsidase beta or migalastat).

5.3.2 Structural chemistry and mode of action

Pegunigalsidase alfa is a PEGylated, cross-linked, chemically modified plant-cell expressed recombinant human α-galactosidase A enzyme, which occurs naturally as a homodimer with non-covalently bound subunits. Pegunigalsidase alfa is expressed by the proprietary ProCellEx® plant-cell-based protein expression system using genetically modified Bright Yellow 2 (Nicotiana tabacum) plant cells (Kizhner et al. 2015). ProCellEx® is an alternative to mammalian cell-based production technology and, as such, does not carry any risk of infection by human or animal pathogens. As described in section 5.2.1, contamination of bioreactors have in the past caused global shortage of ERTs for Fabry disease (European Medicines Agency 2009b). Pegunigalsidase alfa, using plant cells as an expression system, is an alternative to mammalian cell-based production technology and, as such, does not carry any risk of infection by human or animal pathogens. As mentioned in section 5.2.1, the short half-life of current ERTs may be insufficient in preventing the accumulation of lyso-Gb_3 (Schiffmann et al. 2019). Chemical modification with a homo-bifunctional polyethylene glycol (PEG, 2,000 Da) cross-linker attached to the two protein subunits on the α-galactosidase A enzyme results in a PEGylated and covalently bound homodimer (Figure 3). The resulting enzyme has greater stability than its endogenous counterpart, maintaining its catalytic activity and translocation to the lysosome of target cells.

Figure 3: Pegunigalsidase alfa structure

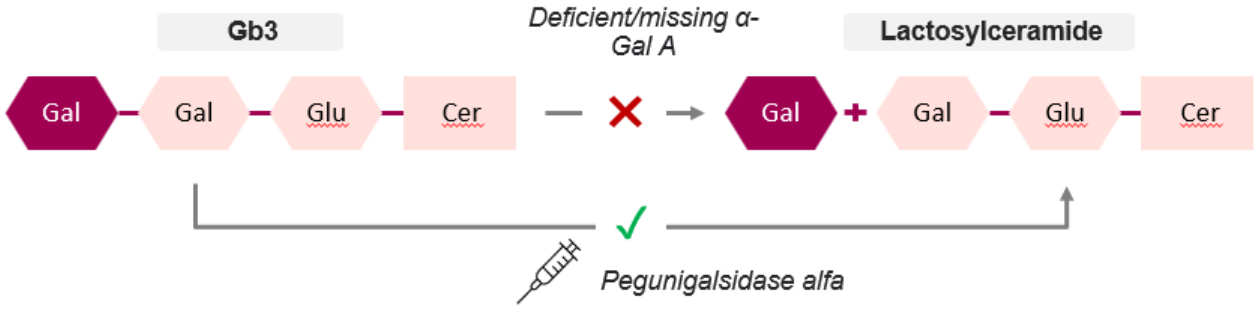


Source: (Ruderfer et al. 2018)

As described in section 5.2.1, anti-drug antibodies, which may have substantial impact both on efficacy and safety, commonly occurs with the ERTs currently available on the market. As part of the chemical modification, additional PEG moieties are attached to surface lysine residues on one subunit only, masking the parts of the enzyme that are usually recognized by the immune system. The result is a potential reduction in the immune response to the enzyme and any cross-reactivity to pre-existing anti-drug antibodies (Ruderfer et al. 2018).

Pegunigalsidase alfa supplements or replaces α-galactosidase-A (Chiesi 2023a). Following administration, it is internalized to the lysosomes of target cells where it hydrolyses terminal α-galactosyl moieties from Gb_3 to yield galactose and lactosylceramide.

Figure 4: Schematic of pegunigalsidase alfa mode of action



Source: Adapted from Figure 3A from (Kok et al. 2021)

5.3.3 Pharmaceutical form

Pegunigalsidase alfa is supplied as a concentrate for solution, for infusion in single-use vials containing 20 mg of pegunigalsidase alfa in a volume of 10 mL at a concentration of 2 mg/mL. Pegunigalsidase alfa is a clear, colourless, sterile, preservative-free solution (Chiesi 2023a). This form is of benefit to health care professionals in comparison against agalsidase beta since the step of mixing the powder for dilution is removed.

5.3.4 Posology and method of administration

Pegunigalsidase alfa treatment should be managed by a physician experienced in the treatment of patients with Fabry disease (Chiesi 2023a).

Appropriate medical support measures should be readily available when pegunigalsidase alfa is administered to patients who have not had treatment before, or who have experienced severe hypersensitivity reactions to pegunigalsidase alfa in the past. Pre-treatment with antihistamines and/or corticosteroids may be advisable for patients who had previously experienced hypersensitivity reactions to pegunigalsidase alfa or to another ERT treatment (Chiesi 2023a).

The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once E2W by IV infusion (Table 10). The initial IV infusion duration should not be less than 3 hours, with an infusion rate of no more than 1.39 mL/min (80 kg patient). After patient tolerance to the infusion, the infusion rate may be increased; however, the overall infusion duration should be no less than 1.5 hours (Chiesi 2023a).

Table 10: Recommended dose and infusion time for intravenous administration of pegunigalsidase alfa

Initial infusion 1 mg/kg of body weight every 2 weeks			
Body weight (Kg)	**Total volume (mL)**	**Infusion time**	**Infusion rate***
up to 70	150ml	not less than 3 hours	0.83 ml/min (50 mL/hr)
70 Kg-100	250ml	not less than 3 hours	1.39 mL/min (83.33 ml/hr),
> 100	500ml	not less than 3 hours	2.78 mL/min (166.67 mL/hr)
Maintenance infusion			
the target infusion duration to be achieved pending patient's tolerability. The increase in the infusion rate should be achieved gradually starting from the initial infusion indication			
1 mg/kg of body weight every 2 weeks			
Body weight (Kg)	**Total volume (mL)**	**Infusion time**	**Infusion rate***
up to 70	150ml	not less than 1.5 hours	1.68 ml/min (100 mL/hr)
70--100	250ml	not less than 1.5 hours	2.78 mL/min (166.67 mL/hr)
> 100	500ml	not less than 1.5 hours	5.56 mL/min (333.33 mL/hr)
Switching treatment from agalsidase alfa or beta			
For the initial 3 months (6 infusions) of treatment with pegunigalsidase alfa, pre-treatment regimen should be preserved with stepwise discontinuation of pre-treatment based on appropriate tolerability of the patients.			

Note: *infusion rate may be adjusted in case of infusion reaction **Source:** Elfabrio SmPC (Chiesi 2023a)

Of note, based on the open-label extension PB-102-F60 study, after confirmation of patient's tolerability, the infusion rate can be increased, but the infusion duration should be not less than 1 hour if well tolerated (Chiesi 2022e).

Special populations

- Renal or hepatic impairment: no dosing adjustment is needed in patients with renal or hepatic impairment
- Elderly (≥65 years old): the safety and efficacy of pegunigalsidase alfa in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients. Elderly patients may be treated with the same dose as other adult patients
- Paediatric population: the safety and efficacy of pegunigalsidase alfa in children and adolescents aged 0 to 17 years have not yet been established. No data are available
    - Of note, a clinical study involving paediatric population aged 2 to <18 years is under discussion with regulatory authorities. Paediatric patients aged <2 years are not included in the study.

Method of administration

For IV use only. Do not infuse pegunigalsidase alfa in the same IV line with other products. After preparation, the dilution should be administered via IV infusion and filtered through an in-line low protein-binding 0.2 µm filter. The patient should be observed for IRRs for two hours after the infusion (Chiesi 2023a).

Dilution

The number of vials required is based on the total dose required for each individual patient and requires calculation for weight-based dosing (Chiesi 2023a).

The required volume of pegunigalsidase alfa has to be withdrawn from the vials and diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, to a total volume based on patient weight:

- Patient weight <70 kg: minimum total infusion volume of 150 mL
- Patient weight 70-100 kg: minimum total infusion volume of 250 mL
- Patient weight >100 kg: minimum total infusion volume of 500 mL

Home administration

Infusion of pegunigalsidase alfa at home and administration by the patient in presence of a responsible adult or administration by the patient's caregiver (self-administration) may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion and/or self-administration should be made after evaluation and recommendation by the treating physician (Chiesi 2023a).

Appropriate training should be given by the treating physician and/or nurse to the patient and/or caregiver prior to initiation of home infusion and/or self-administration. The dose and infusion rate used in the home setting should remain the same as was used in the hospital setting; they should be changed only under the supervision of a healthcare professional and the treating physician. Self-administration should be closely followed by the treating physician (Chiesi 2023a).

Patients experiencing IRRs, including hypersensitivity reactions or anaphylactic reactions during the home infusion/self-administration need to immediately reduce the infusion rate or stop the infusion process considering the severity of the reaction and seek the attention of a healthcare professional (Chiesi 2023a).

5.3.5 Pack size

Pegunigalsidase alfa is available in two different pack sizes, containing one and five vials per carton; 20 mg/ml will be available in both pack sizes in the fall of 2023. The 5 mg/ml x 1 pack will be available in [redacted] (Chiesi 2023a).

6. Literature search and identification of efficacy and safety studies

A systematic literature review (SLR) was conducted to identify and collate clinical evidence related to patients with Fabry disease, irrespective of their previous treatment status and age group.

The objective of the SLR was to identify and collate the efficacy, safety and tolerability data reported in interventional clinical trials of pegunigalsidase alfa, agalsidase beta, agalsidase alfa, migalastat, and other pharmacological therapies for the treatment of Fabry disease.

6.1 Identification and selection of relevant studies

As a head-to-head study comparing pegunigalsidase alfa with a comparator relevant for the case is available, details of the methodology used for the SLR is not reported here.

6.2 List of relevant studies

As the SLR included a head-to-head comparison between pegunigalsidase alfa and a relevant comparator (the BALANCE trial (Chiesi 2022c)), four studies are presented in Table 11 below. For a full description of the included studies, see Appendix B.

Pegunigalsidase alfa is anticipated to be used in both treatment-naïve and treatment experienced patients.

The BALANCE trial is a phase III multicentre, active controlled trial comparing pegunigalsidase alfa with agalsidase beta in adult patients with Fabry disease over 24 months.

The phase I/II study (F01) and extension studies (F02 and F03) are included to provide evidence of the clinical efficacy and safety of pegunigalsidase alfa in treatment-naïve patients. The PB-102-F01 and PB-102-F02 studies were dose-ranging studies on ERT naïve patients or patients who have not received ERT in the past 6 months, and the PB-102-F03 study was an extension study with 5-year follow-up, also confirming the long-term safety of pegunigalsidase alfa.

Since the vast majority of patients with Fabry disease are already receiving ERT, results from both phase III switch-over studies (BRIDGE and BRIGHT) are included to provide evidence of safety and efficacy after switching from agalsidase alfa as well as agalsidase beta. BALANCE included patients previously treated with agalsidase beta, whereas BRIDGE and BRIGHT included patients previously treated with agalsidase alfa and agalsidase alfa or agalsidase beta, respectively. Of note, one Danish patient participated in BRIGHT. The BRIGHT study used a different dosing schedule (2 mg/kg E4W).

Table 11: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Publications/estimated publication dates	Study objective (comparison)

CSR PB-102-F20 (Chiesi 2022c)	BALANCE	NCT02795676	June 2016 – October 2021	Q4 2023	Pegunigalsidase alfa 1.0 mg/kg E2W vs agalsidase beta
CSR PB-102-F30 (Chiesi 2020c)	BRIDGE	NCT03018730	January 2017 – August 2022	Q3 2023	Pegunigalsidase alfa 1.0 mg/kg E2W after switch from Agalsidase alfa
CSR PB-102-F50 (Chiesi 2021)	BRIGHT	NCT03180840	June 2017 – April 2022	Q4 2023	Pegunigalsidase alfa 2.0 mg/kg E4W after switch from agalsidase beta or Agalsidase alfa
CSR PB-102-F01(Chiesi 2017d) CSR PB-102-F02 (Chiesi 2015) (Schiffmann et al. 2019) CSR PB-102-F03 (Chiesi 2020a)	PB-102-F01 PB-102-F02 PB-102-F03	*PB-102-F01 and PB-102-F02:* NCT01678898 *PB-102-F03:* NCT01981720	*PB-102-F01 and PB-102-F02:* Oct 2012 – March 2016 *PB-102-F03:* Dec 2016 – April 2021	PB-102-F01/F02: Schiffmann et al. 2019 PB-102-F03: Q3 2023	Pegunigalsidase alfa in ERT naïve patients or patients who have not received ERT in the past 6 months + extension

Ongoing studies for pegunigalsidase alfa are presented in Table 12.

Table 12: Ongoing studies for pegunigalsidase alfa

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Publications/estimated publication dates	Study objective
PB-102-F60 (BRIDGE / BALANCE / PB-102-F03 extension study; NCT03566017) (Chiesi 2022e)	BRIDGE / BALANCE extension study	NCT03566017	Sept 2018 – Oct 2026	PB-102-F03: Q3 2023	Evaluation of the long-term safety, tolerability, and efficacy parameters of 1 mg/kg pegunigalsidase alfa administered intravenously E2W
BRIGHT extension study PB-102-	BRIGHT extension study	NCT03614234	Nov 2018 – Oct 2024	Date TBD	Evaluation of long-term safety and efficacy of 2 mg/kg

F51 (Chiesi 2022d)					pegunigalsidase alfa E4W

7. Efficacy and safety

7.1 Efficacy and safety of pegunigalsidase alfa in adult patients with Fabry disease

Although Fabry disease is a rare condition, pegunigalsidase alfa has been investigated in 142 adult patients with Fabry disease in a robust clinical trial program, including one randomized, active-controlled Phase III study, two switch-over Phase III trials, two Phase I/II trials and a long-term follow-up Phase I/II extension study. Pegunigalsidase alfa has demonstrated non-inferiority to agalsidase beta in controlling eGFR decline in the head-to-head randomized trial and stability in the rest of efficacy measures as demonstrated in the head-to-head trial and two switch-over studies. A summary of the key findings from the pegunigalsidase alfa clinical trial program is presented in Table 13.

Table 13: Summary of key findings from the pegunigalsidase alfa clinical trial program

• Pegunigalsidase alfa provides a safe alternative option for both ERT-naïve and ERT-experienced patients with an improved tolerability profile and reduced immunogenicity compared to agalsidase beta while maintaining the renal and cardiac functions
• In the H2H trial (BALANCE), pegunigalsidase alfa has demonstrated non-inferiority to agalsidase beta in maintaining the renal function and a similar effect to agalsidase beta in maintaining the cardiac function
• In switch-over studies BRIDGE and BRIGHT (ERT-experienced) and in the phase I/II trial (ERT-naïve or patients that had not received ERT in the last 6 months), pegunigalsidase alfa was able to maintain stability or delay the decline in kidney function and to maintain the cardiac function
• Renal and cardiac benefits as well as the safety and tolerability profile are maintained in long-term studies in either ERT-naïve patients or in patients that had not received ERT in the last 6 months
• Overall, pegunigalsidase alfa provides stability on plasma lyso-Gb3 levels and other Fabry disease biomarkers in ERT-experienced patients as demonstrated in BALANCE, BRIDGE and BRIGHT studies
• Pegunigalsidase alfa decreases Fabry disease biomarkers in ERT-naïve patients
• Pegunigalsidase alfa has a favourable safety profile and is well tolerated, with low rates of TEAEs, a lower incidence of IRRs and reduced infusion premedication use compared to agalsidase beta in both ERT-naïve and ERT-experienced patients
• Pegunigalsidase alfa has a lower risk of inducing ADAs and reduced cross reactivity with pre-existing ADAs to agalsidase beta. Moreover, some patients with pre-existing ADAs to pegunigalsidase alfa may become ADA-negative.

Source: (Chiesi 2021, Chiesi 2020b, Chiesi 2022c)

7.1.1 Relevant studies

The Phase III trials BALANCE, BRIDGE and BRIGHT as well as the phase I/II studies are presented below. For detailed study characteristics, see Appendix B .

Phase III BALANCE study (PB-102-F20)

The BALANCE study (PB-102-F20; NCT02795676) was a Phase III, randomized, double-blind, multinational, active-controlled study designed to assess the efficacy and safety of pegunigalsidase alfa compared with agalsidase beta in adult Fabry disease patients experiencing significant kidney function deterioration while receiving treatment with agalsidase beta for at least 1 year (and received a stable dose for at least 6 months) (Chiesi 2017e). An analysis of the data was performed at 24 months.

The BALANCE study included symptomatic adult Fabry patients aged 18 to 60 years with an eGFR at screening of ≥40 – ≤120 ml/min/1.73 m^2 by CKD-EPI equation and a linear eGFR annualized change (slope) more negative than -2 mL/min/1.73 m2/year. Included patients had treatment with a dose of 1 mg/kg agalsidase beta per infusion E2W for at least 1 year and at least 80% of 13 (10.4) mg/kg total dose over the last 6 months.

Patients received IV infusions of pegunigalsidase alfa or agalsidase beta at a dose of 1 mg/kg E2W, for 24 months. The initial infusion duration was 3 hours, but this could be decreased gradually after tolerability was established and with the Investigator's agreement. After study completion, patients were invited to continue treatment in an extension open-label study (PB-102-F60); patients who were exposed to agalsidase beta in BALANCE were switched to pegunigalsidase alfa at a dose of 1 mg/kg E2W.

Study objectives and endpoints

The primary efficacy parameter in the BALANCE study was the comparison of the median annualized change (slope) in $eGFR_{CKD\text{-}EPI\ equation\ 2009}$ between treatment groups using a 2-stage model with quantile regression. Secondary efficacy parameters included $eGFR_{CKD\text{-}EPI\ 2009}$, LVMi ($g/m^2$) by MRI, Plasma lyso-$Gb_3$, Plasma Gb_3, frequency of pain medication use, exercise tolerance (stress test), short form brief pain inventory (BPI), Mainz severity score index (MSSI) and 5-level EQ-5D (EQ-5D-5L). Secondary safety parameters included frequency, severity, and duration of TEAEs, clinically significant laboratory abnormalities, ECG changes from baseline, injection site reactions following study drug administration, and anti-pegunigalsidase alfa antibodies at baseline and follow-up (Chiesi 2017e).

Phase III BRIDGE study (PB-102-F30)

The BRIDGE study (PB-102-F30; NCT03018730) was a Phase III, open-label, multinational, switchover study designed to assess the safety and efficacy of pegunigalsidase alfa in adults with Fabry disease who were previously treated with agalsidase alfa for at least 2 years (Chiesi 2020c). Patients included were symptomatic Fabry patients aged 18 to 60 years eGFR ≥ 40 ml/min/1.73 m^2 by CKD-EPI equation. The protocol allowed female patients to contribute to only 25% of the total trial population. After a 3-month screening period, eligible patients were switched from their current agalsidase alfa treatment to receive IV infusions of pegunigalsidase alfa 1 mg/kg E2W for 12 months. After completion, patients were offered enrolment in the open-label extension study, PB-102-F60.

For immunogenicity testing, all samples collected were screened for the potential presence of anti-IgG, anti-agalsidase alfa, and anti-pegunigalsidase alfa antibodies at baseline (Chiesi 2017e). Samples that tested positive for anti-pegunigalsidase alfa IgG antibodies were further analysed for antibodies against the PEG cross-linker and plant glycan motifs of pegunigalsidase alfa, and for nAbs. In the cases of hypersensitivity reactions, samples were tested for anti-pegunigalsidase alfa IgE antibodies.

Study objectives and endpoints

The primary objective of the BRIDGE study was to evaluate the safety and tolerability of pegunigalsidase alfa in patients with Fabry disease currently treated with agalsidase alfa. The secondary objective was to evaluate the efficacy of pegunigalsidase alfa in these patients. Safety measures included changes from baseline in clinical laboratory tests, electrocardiogram, TEAEs, requirement for use of premedication to manage infusion reactions and the presence of ADAs. Secondary efficacy parameters included $eGFR_{CKD\text{-}EPI\ 2009}$, LVMi ($g/m^2$) by MRI, Plasma lyso-$Gb_3$, Plasma Gb_3, frequency of pain medication use, exercise tolerance (stress test), short form BPI, MSSI and EQ-5D-5L.

Phase III BRIGHT study (PB-102-F50)

The BRIGHT study (PB-102-F50; NCT03180840) was a Phase III, open-label, multinational, switch-over study designed to assess pharmacokinetics, safety, and efficacy of pegunigalsidase alfa in adults with Fabry disease who have been previously treated with either agalsidase alfa or agalsidase beta for at least 3 years, and on a stable dose (>80% labelled dose/kg) for at least 6 months. The study included Fabry patients aged 18 to 60 years eGFR ≥30 mL/min/1.73 m2 by CKD-EPI equation at screening visit. Following screening, eligible patients were switched from their current ERT to receive IV infusions of pegunigalsidase alfa 2 mg/kg E4W for 12 months (or 14 infusions).

For pharmacokinetic analyses, blood samples were taken from all patients on Day 1 and at the end of the study (infusion 14 at 12 months). Pharmacokinetic parameters were derived from the plasma concentration versus time profiles to determine the pharmacokinetics of the study drug.

Study objectives and endpoints

The objective of the BRIGHT study was to evaluate the safety and efficacy of 2 mg/kg pegunigalsidase alfa E4W in patients with Fabry disease currently treated with agalsidase alfa or agalsidase beta. Safety parameters included changes from baseline in clinical laboratory tests, electrocardiogram, TEAEs, requirement for use of premedication to manage infusion reactions and the presence of ADAs . Efficacy parameters included $eGFR_{CKD\text{-}EPI\ 2009}$, LVMi ($g/m^2$) by MRI, Plasma lyso-$Gb_3$, Plasma Gb_3, frequency of pain medication use, exercise tolerance (stress test), short form BPI, MSSI, 5-level EQ-5D (EQ-5D-5L) and clinical events.

Phase I/II study (PB-102-F01) and extension studies (PB-102-F02 and PB-102-F03)

Study PB-102-F01 was a Phase I/II, open-label, multinational, dose-ranging study designed to assess the safety, tolerability, pharmacokinetics, immunogenicity and exploratory efficacy parameters of pegunigalsidase alfa in adult patients with FD (Schiffmann et al. 2019). The study included adult Fabry patients (≥18 years), Gb3 concentration in urine >1.5 times upper limit of normal, who have never received ERT in the past, or patients who have not received ERT in the past 6 months and have a negative anti-pegunigalsidase alfa antibody test as well as a eGFR ≥60 mL/min/1.73 m^2. Patients were enrolled into one of three treatment groups in a stepwise manner to receive increasing doses of pegunigalsidase alfa: 0.2 mg/kg (n = 6), 1.0 mg/kg (n = 8), or 2.0 mg/kg (n = 4) via IV infusion E2W for 3 months.

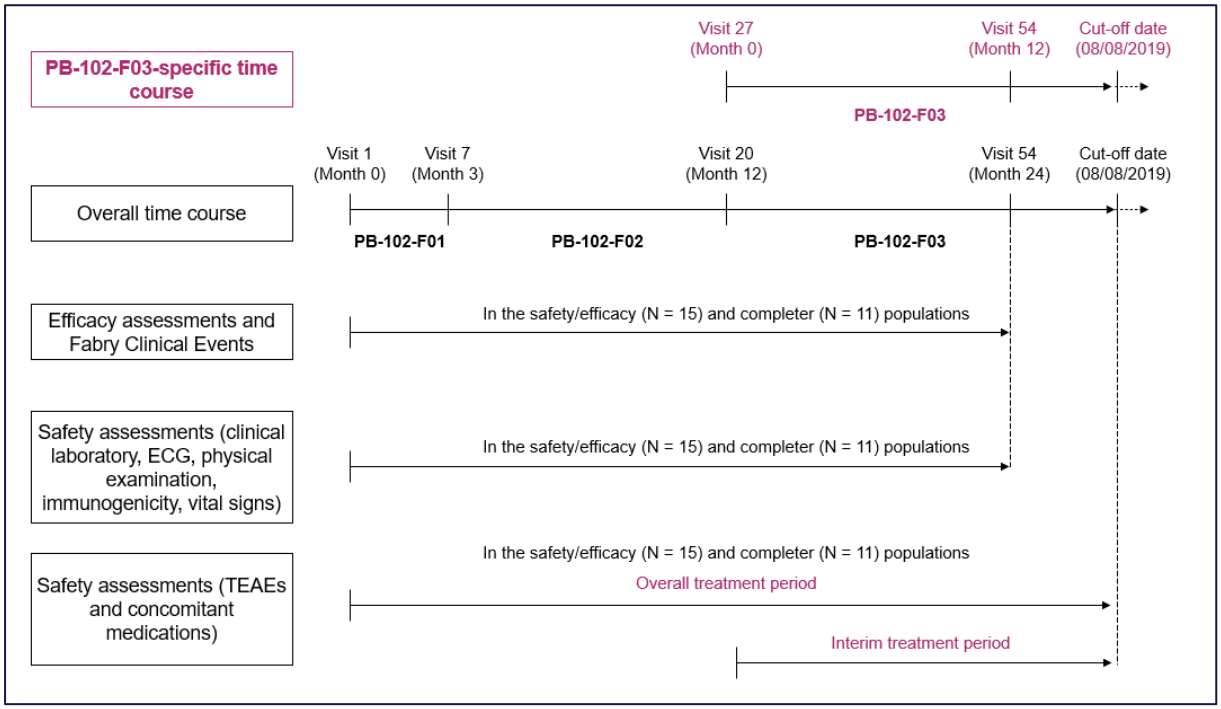
On successful completion of the 3-month study period, patients were eligible for the open-label extension study, PB-102-F02. Two of the patients did not continue in the study; one experienced a hypersensitivity reaction during the first infusion after receiving 25 mL of study drug, and another was found non-compliant and discontinued due to Investigator recommendation after receiving one

infusion (150 mL). In PB-102-F02 (n=16), patients continued to receive the same dose of pegunigalsidase alfa they received in study PB-102-F01, as an IV infusion E2W for 9 months (Chiesi 2017d, Chiesi 2015).

Following completion of both the PB-102-F01 and PB-102-F02 studies (12 months of treatment of pegunigalsidase alfa), patients were eligible to enter the PB-102-F03 extension study. In PB-102-F03, 15 of the 16 patients who completed study PB-102-F02 were enrolled (one patient in the 1 mg/kg treatment group declined further participation), and they were gradually adjusted (for the 0.2 mg/kg and 2.0 mg/kg groups) to receive the 1.0 mg/kg pegunigalsidase alfa dose via IV infusion E2W for up to 60 months and no less than 36 months (Chiesi 2016, Chiesi 2020a).

Figure 5 presents an overview of the Phase I/II study, PB-102-F01, and two extension studies, PB-102-F02 and PB-102-F03, including a breakdown of the time course of efficacy and safety assessments.

Figure 5: Overview of the PB-102-F01, PB-102-F02 and PB-102-F03 studies



Key: ECG, electrocardiogram; TEAE, treatment-emergent adverse events.

Source: PB-102-F03 CSR, 2020 (Chiesi 2020a).

Patients were enrolled into one of three treatment groups in a stepwise manner to receive increasing doses of pegunigalsidase alfa: 0.2 mg/kg (n = 6), 1.0 mg/kg (n = 8), or 2.0 mg/kg (n = 4) via IV infusion E2W for 3 months.

The first patient in the 0.2 mg/kg cohort received at least four consecutive infusions, and if the dose was tolerated, the second patient in the cohort-initiated treatment received the same dose. Once the second patient had received at least four infusions, if the dose was tolerated in both patients, treatment began in the remaining patients in the cohort. After all the patients in the 0.2 mg/kg dose cohort had tolerated at least seven infusions, treatment of the next dose cohort was initiated using the same sequential and stepwise strategy.

On successful completion of the 3-month study period (n = 16), patients were enrolled into the open-label extension study, PB-102-F02 (Chiesi 2017d, Chiesi 2015). Enrolled patients continued to receive the same dose of pegunigalsidase alfa they received in study PB-102-F01, as an IV infusion E2W for 9 months. PB-102-F02 was designed to further assess the safety, tolerability, pharmacokinetics, and exploratory efficacy parameters of pegunigalsidase alfa. Following completion of both the PB-102-F01 and PB-102-F02 studies (12 months of treatment of pegunigalsidase alfa), patients were eligible to enter the PB-102-F03 extension study.

In PB-102-F03, 15 of the 16 patients who completed study PB-102-F02 were enrolled, and they were gradually adjusted (for the 0.2 mg/kg and 2.0 mg/kg groups) to receive the 1.0 mg/kg pegunigalsidase alfa dose via IV infusion E2W for up to 60 months and no less than 36 months (Chiesi 2016, Chiesi 2020a). The screening visit (Day 1) of study PB-102-F03 corresponded to the last infusion visit of study PB-102-F02. Furthermore, the baseline characteristics in the PB-102-F03 study corresponded to the baseline characteristics in study PB-102-F01. PB-102-F03 was designed to further assess the safety, tolerability, and exploratory efficacy parameters of pegunigalsidase alfa.

Study objectives and endpoints

Study PB-102-F01 was a Phase I/II, open-label, multinational, dose-ranging study designed to assess the safety, tolerability, pharmacokinetics, immunogenicity, and exploratory efficacy parameters of pegunigalsidase alfa in adult patients with Fabry disease. Study endpoints included Gb3 concentrations in plasma and urine, lyso-Gb3 concentration in plasma, assessment of gastrointestinal symptoms using the gastrointestinal symptoms assessment (GSA) questionnaire, kidney function as assessed by eGFR and proteinuria, assessment of pain using the short-form BPI questionnaire and safety (Schiffmann et al. 2019).

7.1.2 Efficacy and safety – results per study

Phase III BALANCE study (PB-102-F20)

Patient disposition and baseline characteristics

Detailed presentation of baseline characteristics is found in Appendix C .

A total of 127 prospective subjects were assessed for inclusion, of which 78 were enrolled and randomized. Of the 78 patients, 53 were assigned to the pegunigalsidase alfa arm and 25 to the agalsidase beta arm. All patients, except one, received at least one dose of study product, thus, there were 52 pegunigalsidase alfa patients and 25 agalsidase beta patients in both the safety and intention-to-treat (ITT) analysis populations. Five patients in the pegunigalsidase alfa arm and one patient in the agalsidase beta arm, respectively, terminated the study prematurely while 48 (90.6%) and 24 (96.0%) patients, respectively, completed the 24-month study period. The reasons for discontinuation were AEs (two patients in the pegunigalsidase alfa arm and none in the agalsidase beta arm), and voluntary withdrawal (three and one, respectively). One of the AEs that led to withdrawal, a drug hypersensitivity reaction, was considered related to study treatment (Chiesi 2022c).

Of note, restrictions related to coronavirus disease 2019 (COVID-19) impacted some patients who were enrolled in the study during the pandemic and could not attend site visits. Some visits had to be rescheduled, which in a few cases caused the duration of participation to be prolonged beyond Week 104. During this time, these patients continued to receive treatment (Chiesi 2022c).

In the ITT population, the mean baseline eGFR was 73.3 mL/min/1.73 m^2 and the median was 74.5 mL/min/1.73 m^2, indicating mild to moderate renal impairment. The arms were comparable on all baseline eGFR data with similar medians (73.5 vs. 74.9). The overall mean eGFR slope at baseline was -[redacted] mL/min/1.73 m^2 and was similar between both arms, and the median annualized eGFR slopes at baseline were [redacted] and [redacted] mL/min/1.73 m^2/year in the pegunigalsidase alfa and agalsidase beta arms, respectively. A higher percentage of patients in the agalsidase beta arm ([redacted]%) than in the pegunigalsidase alfa arm (63.5%) had baseline slope values that were below -5 mL/min/1.73 m^2/year. At baseline, the majority of patients (72.7%) had UPCRs of less than or equal to 0.5 gr/gr (69.2% in the pegunigalsidase alfa arm and 80.0% in the agalsidase beta arm), with remaining patients divided about equally between those who were between 0.5 and 1.0 and those who had ratios greater than 1.0. The percentage of patients in the middle category (between 0.5 and 1.0 gr/gr) was higher in the pegunigalsidase alfa arm (17.3%) than in the agalsidase beta arm (8.0%). The percentage of patients receiving ACEi or ARB medications at baseline was higher in the agalsidase beta arm (64.0%) than in the pegunigalsidase alfa arm (50.0%) (Chiesi 2022c).

Of note, 34.6% of patients in the pegunigalsidase alfa arm were positive for anti-pegunigalsidase alfa antibodies at baseline, likely due to antibody cross-reactivity due to the protein backbone of both products being the same. The percentage of patients in the agalsidase beta arm who tested positive for anti-agalsidase beta antibodies was similar (32.0%). All ADA positive patients in the study were male (Chiesi 2022c).

Summary of clinical efficacy

Detailed presentation of efficacy outcomes for the BALANCE trial are presented in Appendix D .

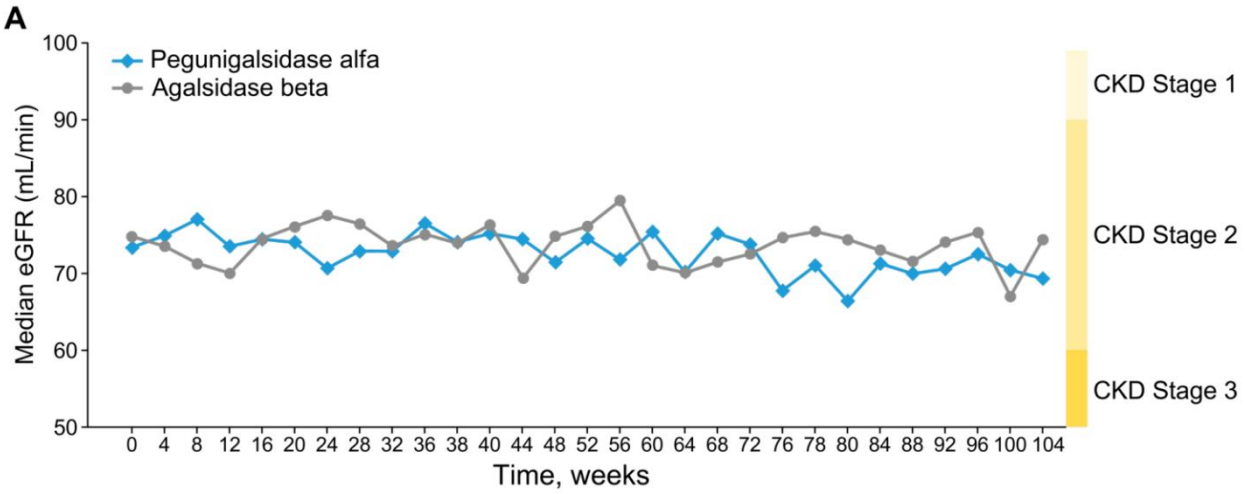
Efficacy results are presented for the ITT population, which comprised 77 patients who completed 24 months of treatment (Chiesi 2022c).

Renal outcomes (eGFR slope)

The primary endpoint was the annualized change in eGFR (slope), which is derived from eGFR assessments over time. The objective of the primary analysis was to assess whether pegunigalsidase alfa was non-inferior to agalsidase beta for this endpoint, based on the data obtained from 24 months of treatment using 2-stage quantile regression (Chiesi 2022c).

For ITT, the estimated median slopes were -2.514 for the pegunigalsidase alfa arm and -2.155 for the agalsidase beta arm, with a high overlap between the 95% CI of the two treatments. The difference in median slopes was -0.359 between the two arms. The 95% CI for the difference in slopes was -2.444 to 1.726 (see Figure 6). For non-inferiority to be indicated, the lower limit of the 95% CI had to be greater than the prespecified non-inferiority margin of -3.0. With -2.444, this criterion was met; hence, non-inferiority was shown for the ITT set (Chiesi 2022c).

Figure 6: Median eGFR values over time in the BALANCE trial: ITT population



Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eGFRCKD-EPI, eGFR chronic kidney disease-epidemiology collaboration equation.

Source: (Wallace et al. 2022)

Results in the PP set were similar. The difference in median slopes between the two arms was - 0.118. The 95% CI for the difference in slopes was -2.450 to 2.213, confirming non-inferiority and suggesting no meaningful impact of protocol deviations on efficacy. Note that for both the ITT and PP, the 95% CI for the difference included 0 (Chiesi 2022c).

In summary, the results indicate that pegunigalsidase alfa is not inferior to agalsidase beta with regards to the primary endpoint. The robustness of the finding that pegunigalsidase alfa was non-inferior to agalsidase beta was confirmed in a wide variety of sensitivity and supportive analyses (Chiesi 2022c).

Secondary efficacy endpoints

For the secondary efficacy endpoints, no statistically significant and/or clinically meaningful differences were found between the study arms. See Appendix D for details.

Summary of safety

Detailed presentation of safety outcomes for the BALANCE trial are presented in Appendix E .

More than [redacted]% of the infusions in the pegunigalsidase alfa arm and [redacted]% of those in the agalsidase beta arm were administered at home, indicating that the treatment was often considered safe for home infusion especially in the pegunigalsidase alfa group. In the pegunigalsidase alfa arm, the mean (min; max) duration was reduced from [redacted] ([redacted]) hours at baseline to [redacted] ([redacted]) hours at Week 104. The reduction in infusion duration was less pronounced in the agalsidase beta arm, where the means (min;max) were [redacted] ([redacted]) hours at baseline and [redacted] ([redacted]) hours at Week 104 (Chiesi 2022c).

Summary of treatment-emergent adverse events

47 (90.4%) patients in the pegunigalsidase alfa arm and 24 (96.0%) in the agalsidase beta arm reported at least one TEAE. Rates for severe TEAEs, serious TEAEs, and related TEAEs were also lower in the pegunigalsidase alfa arm. Two (3.8%) patients in the pegunigalsidase alfa arm, of which one was related, and one was not related to the study drug, vs. none in the agalsidase beta arm experienced TEAEs that led to withdrawal from the study. No deaths were reported during the study (Chiesi 2022c).

Summary of treatment-emergent anti-drug antibodies

Treatment-emergent IgG ADA was observed in six (11.5%) patients in the pegunigalsidase alfa arm and in five (20.0%) in the agalsidase beta arm. At the end of the study, higher portion of patients who were positive for ADA at baseline became ADA negative in the pegunigalsidase alfa arm: [redacted] ([redacted]% of the ADA positives) vs. [redacted] ([redacted]% of the ADA positives) from the agalsidase beta arm.

The low rate of treatment-emergent ADA in the pegunigalsidase alfa arm is highly encouraging, since it might have been expected that a new product would be more likely to induce an immune response compared to one that had been taken for years. In ADA-positive patients, the proportion of patients with neutralizing ADA decreased in the pegunigalsidase alfa arm (from 33 % to 15 %) while it remained stable in the agalsidase beta arm (from 28% to 25 %). This finding in favour of pegunigalsidase alfa is important not only from a safety perspective but also with respect to efficacy, since antibodies developed against an ERT product, especially neutralizing antibodies, may reduce the bioavailability of the enzyme and potentially have an impact on the clinical outcome.

Phase III BRIDGE study (PB-102-F30)

Patient disposition and baseline characteristics

Detailed presentation of baseline characteristics for BRIGDE trial are found in Appendix C .

A total of 22 patients (15 males and seven females) were enrolled and treated. Overall, 20 patients (13 males and seven females) completed the study with 12 months of treatment (per protocol efficacy [PPE] population). Two patients discontinued the study due to AEs, particularly due to serious type 1 hypersensitivity reactions at Visit 1. The safety population included all 22 enrolled and treated patients who received any dose of pegunigalsidase alfa in the study (Chiesi 2020c).

In the PPE population, the mean baseline eGFR was 79.5 mL/min/1.73 m^2, and the mean annualized eGFR slope at baseline was -5.9 mL/min/1.73 m^2/year (Chiesi 2020c). No major differences in these parameters were observed between males and females. Presence of proteinuria (UPCR ≥0.5 g/g) was detected in four (20.0%) male patients and in no female patients at baseline. Residual enzyme activity in leukocytes and plasma was lower in males than in females. Baseline plasma lyso-Gb_3 concentration was increased compared with the normal range (≤2.4 nmol/L) with a mean concentration of 38.5 nmol/L. As expected, baseline plasma lyso-Gb_3 levels were higher in males than in females; however, less pronounced differences were shown for baseline Gb_3 levels. It should also be noted that antibodies against agalsidase alfa and pegunigalsidase alfa were detected in [redacted] patient and in two patients, respectively, at baseline. Baseline characteristics of patients in the safety population were generally similar to those of the PPE population (Chiesi 2020c).

Summary of clinical efficacy

Detailed presentation of efficacy outcomes for the BRIDGE trial are presented in Appendix D .

Efficacy results are presented for the PPE population, which comprised all patients who had completed 12 months of study treatment (n = 20).

Change in $eGFR_{CKD\text{-}EPI}$ and annualized eGFR slope

At baseline (pre-switch), the total mean eGFR was 79.5 mL/min/1.73 m^2, decreasing slightly to [redacted] mL/min/1.73 m^2 after 12 months. At baseline (pre-switch), the total annualized eGFR slope was -5.9 mL/min/1.73 m^2/year, and this was improved with pegunigalsidase alfa to -1.2 mL/min/1.73 m^2/year. For male and female patients, annualized eGFR slopes were similar at baseline, and the mean changes

in the annualized eGFR slope from baseline to 12 months were consistent in male and female patients (both improving by 4.7) (Chiesi 2020c).

Plasma and urine lyso-Gb_3 and plasma Gb_3 were reduced from baseline values over the 12 months of treatment. For the other secondary efficacy measures, stability was observed in general (Chiesi 2020c). Details are found in Appendix D .

Summary of safety

Detailed presentation of safety outcomes for the BRIDGE trial are presented in Appendix E .

Results were presented for the safety population (n = 22), which included all patients who received at least one dose of pegunigalsidase alfa during the study.

Summary of treatment-emergent adverse events

Twenty-one (96%) patients reported a total of 127 TEAEs, of which the majority (123; 97%) were considered mild or moderate in severity. Four TEAEs (3%) were considered severe and occurred in four male patients (18%); note that all severe events were also classified as serious adverse events (SAEs). Of note, almost all TEAEs (90%) were considered unrelated to study treatment. In fact, the incidence of TEAEs considered by the Investigator to be definitely, probably, or possibly related to study treatment was low, with a total of 13 events (10%) in [redacted] ([redacted]%) [redacted] patients. No deaths were reported during the study (Chiesi 2020c).

Most common and severe treatment-emergent adverse events

The most frequently reported TEAEs were nasopharyngitis in seven patients (32%; [redacted] male and [redacted] female patients), headache in five patients (23%; [redacted] male and [redacted] female patients), and dyspnoea in three patients (14%; [redacted] male and [redacted] female patient). All other TEAEs were reported in two patients or less. Severe TEAEs included Type I hypersensitivity in two [redacted] patients (9%), infectious mononucleosis in one [redacted] patient (5%), and urinary tract infection in one [redacted] patient (5%). Only the Type I hypersensitivity events were considered related to study treatment and resulted in two patients discontinuing study treatment (Chiesi 2020c).

All mild and moderate TEAEs (97%) were resolved or were resolving, as were all four serious/severe adverse events. Specifically, the two SAEs considered related to study treatment (Type I hypersensitivity) were resolved within 1 day (Chiesi 2020c).

Phase III BRIGHT study (PB-102-F50)

Patient disposition and baseline characteristics

A detailed presentation of baseline characteristics is found in Appendix C .

A total of 30 patients (24 males and six females) were enrolled and treated in the study, receiving pegunigalsidase alfa 2.0 mg/kg E4W for 52 Weeks. Overall, 29 patients (23 males and six females) completed the study (PPE population); one male patient discontinued as he withdrew his consent after receiving the first infusion of pegunigalsidase alfa 2.0 mg/kg at Visit 1. Of note, the regimen was changed to 1.0 mg/kg E2W for one patient at Week 40. The safety population and the Pharmacokinetic (PK) population included all 30 patients (Chiesi 2021).

In the safety population, the mean baseline eGFR was 99.9 mL/min/1.73 m^2, the mean annualized eGFR slope at baseline was -1.8 mL/min/1.73 m^2/year and was lower in females (-[redacted] mL/min/1.73 m^2/year). Presence of proteinuria (UPCR ≥ 0.5 g/g) was detected in [redacted] ([redacted]%) male patients and in [redacted]

female patients. Baseline plasma Lyso-Gb_3 mean concentration was [redacted] nmol/L and was higher than the normal range (≤ 2.4 nmol/L). As expected, baseline plasma lyso-Gb_3 levels were higher in males than in females. Antibodies against agalsidase beta and pegunigalsidase alfa were detected in [redacted] and [redacted] patients, respectively. No antibodies against agalsidase alfa were detected (Chiesi 2021).

Summary of clinical efficacy

The recommended dose in the SmPC of pegunigalsidase alfa is as mentioned in section 5.3.1 1 mg/kg E2W. In the BRIGHT study, the dose investigated was 2 mg/kg E4W (Chiesi 2021). [redacted]. There are no safety concerns.

Detailed presentation of efficacy outcomes for the BRIGHT trial are presented in Appendix D .

Efficacy results are presented for the PPE population, which comprised 29 patients who had completed 12 months of study treatment.

Change in $eGFR_{CKD-EPI}$ and annualized eGFR slope

Mean change in eGFR from baseline to 12 months (post-switch) was -1.3 (SE 1.4). The mean eGFR slope changed from [redacted] ([redacted]) at baseline to [redacted] ([redacted]) at month 12 (Chiesi 2021).

Summary of safety

Detailed presentation of safety outcomes for the BRIGHT trial are presented in Appendix E .

Results were presented for the safety population (n = 30), which included all patients who received at least one dose of pegunigalsidase alfa during the study. However, it should be noted that the results of immunogenicity testing post-treatment were only available for the PPE population (n = 29) (Chiesi 2021).

Summary of treatment-emergent adverse events

Of the 183 TEAEs that were reported in 27 (90%) patients, the majority of whom were considered mild or moderate in severity (180 TEAEs in 90% of patients), the TEAEs were resolved or resolving at the end of the study. Three TEAEs were considered severe and affected two (6.7%) male patients, and two of these were also a serious TEAE. The majority of TEAEs (70%), including the two serious TEAEs, were considered unrelated to the treatment; the remaining 30% were considered treatment-related and were mild or moderate in severity. No deaths were reported during the study (Chiesi 2021).

Most common and severe treatment-emergent adverse events

The most frequently reported TEAEs were nasopharyngitis in [redacted] ([redacted]%) patients, fatigue in [redacted] ([redacted]%) patients, and IRRs in [redacted] ([redacted]%) patients. All other TEAEs were reported in <[redacted] patients. The [redacted] severe TEAEs and [redacted] serious TEAEs ([redacted] also severe) occurred in [redacted] patients with Fabry disease who had a positive ADA status at baseline and had been previously treated with agalsidase beta. The [redacted] severe TEAEs comprised [redacted] events (pyrexia and IRR) in [redacted] patient, and [redacted] event (road traffic accident) in [redacted] patient. Serious TEAEs included [redacted] severe event in [redacted] patient who had a road traffic accident, which required surgery and lead to the patient's withdrawal, and [redacted] moderate event (carbamazepine overdose) in [redacted] patient, which was resolved. None of these was considered treatment related (Chiesi 2021).

The most frequently reported treatment-related TEAE was IRR, with [redacted] events reported in [redacted] ([redacted]%) patients (Chiesi 2021).

All [redacted] ([redacted]%) patients with a positive ADA status at baseline were reported with TEAEs ([redacted] events) compared with [redacted]/[redacted] ([redacted]%) patients with a negative ADA status at baseline ([redacted] events). All [redacted] ([redacted]%) patients previously treated with agalsidase beta were reported with TEAEs ([redacted] events) compared with [redacted]/[redacted] ([redacted]%) patients previously treated with agalsidase alfa ([redacted] events) (Chiesi 2021).

Injection-site and infusion-related reactions following study drug administration

A total of 27 IRRs were reported in five (16.7%) patients (all males; [redacted] with classic Fabry disease), and all events were considered non-serious, mild, or moderate in severity and were resolved, all but one within a day. No IRRs led to study discontinuation. [redacted], the infusion was interrupted (a partial dose was administered) and the event was considered unrelated to the study and resolved the same day. For the [redacted] patients who recorded the majority of the IRRs ([redacted]/[redacted] events), premedication had been administered during previous ERT therapy and was maintained during the study; these patients also had a medical history of IRRs (Chiesi 2021).

Four out of five patients with IRRs had been previously treated with agalsidase beta and also tested positive for IgG ADAs to pegunigalsidase alfa at screening and throughout the study (Chiesi 2021).

Treatment-emergent anti-pegunigalsidase alfa antibodies

In summary, only patients with pre-existing IgG antibodies were positive for ADAs to pegunigalsidase alfa during the study; no patients developed ADAs de-novo following the switch to pegunigalsidase alfa (Chiesi 2021).

Phase I/II study (PB-102-F01) and extension studies (PB-102-F02 and PB-102-F03)

Patient disposition and baseline characteristics (PB-102-F01 and PB-102-F02)

A total of 19 patients were enrolled from 11 sites; however, one patient in the 1.0 mg/kg group voluntarily withdrew from the study before receiving the study treatment. Thus, the safety population comprised 18 patients receiving any dose of study drug. A further two male patients in the 1.0 mg/kg treatment group discontinued the study: one experienced a hypersensitivity reaction (bronchospasm) during the first infusion, and one was noncompliant; therefore, a total of 16 patients completed the 3 months of treatment in study PB-102-F01. All 16 patients (nine male and seven female patients) enrolled into and completed the 9-month extension study, PB-102-F02, during which patients continued to receive the same dose assigned in PB-102-F01. All 16 patients completed the PB-102-F02 9-month extension study as well. Note that of the 16 patients, one female and nine male patients were characterized as having classic Fabry disease (Schiffmann et al. 2019).

In the safety population, 11 male patients and one female patient were classified as having classic Fabry disease. For this study, classic Fabry disease was defined as patients with low (<30% of the normal laboratory mean) values of α-galactosidase A activity and at least one Fabry-specific symptom, such as neuropathic pain, cornea verticillata or clustered angiokeratoma (Schiffmann et al. 2019).

A detailed presentation of baseline characteristics in the safety population is found in Appendix C .

Patient disposition and baseline characteristics (PB-102-F03)

A total of 16 patients (nine males and seven females) successfully completed the PB-102-F02 study, one male patient (originally in the 1.0 mg/kg treatment group) declined further participation, and therefore, 15 patients (eight males and seven females) were enrolled into the PB-102-F03 extension study for an additional 60 months of treatment. A total of five patients (33.3%) discontinued from the

study: three withdrew voluntarily, one due to pregnancy and one due to a fatal TEAE (chronic obstructive pulmonary disease [COPD]); therefore, as of 8 August 2019, a total of 10 patients (66.7%) (six males and four females) were continuing in study PB-102-F03 (Chiesi 2020a).

Summary of clinical efficacy from the PB-102-F01 and PB-102-F02 studies

Detailed presentation of efficacy outcomes for the PB-102-F01 and PB-102-F02 trials is presented in Appendix D .

Plasma Gb_3 and lyso-Gb_3 concentrations

At both 6 and 12 months, reductions in mean plasma Gb_3 concentrations were observed in both men and women across all treatment groups. For the nine patients with classic Fabry disease, a total mean reduction from baseline in plasma Gb_3 concentration was observed at both 6 and 12 months, decreasing by 30.4% ([redacted]%) and 33.3% ([redacted] %), respectively (Chiesi 2017d).

Reductions in mean plasma lyso-Gb3 levels were also observed throughout the study for the entire study population. At both 6 and 12 months, reductions in plasma lyso-Gb_3 concentrations were observed in both males and females across all treatment groups. For the 10 patients with classic Fabry disease, a total mean reduction from baseline in plasma lyso-Gb_3 concentration was observed at both 6 and 12 months, decreasing by [redacted]% ([redacted]%) and [redacted]% ([redacted]%), respectively (Chiesi 2017d).

Gb_3 deposition in the kidney

Kidney biopsies analysing Gb_3 deposition in kidney peritubular capillaries were performed at baseline and following 6 months of treatment with pegunigalsidase alfa; data were available from 13 patients. From baseline to 6 months, the total mean Barisoni Lipid Inclusion Scoring System (BLISS) score decreased by 67.8% (SE 8.9%), reducing from 4.26 to 0.83 (Schiffmann et al. 2019, Chiesi 2017d). The eight patients with classic Fabry disease had a greater mean decrease in the BLISS score compared with that of the total study population (-84.1% versus -67.8%) (Chiesi 2017d).

Change in eGFR and annualized eGFR slope

Overall, the eGFR results indicate stability in kidney function after 12 months of treatment with pegunigalsidase alfa (Schiffmann et al. 2019, Chiesi 2017d). For the total population, mean eGFR at baseline was 111.2 (SD 20.9; range: 78–156) mL/min/1.73 m^2, decreasing to [redacted] (SD [redacted]; range: [redacted]–[redacted]) mL/min/1.73 m^2 after 6 months, and 110.5 (SD 23.4; range: 68–152) mL/min/1.73 m^2 after 12 months; a mean decrease of -1.0 and -0.8 mL/min/1.73 m^2, respectively (Chiesi 2017a, Schiffmann et al. 2019).

Overall, [redacted] patients ([redacted]%) had a positive eGFR slope and [redacted] patients ([redacted]%) had a negative eGFR slope (Chiesi 2017d). Of the [redacted] patients with negative eGFR slopes, [redacted] were considered to have stable renal function, [redacted] had progressive renal disease, and [redacted] had fast-progressive renal disease.

The majority of patients in the 1.0 mg/kg dose group had positive annualized eGFR slopes; however, [redacted] patient had a negative eGFR slope of -[redacted] (i.e., progressive renal disease), and [redacted] patient had a negative eGFR slope of -[redacted] (i.e., fast-progressive renal disease). Note that the [redacted] patient was suspected to be influenced by intermittent treatment with doxycycline, which is known to transiently exacerbate renal disease (Chiesi 2017d).

For the 10 patients with classic Fabry disease, the mean annualized eGFR slope was -1.8 mL/min/1.73 m^2/year (range: -18.18–6.35 mL/min/1.73 m^2/year). On excluding the male patient who was treated

with doxycycline, the remaining nine patients demonstrated a positive mean eGFR slope of 0.01 mL/min/1.73 m^2/year (range: -6.35–6.35 mL/min/1.73 m^2/year) (Chiesi 2017d).

Summary of clinical efficacy from the PB-102-F03 study

Plasma Gb_3 and lyso-Gb_3 concentrations

A reduction in the total mean plasma lyso-Gb_3 concentration was observed from baseline following treatment with pegunigalsidase alfa, decreasing by 3.4 µg/mL (22.9% reduction from baseline) at 12 months and a similar reduction was maintained up to 48 months of treatment. At Month 60, a smaller mean reduction of -2.8 µg/mL (-8.5%) was observed due to an increase in values in female patients at that timepoint. A continuous strong reduction in the total mean plasma lyso-Gb_3 concentration was observed from baseline (Visit 1 of study PB-102-F01) up to approximately Month 24, followed by a stabilization at approximately [redacted]% reduction for [redacted] and [redacted]% reduction for [redacted] throughout the remainder of the study (Chiesi 2020a).

Change in eGFR and annualized eGFR slope.

A relatively stable eGFR was observed over the 60-month treatment period. At baseline, the mean eGFR was [redacted] mL/min/1.73 m^2 (range: [redacted] mL/min/1.73 m^2), slightly decreasing by -0.4 mL/min/1.73 m^2 at Month 24 and by -10.9 mL/min/1.73 m^2 at Month 60. The mean annualized eGFR slope was -1.6 mL/min/1.73 m^2/year (range: -[redacted] mL/min/m^2/year)(Table 69). The mean annualized eGFR slopes were more negative (indicating a higher decrease in eGFR over time) in male versus female patients and in long-term treated patients compared with the overall population (Chiesi 2020a).

LVM

In male patients 20 to 60 years of age, the normal range for LVM is 107-187 g, in female patients 20 to 60 years of age, the normal range is 70 -142 g (Kawel-Boehm et al. 2015).

The mean LVM absolute value at baseline was 115.6 g for male patients and 70.8 for female patients and considered within normal ranges. At Month 24, cardiac MRI showed a mean slight increase among female patients ([redacted] g), whereas in male patients, there was a slight mean decrease of [redacted] g. At Month 60, the mean increase observed in both subgroups was more pronounced in female patients ([redacted] g) compared with male patients ([redacted] g). Although an increase from baseline was observed for male and female patients, the mean absolute LVM values remained normal at Month 24 and Month 60 (Chiesi 2020a).

Summary of safety from the PB-102-F01 and PB-102-F02 studies

In the safety population (n = 18), 17 patients reported a total of 223 TEAEs, of which 169 (76%) were considered unrelated or unlikely to be related to treatment. Almost all TEAEs were of mild or moderate intensity, with only four patients reporting a severe TEAE: these included pain in extremities, renal haematoma due to kidney biopsy at baseline, migraine, and bronchospasm. Of these four events, migraine and bronchospasm were considered possibly related and definitely related to treatment, respectively. Of note, the bronchospasm event occurred 40 minutes after the first infusion of pegunigalsidase alfa, and the patient was treated with epinephrine and corticosteroids, which resolved the issue. The patient was withdrawn from the study per protocol, and this event was reported as a treatment-related serious adverse event. It should also be noted that this patient had pre-existing anti-pegunigalsidase alfa IgE antibodies (Chiesi 2017d).

Of the 223 TEAEs in the safety population, the most common were fatigue (n = 6; 33%), nausea (n = 5; 28%) and vomiting (n = 5; 28%). The most common TEAEs considered possibly related to treatment were nausea (n = 4; 25%) followed by chest discomfort, dizziness, maculopapular rash, and fatigue (all n = 2; 13%). Eight patients (including the patient with bronchospasm) experienced a total of 30 IRRs, defined as TEAEs that occurred during or within 2 hours after pegunigalsidase alfa infusion; 24 of these were considered probably, possibly, or definitely related to treatment. The majority of laboratory haematology, biochemistry and urinalysis parameters remained within normal levels, and no clinically important mean changes from baseline were observed during the study (Chiesi 2017d).

Summary of safety from the PB-102-F03 study

Results in this section are presented for the overall treatment period (beginning with study PB-102-F01) unless otherwise stated, and are reported for the safety population, defined as all patients who received at least one dose of pegunigalsidase alfa during PB-102-F03. The safety population comprised 15 patients (eight males and seven females). Eleven (seven male and four female) of the 15 patients were treated for at least three years, and 10 (six male and four female) of the 15 patients were treated for at least five years (Chiesi 2020a).

In the safety population, all 15 patients reported at least one TEAE. There was a total of 440 TEAEs. A total of nine patients (60.0%) were reported with 59 out of 440 TEAEs (13.4%) assessed as possibly, probably, or definitely related to study treatment. No patients discontinued the studies due to a treatment-related TEAE (Chiesi 2020a).

Almost all (97.5%) were mild or moderate in severity and resolved over time. A total of 11 severe TEAEs (2.5%) were reported in 5 male patients (33.3% of patients overall); none were reported in female patients. The only TEAEs of severe intensity reported in ≥2 patients were abdominal pain/discomfort and headache, each reported in two patients (xxxx%). Only one severe TEAE (migraine), reported in one patient (6.7%), was considered as being possibly related to study treatment. Three severe TEAEs were reported as serious: one TEAE of perirenal hematoma reported in one patient (6.7%) in study PB-102-F01 and two TEAEs of clavicle fracture and COPD reported in one patient (6.7%) each, both reported in study PB-102-F03. One severe, serious and unrelated TEAE of COPD was fatal and thus led to discontinuation of one patient (Chiesi 2020a).

The most commonly experienced TEAEs were fatigue (eight patients [53.3%]), back pain (six patients [40.0%]), and abdominal pain, nausea, upper respiratory tract infection, nasopharyngitis, headache, paraesthesia, vomiting, rash, and cough (each experienced by five patients [33.3%]). The most common TEAEs considered possibly related to treatment were nausea ([redacted] patients [[redacted]%]), and chest discomfort, fatigue, headache, vertigo, diarrhoea and dizziness (all reported in [redacted] patients [[redacted]]) (Chiesi 2020a).

7.1.3 Comparative analyses of efficacy and safety

A comparative analysis of efficacy and safety is not considered relevant in this case as there is a head-to-head comparison available for a relevant comparator, the Phase III BALANCE study.

8. Health economic analysis

A health economic model was developed to estimate the incremental costs of pegunigalsidase alfa compared to the most relevant comparator, agalsidase beta, in adult patients diagnosed with Fabry disease. A cost-minimization approach was taken based on the Phase III BALANCE trial results which demonstrated non-inferiority to agalsidase beta (Chiesi 2022f).

8.1 Model

The primary treatment goal for people with Fabry disease is prevention of progression in accumulation of GB3 and Lyso-GB3 in the lysosomes in cells leading to tissue damage and organ failure. A cost model was developed in Microsoft Excel® to represent the treatment objective. Cost outcomes were captured for drug acquisition costs and administration costs.

8.1.1 Cycle length and time horizon

The model uses a 2-year time horizon where costs are estimated separately for the first and second year of treatment. Costs following the second year of treatment are assumed to be the same as in the second year.

8.1.2 Perspective and discounting

The analysis was conducted from the Danish limited societal perspective (without productivity related costs). A discount rate of 4% per annum was applied for costs.

The base case model perspective was that of the Danish limited societal perspective which included drug costs and administration fees.

8.1.3 Model structure

The model calculates the cost of drug acquisition and administration for both pegunigalsidase alfa and agalsidase beta for year 1 and year 2 of treatment. The annual costs of treatments are expected be different for the first and subsequent years due to the longer administration duration that is assumed for the first six infusion (e.g., first 3 months of treatment) for both pegunigalsidase alfa and agalsidase beta. The annual costs of treatments are compared between pegunigalsidase alfa and agalsidase beta.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for country specific clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The inputs data used in the model are summarised in the table below. The inputs presented for agalsidase alfa and migalastat were only used for the budget impact calculations and not for the cost-minimisation analysis.

Table 14: Input data used in the model:

Parameters	Input value used in the model	How is the input value obtained/estimated
Mean weight	75kg	Estimate based on clinical expert input
Drug costs – pegunigalsidase alfa 20mg vial	[redacted] DKK	Elfabrio pharmacy purchasing price
Drug costs – pegunigalsidase alfa 5mg vial	[redacted] DKK	Elfabrio pharmacy purchasing price
Drug costs – agalsidase beta 5mg acquisition cost	3 606 DKK	Lægemiddelsstyrelsen (2023) pharmacy purchasing price. (Lægemiddelsstyrelsen 2023)
Drug costs – agalsidase beta 35mg acquisition cost	21 950 DKK	Lægemiddelsstyrelsen (2023) pharmacy purchasing price. (Lægemiddelsstyrelsen 2023)
Drug costs - agalsidase alfa 4mg acquisition cost	13 075,01 DKK	Lægemiddelsstyrelsen (2023) pharmacy purchasing price. (Lægemiddelsstyrelsen 2023)
Drug costs – migalastat acquisition cost 123mg 14 tablets	157 218 DKK	Lægemiddelsstyrelsen (2023) pharmacy purchasing price. (Lægemiddelsstyrelsen 2023)
Duration of infusion – initial - pegunigalsidase alfa	3 hours	Based on pegunigalsidase alfa SmPC (Chiesi 2023a)
Duration of infusion – initial - agalsidase beta	5.3 hours	Based on agalsidase beta SmPC (Fabrazyme SmPC 2020)
Duration of infusion – initial - agalsidase alfa	0.7 hours	Based on agalsidase alfa SmPC (Replagal® SmPC 2020)
Duration of infusion – follow-up - pegunigalsidase alfa	1.5 hours	Based on pegunigalsidase alfa SmPC (Chiesi 2023a)
Duration of infusion – follow-up - agalsidase beta	1.5 hours	Based on agalsidase beta SmPC (Fabrazyme SmPC 2020)

Duration of infusion – follow-up - agalsidase alfa	0.7 hours	Based on agalsidase alfa SmPC (Replagal® SmPC 2020)
Dosing frequency - Infusions per year - pegunigalsidase alfa	26.1	Infusions every two weeks for a year (365.25/7/2)
Dosing frequency - Infusions per year - agalsidase beta	26.1	Infusions every two weeks for a year (365.25/7/2)
Dosing frequency - Infusions per year - agalsidase alfa	26.1	Infusions every two weeks for a year (365.25/7/2)
Dosing frequency - Number of infusions at initial duration - pegunigalsidase alfa	6	Based on pegunigalsidase alfa SmPC (Chiesi 2023a)
Dosing frequency - Number of infusions at initial duration - agalsidase beta	6	Based on agalsidase beta SmPC (Fabrazyme SmPC 2020)
Dosing frequency - Number of infusions at initial duration - agalsidase alfa	6	Based on agalsidase alfa SmPC (Replagal® SmPC 2020)
Dosing frequency – number of capsules per year - migalastat	182.63	1 capsule every other day (365.25/7)*3.5
Administration costs – Cost of nurse visit (per hour)	542	AMGROS. Estimating unit costs. Version 1.1. Nurse hourly cost from Table 2.
Administration costs – Cost of patient's time per hour	208	Average hourly rate of an employee in Denmark after taxes (Statistics Denmark 2022)
Administration costs – Cost of Transportation	100	AMGROS. Estimating unit costs. Version 1.1
Compliance (all drugs)	90%	Estimate based on clinical expert input

Patient population

Pegunigalsidase alfa is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase) (Elfabrio SmPC 2022).

The expected population relevant for treatment with pegunigalsidase alfa are treatment naïve Fabry patients as well as patients previously treated with existing treatments (agalsidase alfa, agalsidase beta or migalastat). The number of patients eligible for treatment is not expected to increase with the introduction of pegunigalsidase alfa.

Table 15: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison	Used in the model (number/value including source)	Country specific clinical practice (including source)

	etc. (including source)		
Mean weight	79 kg based on BALANCE BRIDGE & BRIGHT	75 kg based on Swedish clinical expert input	75 kg based on Swedish clinical expert input

Source: (Chiesi 2022c, Chiesi 2020b, Chiesi 2021, Chiesi 2020c, Chiesi 2023b)

Intervention

Intervention as expected in country specific clinical practice (as defined in section 2.2): pegunigalsidase alfa (ATC: A16AB20)

Intervention in the clinical documentation submitted: pegunigalsidase alfa (ATC: A16AB20) is a novel, PEGylated, chemically modified form of the enzyme α-galactosidase A, developed as an ERT for the treatment of Fabry disease. It is a next generation ERT that is designed to have improved safety and tolerability vs other ERTs on the market while maintaining efficacy.

Intervention as in the health economic analysis submitted: pegunigalsidase alfa (ATC: A16AB20).

Table 16: Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Country specific clinical practice (including source)
Posology	The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight E2W administered by IV infusion	Posology according to approved label: 100% receive 1 mg/kg administration of pegunigalsidase alfa E2W	Posology according to approved label: 100% receive 1 mg/kg administration of pegunigalsidase alfa E2W
The pharmaceutical's position in country specific clinical practice	1st line	1st line	1st line
Packaging – types, sizes/number of units, and concentrations	Pegunigalsidase alfa 20 mg is supplied in vials. Package sizes: 1 or 5 vials per carton. Pegunigalsidase alfa 5 mg is supplied in vials. Package sizes: 1 vial per carton.	The model uses two vial options: 20mg and 5mg vials	Two vial options are available: 20mg and 5mg vials

Source: (Chiesi 2022c, Chiesi 2020b, Chiesi 2021, Elfabrio SmPC 2022, Chiesi 2020c)

Comparator

The current country specific clinical practice (as described in 5): In Denmark, all patients eligible for treatment receive treatment of Fabry disease consisting of ERT, i.e., agalsidase beta or agalsidase alfa or migalastat. In Denmark, the majority (67%) of Fabry patients receive agalsidase beta, which is considered the standard of care.

Comparator(s) in the clinical documentation submitted: Fabrazyme (agalsidase beta [ATC: A16AB04]).

Comparator(s) in the health economic analysis submitted: as described in section 5.2.2, agalsidase beta was chosen as the most relevant comparator in the health economic analysis as it is the most used treatment in Denmark, as well as current gold standard of Fabry treatments.

Table 17: Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Country specific clinical practice (including source)
Posology	Agalsidase beta is administered 1 mg/kg body weight E2W as an IV infusion	In line with the clinical documentation	In line with the clinical documentation
The comparator's position in country specific clinical practice	The comparator in the pivotal study for pegunigalsidase alfa, the head-to-head RCT BALANCE with 24 months follow-up shares the same mechanism of action and posology as pegunigalsidase alfa and is the drug most likely to be replaced by pegunigalsidase alfa	Used as a comparator in the model	Agalsidase beta is the most commonly used ERT for the treatment of Fabry disease in Denmark
Packaging – types, sizes/number of units, and concentrations	Agalsidase beta 35 mg is supplied in 20 ml vials. Package sizes: 1, 5 and 10 vials per carton. Agalsidase beta 5 mg is supplied in 5 ml vials. Package sizes: 1, 5 and 10 vials per carton	The model uses two vial options: 35 mg and 5 mg vials	Two vial options are available 35 mg and 5 mg vials

Source: (Elfabrio SmPC 2022, Genzyme Corporation 2001)

Relative efficacy outcomes

Due to the cost-minimisation analysis approach it was assumed that pegunigalsidase alfa has the same efficacy to agalsidase beta which is supported by the non-inferiority result in the primary efficacy endpoint of the Balance trial.

Adverse reaction outcomes

Adverse reaction outcomes were not considered in the cost model because the estimated difference in adverse event costs were deemed marginal compared to the drug acquisition and administration cost differences. Note that exclusion of adverse event costs from the analysis is conservative, as safety outcomes of the head-to-head BALANCE trial favoured pegunigalsidase alfa over agalsidase beta (Chiesi 2022c).

8.3 Extrapolation of relative efficacy

Not applicable as a cost-minimization analysis was performed with no extrapolation of relative efficacy.

8.4 Documentation of health-related quality of life (HRQoL)

Not applicable, because cost-minimization analysis was performed where health outcomes were not considered.

8.5 Resource use and costs

Although agalsidase beta is the relevant comparator for pegunigalsidase alfa in the cost comparison, agalsidase alfa and migalastat are included in the budget impact analysis and therefore dosing, resource and costs are presented in this section for these drugs.

Drug dosing for agalsidase alfa, agalsidase beta, and migalastat were sourced from the Summary of Product Characteristics (SmPC) (Table 18). Dosing for pegunigalsidase alfa was based on the pivotal trials BALANCE and BRIDGE. As illustrated in Table 18, and in line with the administration schedule, pegunigalsidase alfa, agalsidase beta and agalsidase alfa have an initial infusion period which is gradually reduced in the first 6 infusions to a minimum infusion time.

Drug costs for agalsidase beta, agalsidase alfa, and migalastat were sourced from Lægemiddelsstyrelsen (Lægemiddelsstyrelsen 2023). The drug acquisition costs were calculated based on the mean patient weight of 75 kg. Based on clinical expert input no vial sharing was assumed. For pegunigalsidase alfa it was assumed that three 20 mg vials and three 5 mg vials were needed. For agalsidase beta it was assumed that two 35 mg vials and one 5 mg vials were needed. For all drug treatments a 90% compliance rate was assumed in the model. The drug costs are displayed in Table 19.

Treatment administration costs were based on a simplified approach where all patients were assumed to receive their infusion in the clinic while being assisted by a nurse for the full infusion time, based on clinical expert input (Chiesi 2023b). The hourly cost of nurse's time was then multiplied by the duration of infusions and the number of infusions per year. In addition, the treatment-related costs of patients, such as time consumption and transport costs were included in the model and calculated as part of the treatment administration costs. The administration unit costs used in the model are presented in Table 20 and the total annual administration costs are displayed in Table 21.

The model included drug wastage of residual vial contents as this best reflects clinical practice. In the model base case, a simplistic approach was adopted to account for wastage. When more than two vial composites were available, the model considered the one with the cheapest cost per mg.

Table 18: Dosing schedule

Drug	Dosing per administration	Dosing schedule	Infusion duration (hrs)		Infusion/ pack per year	No. of initial infusions	Source
			Initial	Reduction			
Pegunigalsidase alfa	1 mg/kg	E2W IV	3	1.5	26.1	6	Chiesi clinical expert survey
Agalsidase alfa	0.2 mg/kg	E2W IV	0.7	0.7	26.1	6	Agalsidase alfa SmPC (European Medicines Agency 2008)
Agalsidase beta	1 mg/kg	E2W IV	5.3	1.5	26.1	6	Agalsidase beta SmPC (European Medicines Agency 2009a)
Migalastat	123 mg	Once, EOD orally	0	0	13.04	0	Migalastat SmPC (European Medicines Agency 2016)

Key: IV, Intravenous infusion; E2W, Every two weeks; EOD, Every other day

Table 19: Drug costs

Drug	Cost per pack (DKK)	Pack / vial size	Unit strength	Cost per mg	Source
Pegunigalsidase alfa	[redacted]	1 vial	20 mg	[redacted]	Chiesi
Pegunigalsidase alfa	[redacted]	1 vial	5 mg	[redacted]	Chiesi
Agalsidase alfa	13 075	1 mg/ml	3.5 mg	3 735,7	Lægemiddelsstyrelsen (2023). Pharmacy purchasing price. Medicinpriser (Lægemiddelsstyrelsen 2023)
Agalsidase beta	3 606	1 vial	5 mg	721,2	
	21 950	1 vial	35 mg	627,1	

Drug	Cost per pack (DKK)	Pack / vial size	Unit strength	Cost per mg	Source
Migalastat	157 218	14 tablets	123 mg	11 229,9	

Table 20: Treatment administration unit costs

Administration type	Unit cost (DKK)	Source
Nurse cost per hour	542	AMGROS. Estimating unit costs. Version 1.1. Nurse hourly cost from Table 2.
Cost of patient's time per hour	208	Average hourly rate of an employee in Denmark after taxes (Statistics Denmark 2022)
Cost of transportation	100	AMGROS. Estimating unit costs. Version 1.1

Table 21: Total administration cost per year

Drug	Annual administration costs (DKK)	
	Year 1	Year 2+
Pegunigalsidase alfa	[redacted]	[redacted]
Agalsidase alfa	14 675	14 675
Agalsidase beta	44 019	28 763
Migalastat	0	0

8.6 Results

8.6.1 Base case overview

An overview of the base case including the central aspects and assumptions are presented below in Table 22.

Table 22: Base case overview

Parameter	Setting
Intervention	Pegunigalsidase alfa
Comparator	Agalsidase beta
Type of model	Cost-minimisation cost model
Time horizon	2 years
Discount rate on costs	4%
Mean weight	75 kg
Treatment line	1st line
Measurement and valuation of health effects	Not included due to the cost-minimisation approach.
Included costs	Treatment acquisition and administration Costs of transportation and treatment time included
Dosage of pharmaceutical	Based on weight
Compliance (all drugs)	90%
Posology	Intervention: 100% E2W IV 5 mg vial 20 mg vial Comparator: 100% E2W IV 5 mg vial 35 mg vial

8.6.2 Base case results

Base case cost-minimisation analysis results are reported in Table 23. The incremental difference between pegunigalsidase alfa and agalsidase beta show a cost saving of 20,227 DKK and 10,213 DKK in the first and the following years, respectively.

Table 23: Base case results

Technologies	Year 1	Year 2+	Total
Pegunigalsidase alfa	1 139 249	1 047 683	2 186 932
Agalsidase beta	1 159 476	1 057 896	2 217 372
Incremental difference	20 227	10 213	30 441

8.7 Sensitivity analyses

8.7.1 Scenario analyses

Table 24 presents the results of the scenario analyses.

Table 24: Scenario analysis results

Parameters	Base case setting	Scenario	Reason / Rational / Source	Total costs for pegunigalsidase alfa	Total costs for agalsidase beta	Incremental cost (DKK)
Base case				2 186 932	2 217 372	-30 441
Perspective	Danish limited societal perspective (without productivity related costs) Costs of transport & treatment time included	Health-service perspective (costs of transport and treatment time excluded)		2 166 629	2 194 523	-27 894
Discount rate	4%	0%		2 272 423	2 303 697	-31 274
		3%		2 207 374	2 238 014	-30 640
		5%		2 167 071	2 197 318	-30 247
Mean weight	75 kg	70	Lower weight	2 045 232	2 054 417	-9 185
		79	Mean patient weight from Attract	2 328 632	2 380 327	-51 696

8.8 Health economic analysis of pegunigalsidase alfa vs no treatment

The Medicines Council has requested a health economic analysis of pegunigalsidase alfa in comparison with no treatment in addition to a clinically relevant comparison with other ERTs. As all patients eligible for treatment with disease modifying drugs in Denmark are already on treatment with ERTs or migalastat, a comparison with no treatment is not aligned with clinical practice and strictly hypothetical. Moreover, as disease modifying treatment prevents organ damage, a no treatment comparison based on the currently treated Fabry disease population would be misleading due to the benefit of previous treatment in the comparator arm.

Due to limitations in data availability, a simplified analysis was made based on a scenario in which pegunigalsidase treatment is initiated in male patients with Fabry disease prior to the manifestation of symptoms and irreversible organ damage, as these patients based on clinical expert statements can be assumed to have a near normal life expectancy and quality of life (Chiesi 2023b). The comparator was no treatment in addition to best supportive care, defined as treatment of Fabry disease related symptoms (e.g., pain) and complications (end stage renal disease, cerebrovascular events, and heart failure). Historical mortality and quality of life data of untreated patients was used to model the cost-effectiveness of pegunigalsidase alfa.

For the comparison, a cost-utility approach was taken, which builds upon the cost model presented in section 8.

8.8.1 Model

A simple cost-utility model was developed in Microsoft Excel® to compare the costs and health benefits between pegunigalsidase alfa vs no treatment. Cost outcomes were captured for drug acquisition costs, administration costs and health care resource use costs. Health outcomes were captured by quality adjusted life years (QALYs) and life years.

8.8.2 Cycle length and time horizon

The model uses a lifetime (82 years) horizon and a one-year cycle length.

8.8.3 Perspective and discounting

The analysis was conducted from the Danish limited societal perspective (without productivity related costs). The base case model included drug costs, administration fees and health care resource use costs.

A uniform discount rate of 4% per annum was applied for costs and health outcomes. However, differential discounting approach (e.g., 4% for costs and 2% of health outcomes) is more appropriate when modelling life-extending therapies where the health benefits are realized far into the future. Due to the chronic nature of Fabry disease and because pegunigalsidase alfa is taken over a patient's lifetime, drug costs are accrued from the beginning of the model horizon (when the discounting is low), while survival benefits that occur far into the future are heavily discounted. Using a uniform discount rate for cost and health outcomes disproportionately impacts the denominator of the cost-per-QALY and cost-per-life year calculation. Results using differential discounting are presented in the scenario analysis.

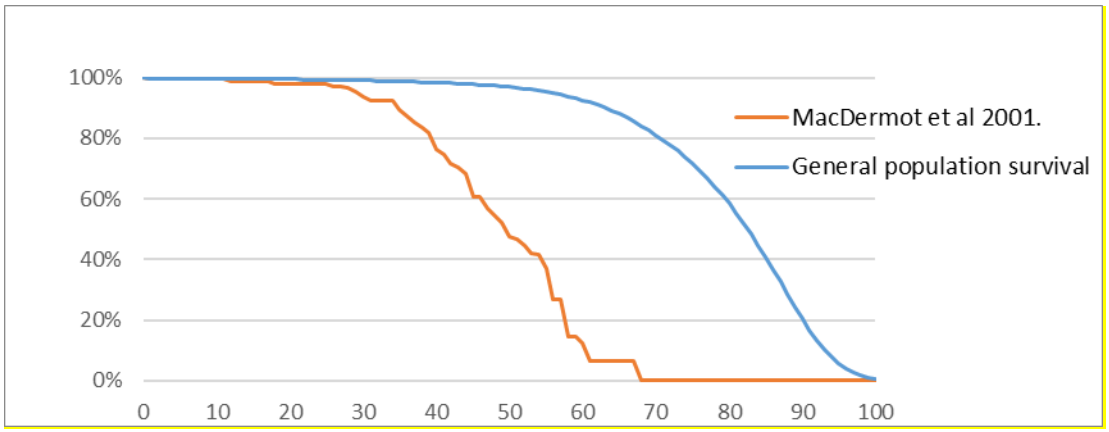
8.8.4 Model structure

The cost utility analysis was based on a simple survival model where the costs and health outcomes were calculated according to the proportion of patients survived each year. For pegunigalsidase alfa, general population overall survival estimates were used, while for no treatment, overall survival estimates were taken from a study by MacDermot and coworkers (MacDermot et al. 2001b). For further details see section 8.8.5.

8.8.5 Extrapolation of relative efficacy

The relative efficacy of pegunigalsidase alfa is captured via overall survival estimates. Based on clinical expert input, a patient initiating treatment at an early stage before the life limiting complications appear are likely to have the same mortality as the general population (Chiesi 2023b). Thus, in the cost-utility model patients treated with pegunigalsidase alfa are assumed to have an overall survival equal to the male general population based on Statistics Denmark estimates (Danmarks Statistik 2023b). Patients in the no treatment arm were assumed to have an overall survival equal to the estimates presented in the study by MacDermot and coworkers (MacDermot et al. 2001b). The comparison of overall survival estimates applied in the cost-utility analysis is presented in Figure 7.

Figure 7: Overall survival estimates applied in the cost-utility analysis



Source: (MacDermot et al. 2001b)

8.8.6 Documentation of health-related quality of life (HRQoL)

The utility values used in the pegunigalsidase alfa arm of the cost-utility analysis were assumed to equal general population utility. These general population utilities were sourced from the Swedish study by Burström and coworkers (Burstrom et al. 2001). Utility values in the no treatment arm were based on the study by Moore and coworkers and were equal to 0.56 (Moore et al. 2007). This utility value was obtained by bootstrapping of normal distributions based on a previous study that collected QoL data from 38 male Fabry disease patients from the AFD registry in the UK (Miners et al. 2002). The patients had a variety of symptoms, and the utility value thus captures patients in early as well as later stages of the disease. Considering Fabry disease in males is associated with neuropathic pain in the majority of patients with a mean age of onset of 10.1 years, a reduced QoL over the patients lifetime is to be expected (MacDermot et al. 2001b). This utility value was then age adjusted with a multiplicative method based on the utility values of Burström and coworkers (Burstrom et al. 2001) and a starting age of 35 years which is the mean cohort age in the study by MacDermot and coworkers (MacDermot et al. 2001b). This method results in higher utility values than 0.56 between the ages of

18 and 35, and lower values thereafter which are in proportion to the changes in the general population utility values.

Resource use and costs

The simple cost-utility analysis considers the drug cost, drug administration fees and health care resource utilization costs. The drug and administration costs of the cost analyses feed into the cost — utility analysis. These costs are presented in detail in section 8.5.

The health care resource utilization costs are based on complication costs and their distribution that are applied from a specified age onset. Age of onset of Fabry related symptoms and complications were based on the study by MacDermot and coworkers (MacDermot et al. 2001b) and a study by Connock and coworkers (Connock et al. 2006). Additionally, end of life costs based on the Medicine Council's assessment of imlifidase were applied (Medicinrådet 2023). Initiation of treatment with pegunigalsidase alfa at an early age was assumed to prevent the occurrence of Fabry related complications, based on statements from clinical experts (Chiesi 2023b). Thus, the proportion of patients incurring the complication costs were assumed to be 0% for pegunigalsidase alfa, while in the no treatment arms the proportions were based on the studies by MacDermot (MacDermot et al. 2001b) and Connock (Connock et al. 2006). The distribution and age at onset of Fabry related complications are presented in Table 25. The health care resource use costs applied in the cost-utility analysis are presented in Table 26.

Table 25: Distribution of health care resource use and age at onset

Complication	Pegunigalsidase alfa %	Source (pegunigalsidase alfa)	No treatment %	Age at onset (no treatment)	Source (no treatment)
Acroparaesthesia/ Pain	0%	Assumption	77%	10,1	(MacDermot et al. 2001b)
ESRD (dialysis)	0%	Assumption	31%	36,7	(MacDermot et al. 2001b)
ESRD (graft transplant)	0%	Assumption		40	(MacDermot et al. 2001b)
Cardiac complication (left ventricular hypertrophy)	0%	Assumption	88%	42	(MacDermot et al. 2001b)
Cerebrovascular accident	0%	Assumption	24%	40,4	(MacDermot et al. 2001b)

Table 26: Health care resource use of complications

Complication	Proportion (%)	Unit costs	Total costs per year	Source for unit costs	Source for resource use
Acroparaesthesia/ Pain	100%	6 322	6 322	Based on a study by Langley et al 2012 (Langley et al. 2013). 350.16 EUR per 6 months. Costs for 12 months, converted to DKK and inflated to 2023 costs using the Oanda currency converter (Oanda 2023) and the Danish net price index (Danmarks Statistik 2023a)	(National Institute for Health and Care Excellence (NICE) 2016)
ESRD (end stage renal disease)					
Renal dialysis	57%	361 734	206 188	Based on a health economic analysis by Connock et al 2006 (Connock et al. 2006). Converted to DKK and inflated to 2023 costs using the Oanda currency converter (Oanda 2023) and the Danish net price index (Danmarks Statistik 2023a)	(Connock et al. 2006)
Graft transplant	43%	157 735	67 826		
Cardiac complication					
Left ventricular hypertrophy	49%	74 131	36 324	Assumed equal cost as for heart failure based on a study by Stålhammar et al. 2012 (Stalhammar et al. 2012). Converted to DKK and inflated to 2023 costs using the Oanda currency converter (Oanda 2023) and the Danish net price index (Danmarks Statistik 2023a)	(Chiesi 2023b)
Cerebrovascular accident					
Mild stroke	65%	20 992	13 645	Based on a health economic analysis by Connock et al 2006 (Connock et al. 2006). Converted to DKK and inflated to 2023 costs using the Oanda currency converter (Oanda 2023) and the Danish net price index (Danmarks Statistik 2023a)	(Connock et al. 2006)
Disabling stroke	35%	217 773	76 221		
End of life costs					
End of life costs	1	35456	35 456	Sundhedsdatastyrelsen DRG 2023: 11MA02 based on Bilag til Medicinrådets anbefaling vedr. Imlifidase til nyretransplantation	(Medicinrådet 2023, Sundhedsdatastyrelsen 2023)

Langliggertakst	16 days	2185	34 960	Bilag til Medicinrådets anbefaling vedr. Imlifidase til nyretransplantation	(Medicinrådet 2023)

8.8.7 Results

Base case overview

An overview of the base case including the central aspects and assumptions are presented below in Table 27.

Table 27: Base case overview

Parameter	Setting
Intervention	Pegunigalsidase alfa
Comparator	No treatment
Type of model	Cost-utility analysis
Time horizon	Lifetime horizon (82 years)
Discount rate on costs	4%
Discount rate on health outcomes	4%
Mean weight	75 kg
Starting age	18
Treatment line	1st line
Measurement and valuation of health effects	Intervention: utility values based on general population (Burstrom et al. 2001) Comparator: utility 0.56 based on (Moore et al. 2007), age adjusted based on mean age (35 years) in (MacDermot et al. 2001b).
Included costs	Treatment acquisition and administration Health care resource use Costs of transportation and treatment time included
Dosage of pharmaceutical	Based on weight
Compliance (all drugs)	90%
Posology	Intervention: 100% E2W IV 20 mg vial 5 mg vial
Overall survival	Intervention: general population Comparator: (MacDermot et al. 2001b).

Base case results

The base case cost-utility analysis comparing pegunigalsidase alfa with no treatment are reported in Table 28. The ICER was estimated to 2 353 768 DKK/QALY gained using a life-time horizon. The analysis also shows the substantial amount of life years gained with the treatment of pegunigalsidase alfa, 62.18 vs 31.05 for pegunigalsidase alfa and no treatment, respectively.

Table 28: Base case results

Technologies	Total QALYs	Total life years (undiscounted)	Total Costs	Incremental QALYs	Incremental costs	ICER
Pegunigalsidase alfa	20,57	62,18	26 506 919	10,78	25 371 519	2 353 768
No treatment	9,80	31,05	1 135 401			

The disaggregated model results for the costs outcomes for each arm are detailed in Table 29.

Table 29: Disaggregated results - costs outcomes

Technologies	Drug costs	Administration costs	Health care resource use costs
Pegunigalsidase alfa	25 710 329	675 649	120 942
No treatment	-	-	1 135 401

Scenario analysis results

A differential discounting approach (e.g., 4% for costs and 2% of health outcomes) is more appropriate than a uniform discount rate when modelling life-extending therapies where the health benefits are realized far into the future as in the present case. Using a uniform discount rate for cost and health outcomes disproportionately impacts the denominator of the cost-per-QALY calculation. Results using differential discounting are presented in Table 30.

Table 30: Scenario analysis results (differential discounting: 4% costs and 2% health outcomes)

Technologies	Total QALYs	Total Costs	Incremental QALYs	Incremental costs	ICER
Pegunigalsidase alfa	30,93	26 506 919	18,27	24 767 692	1 355 780
No treatment	12,66	1 739 227			

9. Budget impact analysis

Base case

For the budget impact calculations results of the cost model were used. As the cost model included only cost estimates for pegunigalsidase alfa and the comparator agalsidase beta the costs of agalsidase alfa and migalastat had to be considered too to estimate the real budget impact. The cost of annual and total budget impact was estimated for 5 years between two scenarios: if pegunigalsidase alfa is introduced to the market vs if pegunigalsidase alfa is NOT introduced to the market.

Number of patients

The number of patients expected to be treated over the next five-year period is presented in the table below. The patient numbers were obtained from clinical experts (Chiesi 2023b).

Table 31: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Pegunigalsidase alfa	0	0	0	0	0
Agalsidase beta	39	40	40	41	42
Agalsidase alfa	6	6	6	6	6
Migalastat	13	13	14	14	14
Total number of patients	58	59	60	61	62

Table 32: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Pegunigalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	58	59	60	61	62

Expenditure per patients

Table 33: Costs per patient per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Pegunigalsidase alfa	-	-	-	-	-
Agalsidase beta	779 648	776 001	762 814	769 316	775 363
Agalsidase alfa	160 314	157 597	154 970	152 430	149 971

Migalastat	413 706	406 695	430 679	423 619	416 786

Table 34: Costs per patient per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Pegunigalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agalsidase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migalastat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 35: Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is NOT recommended					
Drug costs	76 707 973	77 823 430	79 669 197	80 784 654	81 900 111
Administration costs	1 804 803	1 253 845	1 238 589	1 282 608	1 311 372
Total	78 512 776	79 077 274	80 907 786	82 067 262	83 211 482
Cost per patient	1 353 669	1 340 293	1 348 463	1 345 365	1 342 121
Minus *The pharmaceutical under consideration is recommended*					
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation					
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Discussion on the submitted documentation

There is a clear unmet need for patients with Fabry disease in Denmark due to limitations with current treatment. In clinical trials, pegunigalsidase alfa has shown an improved safety and tolerability profile compared with the current gold standard, agalsidase beta.

This cost-minimisation analysis was conducted to evaluate the cost impact of treating adult patients with Fabry disease with pegunigalsidase alfa. Pegunigalsidase alfa was a less costly therapy option compared to agalsidase beta at similar efficacy.

The cost model optimizes the use of the available data in this patient population, while fully accounting for the economically relevant parameters in the decision problem. The cost model structure adopted is fully aligned with goal of the evaluation. Key model assumptions and uncertainties were extensively explored through sensitivity analyses.

This economic model provides clear evidence of the cost-savings of pegunigalsidase alfa versus the relevant clinical comparator agalsidase beta for the treatment of Fabry disease, which was robust to the majority of values and assumptions tested. In other words, introducing pegunigalsidase alfa in clinical practice will not increase treatment costs for Fabry disease but rather reduce pharmaceutical spending.

The Medicines Council has in addition requested a health economic analysis of pegunigalsidase alfa in comparison with no treatment. As all patients eligible for treatment with disease modifying drugs in Denmark are already on treatment with ERTs or migalastat, a comparison with no treatment is not aligned with clinical practice and strictly hypothetical. Moreover, as disease modifying treatment prevents organ damage, a no treatment comparison based on the currently treated Fabry disease population would be misleading due to the benefit of previous treatment. The comparison has therefore been made based on limited historical data in which all benefits of disease modifying treatments might not have been captured.

Due to limitations in data availability, a simplified analysis was for this reason made based on a scenario in which pegunigalsidase treatment is initiated in younger male patients with Fabry disease, prior to the manifestation of symptoms and irreversible organ damage. If these patients are initiated early on treatment, they can be assumed to achieve a near to normal life expectancy and quality of life. The comparator was no treatment in addition to best supportive care, defined as treatment of Fabry disease related symptoms (e.g., pain) and complications (end stage renal disease, cerebrovascular events, and heart failure). Historical mortality and quality of life data of untreated patients was used to model the cost-effectiveness of pegunigalsidase alfa. The base case results of the analysis show that the ICER of pegunigalsidase alfa vs no treatment is approximately 2 353 768 DKK/QALY. Given the results of the cost-minimization analysis pegunigalsidase alfa is likely more cost-effective compared to no treatment than the other ERTs. Compared with no treatment, pegunigalsidase alfa also led to a substantial life year gain (62.2 undiscounted life years for pegunigalsidase alfa vs 31.1 undiscounted life years for no treatment). When modelling progressive diseases and life-extending therapies where the health benefits are realized far into the future as in the present case, a differential discounting approach is more appropriate than the uniform discount rate used in the base case calculation and should be considered. Using a 4% discount rate for costs and 2% for QALYS the ICER of pegunigalsidase alfa vs no treatment amounted to 1 355 780 DKK/QALY gained.

11. List of experts

Ulla Feldt-Rasmussen, MD, DMSc

Professor, Senior Consultant Medical Endocrinology

Chief of Endocrine Research laboratory 2131/2

Chief of National Expert Fabry Center

Department of Endocrinology and Metabolism

Rigshospitalet, Copenhagen University Hospital

12. References

Amicus Therapeutics Europe Limited. 2017. *Migalastat product monograph* [Online]. Available: https://pdf.hres.ca/dpd_pm/00041104.PDF [Accessed 6 April 2020].

Amicus Therapeutics Europe Limited. 2019. Galafold 123 mg hard capsules *Summary of product characteristics.*

Amodio, F., Caiazza, M., Monda, E., Rubino, M., Capodicasa, L., Chiosi, F., Simonelli, V., Dongiglio, F., Fimiani, F., Pepe, N., Chimenti, C., Calabro, P. & Limongelli, G. 2022. An Overview of Molecular Mechanisms in Fabry Disease. *Biomolecules,* 12.

Arends, M., Hollak, C. E. & Biegstraaten, M. 2015. Quality of life in patients with Fabry disease: a systematic review of the literature. *Orphanet J Rare Dis,* 10**,** 77.

Arends, M., Korver, S., Hughes, D. A., Mehta, A., Hollak, C. E. M. & Biegstraaten, M. 2018. Phenotype, disease severity and pain are major determinants of quality of life in Fabry disease: results from a large multicenter cohort study. *J Inherit Metab Dis,* 41**,** 141-149.

Banikazemi, M., Bultas, J., Waldek, S., Wilcox, W. R., Whitley, C. B., Mcdonald, M., Finkel, R., Packman, S., Bichet, D. G., Warnock, D. G. & Desnick, R. J. 2007. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med,* 146**,** 77-86.

Barba-Romero, M. A., Serena, J., Puig, J. M., Valverde, C. V., Climent, V., Herrero, J. A., Huertas, R. & Torra, R. 2019. Clinical profile of women diagnosed with Fabry disease non receiving enzyme replacement therapy. *Med Clin (Barc),* 153**,** 47-55.

Beck, M. 2006. The Mainz Severity Score Index (MSSI): development and validation of a system for scoring the signs and symptoms of Fabry disease. *Acta Paediatr Suppl,* 95**,** 43-6.

Bénichou, B., Goyal S Fau - Sung, C., Sung C Fau - Norfleet, A. M., Norfleet Am Fau - O'brien, F. & O'brien, F. 2009. 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,* 96.

Biegstraaten, M., Arngrimsson, R., Barbey, F., Boks, L., Cecchi, F., Deegan, P. B., Feldt-Rasmussen, U., Geberhiwot, T., Germain, D. P., Hendriksz, C., Hughes, D. A., Kantola, I., Karabul, N., Lavery, C., Linthorst, G. E., Mehta, A., Van De Mheen, E., Oliveira, J. P., Parini, R., Ramaswami, U., Rudnicki, M., Serra, A., Sommer, C., Sunder-Plassmann, G., Svarstad, E., Sweeb, A., Terryn, W., Tylki-Szymanska, A., Tondel, C., Vujkovac, B., Weidemann, F., Wijburg, F. A., Woolfson, P. & Hollak, C. E. 2015. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet J Rare Dis,* 10**,** 36.

Bouwman, M. G., Rombach, S. M., Schenk, E., Sweeb, A., Wijburg, F. A., Hollak, C. E. & Linthorst, G. E. 2012. Prevalence of symptoms in female Fabry disease patients: a case-control survey. *J Inherit Metab Dis,* 35**,** 891-8.

Burstrom, K., Johannesson, M. & Diderichsen, F. 2001. Swedish population health-related quality of life results using the EQ-5D. *Qual Life Res,* 10**,** 621-35.

Cadth 2018. CADTH COMMON DRUG REVIEW – MIGALASTAT.

Cairns, T., Muntze, J., Gernert, J., Spingler, L., Nordbeck, P. & Wanner, C. 2018. Hot topics in Fabry disease. *Postgrad Med J,* 94**,** 709-713.

Chiesi 2015. PB-102-F02: An Extension of Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 38 Weeks (9 Months) to Adult Fabry Patients. *Clinical study protocol.*

Chiesi 2016. PB-102-F03: A Multi Center Extension Study of PRX-102 Administered by Intravenous Infusions Every 2 Weeks for up to 60 Months to Adult Fabry Patients. *Clinical study protocol.*

Chiesi 2017a. PB-102-F01/PB-102-F02: CSR data table - 14.2.2.3.1.

Chiesi 2017b. PB-102-F01/PB-102-F02: CSR data table - 14.2.2.3.1.1.

Chiesi 2017c. PB-102-F01/PB-102-F02: CSR data table - 14.2.2.9.1.

Chiesi 2017d. PB-102-F01: A Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of PRX-102 Administered by Intravenous Infusion Every 2 Weeks for 12 Weeks to Adult Fabry Patients. *Clinical study report.*

Chiesi 2017e. Protocol 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. *Clinical study protocol.*

Chiesi 2017f. Protocol PB-102-F50: A Phase 3, Open Label, Switch Over Study to Assess the Safety, Efficacy and Pharmacokinetics of pegunigalsidase alfa (PRX-102) 2 mg/kg Administered by Intravenous Infusion Every 4 Weeks for 52 weeks in Patients with Fabry Disease Currently Treated with Enzyme Replacement Therapy: Fabrazyme® (agalsidase beta) or Replagal™ (agalsidase alfa). *Clinical study protocol.*

Chiesi 2018. Accelerating CHF 6657 and Chiesi in Fabry.

Chiesi 2020a. PB-102-F03 clinical study report: A Multi Center Extension Study of PRX-102 Administered by Intravenous Infusions Every 2 Weeks for up to 60 Months to Adult Fabry Patients. *Clinical study report.*

Chiesi 2020b. PB-102-F30 Clinical study report: An Open Label Study to Assess the Safety and Efficacy of PRX-102 in Patients with Fabry Disease Currently Treated With REPLAGAL® (Agalsidase Alfa). *Clinical study report.*

Chiesi 2020c. PB-102-F30: An Open Label Study to Assess the Safety and Efficacy of PRX-102 in Patients with Fabry Disease Currently Treated With REPLAGAL® (Agalsidase Alfa). *Clinical study report.*

Chiesi 2021. PB-102-F50: A Phase 3, Open Label, Switch Over Study to Assess the Safety, Efficacy and Pharmacokinetics of Pegunigalsidase Alfa (PRX-102) 2.0 mg/kg Administered by Intravenous Infusion Every 4 Weeks for 52 Weeks in Patients with Fabry Disease Currently Treated With Enzyme Replacement Therapy: Fabrazyme® (Agalsidase Beta) or Replagal™ (Agalsidase Alfa). Clinical study report.

Chiesi 2022a. Internal information.

Chiesi 2022b. Marketing deck 2022_02_Fabry disease and PRX-102.

Chiesi 2022c. 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 (The BALANCE Study), in Clinical Study Report.

Chiesi 2022d. PB-102-F51: Open Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegunigalsidase Alfa (PRX-102) 2 mg/kg Administered by Intravenous Infusion Every 4 Weeks in Patients with Fabry Disease. Clinical study protocol.

Chiesi 2022e. 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. Clinical study protocol.2022.

Chiesi. 2022f. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Topline Results from the 24-Month Phase III BALANCE Clinical Trial of PRX-102 for the Treatment of Fabry Disease. Available: https://www.chiesi.com/en/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-topline-results-from-the-24-month-phase-iii-balance-clinical-trial-of-prx-102-for-the-treatment-of-fabry-disease/.

Chiesi. 2023a. *Elfabrio. Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/elfabrio-epar-product-information_en.pdf [Accessed 12 May 2023].

Chiesi 2023b. Nordic clinical expert interview. *Data on file*.

Chimenti, C., Nencini, P., Pieruzzi, F., Feriozzi, S., Mignani, R., Pieroni, M., Pisani, A. & Group, G. W. 2020. The GALA project: practical recommendations for the use of migalastat in clinical practice on the basis of a structured survey among Italian experts. *Orphanet J Rare Dis,* 15**,** 86.

Colon, C., Ortolano, S., Melcon-Crespo, C., Alvarez, J. V., Lopez-Suarez, O. E., Couce, M. L. & Fernández-Lorenzo, J. R. 2017. Newborn screening for Fabry disease in the north-west of Spain. *European Journal of Pediatrics,* 176**,** 1075-1081.

Connock, M., Juarez-Garcia, A., Frew, E., Mans, A., Dretzke, J., Fry-Smith, A. & Moore, D. 2006. A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1. *Health Technol Assess,* 10**,** iii-iv, ix-113.

Danmarks Statistik. 2023a. *Nettoprisindeks* [Online]. Available: https://www.dst.dk/da/Statistik/emner/oekonomi/prisindeks/nettoprisindeks [Accessed 19 April 2023].

Danmarks Statistik. 2023b. *Statistikbanken* [Online]. Available: https://statistikbanken.dk/statbank5a/default.asp?w=1280 [Accessed 19 April 2023].

El-Abassi, R., Singhal, D. & England, J. D. 2014. Fabry's disease. *J Neurol Sci,* 344**,** 5-19.

Elfabrio Smpc. 2022. *Summary of Product Characteristics* [Online]. [Accessed].

Eng, C., Banikazemi, M., Gordon, E., Goldman, M., Phelps, R., Kim, L., Gass, A. & Winston, J. 2001a. A Phase 1/2 Clinical Trial of Enzyme Replacement in Fabry Disease: Pharmacokinetic, Substrate Clearance, and Safety Studies. *Am. J. Hum. Genet.,* 68**,** 711–722.

Eng, C., Guffon, N., Wilcox, W. R., Germain, D. P., Lee, P., Waldek, S., Caplan, L. & Linthorst, G. 2001b. Safety and efficacy of recombinant human a-galactosidase a replacement therapy in fabry's disease. *N. Engl. J. Med.,* 345.

Eng, C. M., Fletcher, J., Wilcox, W. R., Waldek, S., Scott, C. R., Sillence, D. O., Breunig, F., Charrow, J., Germain, D. P., Nicholls, K. & Banikazemi, M. 2007. Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *Journal of Inherited Metabolic Disease,* 30**,** 184-192.

European Medicines Agency. 2008. *Replagal(R) Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/replagal [Accessed].

European Medicines Agency. 2009a. *Fabrazyme(R) Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/fabrazyme [Accessed].

European Medicines Agency. 2009b. *Supply shortages of Cerezyme and Fabrazyme - priority access for patients most in need of treatment recommended* [Online]. Available: https://www.ema.europa.eu/en/news/supply-shortages-cerezyme-fabrazyme-priority-access-patients-most-need-treatment-recommended [Accessed 4 April 2023].

European Medicines Agency. 2016. *Galafold(R) Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/galafold [Accessed].

European Medicines Agency (Ema). 2014. *Relevant sources for orphan disease prevalence data* [Online]. Available: https://www.ema.europa.eu/en/documents/other/relevant-sources-orphan-disease-prevalence-data_en.pdf [Accessed 26 February 2020].

Fabrazyme Smpc. 2020. *Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/fabrazyme-epar-product-information_en.pdf [Accessed].

Fabry Institute. 2021. *Striving for Organ Protection - Fabry Disease: Renal considerations for diagnosis* [Online]. Available: https://www.fabry-institute.com/ [Accessed].

Garner, K. K., Pomeroy, W. & Arnold, J. J. 2017. Exercise Stress Testing: Indications and Common Questions. *Am Fam Physician,* 96**,** 293-299.

Genzyme Corporation 2001. Fabrazyme® (agalsidase beta). *Summary of product characteristics.*

Germain, D. P. 2012. *Fabry disease* [Online]. Available: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=324 [Accessed 26 February 2020].

Guest, J. F., Jenssen, T., Houge, G., Aaseboe, W., Tondel, C. & Svarstad, E. 2010. Modelling the resource implications of managing adults with Fabry disease in Norway favours home infusion. *Eur J Clin Invest,* 40**,** 1104-12.

Hollak, C. E. & Linthorst, G. E. 2009. Immune response to enzyme replacement therapy in Fabry disease: impact on clinical outcome?

Hopkins, P. V., Klug, T., Rogers, S. V. & Kiesling, J. 2017. State-wide newborn screening for four lysosomal diseases reveals high incidence rate for Pompe and Fabry diseases. *Molecular Genetics and Metabolism,* 120**,** S66.

Hughes, D., Nicholls, K., Shankar, S. P., Sunder-Plassmann, G. & Koeller, D. 2017. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet,* 54**,** 288–296.

Hughes, D. A., Nicholls, K., Sunder-Plassmann, G., Jovanovic, A., Feldt-Rasmussen, U., Schiffmann, R., Giugliani, R., Jain, V., Viereck, C., Castelli, J. P., Skuban, N., Barth, J. A. & Bichet, D. G. 2019. Safety of switching to Migalastat from enzyme replacement therapy in Fabry disease: Experience from the Phase 3 ATTRACT study. *Am J Med Genet A,* 179**,** 1069-1073.

Hult, M., Darin, N., Döbeln, U. V. & Månsson, J. E. 2014. Epidemiology of lysosomal storage diseases in Sweden. *Acta Paediatrica, International Journal of Paediatrics,* 103**,** 1258-1263.

Ivleva, A., Weith, E., Mehta, A. & Hughes, D. A. 2018. The Influence of Patient-Reported Joint Manifestations on Quality of Life in Fabry Patients. *JIMD Rep,* 41**,** 37-45.

Kawel-Boehm, N., Maceira, A., Valsangiacomo-Buechel, E. R., Vogel-Claussen, J., Turkbey, E. B., Williams, R., Plein, S., Tee, M., Eng, J. & Bluemke, D. A. 2015. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson,* 17**,** 29.

Kdigo 2012. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *International society of haematology,* 2.

Kidney Disease: Improving Global Outcomes. 2012. *KDIGO Clinical Practice Guideline for Acute Kidney Injury* [Online]. Available: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf [Accessed 20 April 2023].

Kim, J. H., Lee, B. H., Hyang Cho, J., Kang, E., Choi, J. H., Kim, G. H. & Yoo, H. W. 2016. Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes. *J Hum Genet,* 61**,** 923-929.

Kizhner, T., Azulay, Y., Hainrichson, M., Tekoah, Y., Arvatz, G., Shulman, A., Ruderfer, I., Aviezer, D. & Shaaltiel, Y. 2015. Characterization of a chemically modified plant cell culture expressed human α-Galactosidase-A enzyme for treatment of Fabry disease. *Molecular Genetics and Metabolism,* 114**,** 259–267.

Kok, K., Zwiers, K. C., Boot, R. G., Overkleeft, H. S., Aerts, J. & Artola, M. 2021. Fabry Disease: Molecular Basis, Pathophysiology, Diagnostics and Potential Therapeutic Directions. *Biomolecules,* 11.

Lægemiddelsstyrelsen. 2023. *Medicinpriser, AIP* [Online]. Available: http://www.medicinpriser.dk/default.aspx [Accessed 31 Jan 2023].

Laney, D. A., Bennett, R. L., Clarke, V., Fox, A., Hopkin, R. J., Johnson, J., O'rourke, E., Sims, K. & Walter, G. 2013. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. *J Genet Couns,* 22**,** 555-64.

Langley, P. C., Van Litsenburg, C., Cappelleri, J. C. & Carroll, D. 2013. The burden associated with neuropathic pain in Western Europe. *J Med Econ,* 16**,** 85-95.

Lenders, M. & Brand, E. 2018. Effects of Enzyme Replacement Therapy and Antidrug Antibodies in Patients with Fabry Disease. *J Am Soc Nephrol,* 29**,** 2265-2278.

Lenders, M. & Brand, E. 2021. Fabry Disease: The Current Treatment Landscape. *Drugs,* 81**,** 635-645.

Lenders, M., Neusser, L. P., Rudnicki, M., Nordbeck, P., Canaan-Kuhl, S., Nowak, A., Cybulla, M., Schmitz, B., Lukas, J., Wanner, C., Brand, S. M. & Brand, E. 2018. Dose-Dependent Effect of Enzyme Replacement

Therapy on Neutralizing Antidrug Antibody Titers and Clinical Outcome in Patients with Fabry Disease. *J Am Soc Nephrol,* 29**,** 2879-2889.

Lenders, M., Stypmann, J., Duning, T., Schmitz, B., Brand, S. M. & Brand, E. 2016. Serum-Mediated Inhibition of Enzyme Replacement Therapy in Fabry Disease. *J Am Soc Nephrol,* 27**,** 256-64.

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., Coresh, J. & Ckd, E. P. I. 2009. A new equation to estimate glomerular filtration rate. *Ann Intern Med,* 150**,** 604-12.

Linthorst, G. E., Hollak, C. E., Donker-Koopman, W. E., Strijland, A. & Aerts, J. M. 2004. Enzyme therapy for Fabry disease: neutralizing antibodies toward agalsidase alpha and beta. *Kidney Int,* 66**,** 1589-95.

Macdermot, K. D., Holmes, A. & Miners, A. H. 2001a. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet,* 38**,** 769-75.

Macdermot, K. D., Holmes, A. & Miners, A. H. 2001b. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet,* 38**,** 750-60.

Macrotrends. 2023. *Denmark death rate 1959-2023* [Online]. Available: https://www.macrotrends.net/countries/DNK/denmark/death-rate [Accessed 18 April 2023].

Mauhin, W., Lidove, O., Amelin, D., Lamari, F., Caillaud, C., Mingozzi, F., Dzangué-Tchoupou, G., Arouche-Delaperche, L., Douillard, C., Dussol, B., Leguy-Seguin, V., D'halluin, P., Noel, E., Zenone, T., Matignon, M., Maillot, F., Ly, K. H., Besson, G., Willems, M., Labombarda, F., Masseau, A., Lavigne, C., Froissart, R., Lacombe, D., Ziza, J. M., Hachulla, E. & Benveniste, O. 2018. Deep characterization of the anti-drug antibodies developed in Fabry disease patients, a prospective analysis from the French multicenter cohort FFABRY. *Orphanet J Rare Dis,* 13**,** 127.

Medicinrådet. 2023. *Medicinrådets anbefaling vedr. imlifidase til nyretransplantation* [Online]. Available: https://medicinraadet.dk/media/f01dfede/medicinr%C3%A5dets-anbefaling-vedr-imlifidase-til-nyretransplantation-vers-1-0-x.pdf [Accessed 19 April 2023].

Mehta, A., Clarke, J. T. R., Giugliani, R., Elliott, P., Linhart, A., Beck, M. & Sunder-Plassmann, G. 2009. Natural course of Fabry disease: Changing pattern of causes of death in FOS - Fabry Outcome Survey. *Journal of Medical Genetics,* 46**,** 548-552.

Miners, A. H., Holmes, A., Sherr, L., Jenkinson, C. & Macdermot, K. D. 2002. Assessment of health-related quality-of-life in males with Anderson Fabry Disease before therapeutic intervention. *Quality of Life Research,* 11.

Moore, D. F., Ries, M., Forget, E. L. & Schiffmann, R. 2007. Enzyme replacement therapy in orphan and ultra-orphan diseases: The limitations of standard economic metrics as exemplified by Fabry-Anderson disease. *PharmacoEconomics,* 25**,** 201-208.

Muntze, J., Gensler, D., Maniuc, O., Liu, D., Cairns, T., Oder, D., Hu, K., Lorenz, K., Frantz, S., Wanner, C. & Nordbeck, P. 2019. Oral Chaperone Therapy Migalastat for Treating Fabry Disease: Enzymatic Response and Serum Biomarker Changes After 1 Year. *Clin Pharmacol Ther,* 105**,** 1224-1233.

National Institute for Health and Care Excellence (Nice). 2016. Highly Specialised Technology Evaluation Migalastat for treating Fabry disease [ID868],. Available: https://www.nice.org.uk/guidance/hst4/documents/committee-papers.

Oanda. 2023. *Currency converter* [Online]. Available: https://www.oanda.com/currency-converter/en/ [Accessed 19 April 2023].

Orphanet. 2022. *Fabry disease* [Online]. Available: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=324 [Accessed].

Ortiz, A., Germain, D. P., Desnick, R. J., Politei, J., Mauer, M., Burlina, A., Eng, C., Hopkin, R. J., Laney, D., Linhart, A., Waldek, S., Wallace, E., Weidemann, F. & Wilcox, W. R. 2018. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab,* 123**,** 416-427.

Replagal® Smpc. 2020. *Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/replagal-epar-product-information_en-0.pdf [Accessed].

Rombach, S., Hollak, C., Linthorst, G. & Dijkgraaf, M. 2013a. Cost-effectiveness of enzyme replacement therapy for Fabry disease. *Orphanet Journal of Rare Diseases XYR: 2013,* 8**,** 29 XPT: Journal article XST: .

Rombach, S. M., Aerts, J. M., Poorthuis, B. J., Groener, J. E., Donker-Koopman, W., Hendriks, E., Mirzaian, M., Kuiper, S., Wijburg, F. A., Hollak, C. E. & Linthorst, G. E. 2012. 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,* 7**,** e47805.

Rombach, S. M., Hollak, C. E. M., Linthorst, G. E. & Dijkgraaf, M. G. W. 2013b. Cost-effectiveness of enzyme replacement therapy for Fabry disease. *Orphanet Journal of Rare Diseases,* 8**,** 29.

Ruderfer, I., Shulman, A., Kizhner, T., Azulay, Y., Nataf, Y., Tekoah, Y. & Shaaltiel, Y. 2018. Development and Analytical Characterization of Pegunigalsidase Alfa, a Chemically Cross-Linked Plant Recombinant Human alpha-Galactosidase-A for Treatment of Fabry Disease. *Bioconjug Chem,* 29**,** 1630-1639.

Schiffmann, R., Goker-Alpan, O., Holida, M., Giraldo, P., Barisoni, L., Colvin, R. B., Jennette, C. J., Maegawa, G., Boyadjiev, S. A., Gonzalez, D., Nicholls, K., Tuffaha, A., Atta, M. G., Rup, B., Charney, M. R., Paz, A., Szlaifer, M., Alon, S., Brill-Almon, E., Chertkoff, R. & Hughes, D. 2019. 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,* 42**,** 534-544.

Schiffmann, R., Ries, M., Timmons, M., Flaherty, J. T. & Brady, R. O. 2006. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. *Nephrol Dial Transplant,* 21**,** 345-54.

Schiffmann, R., Warnock, D. G., Banikazemi, M., Bultas, J., Linthorst, G. E., Packman, S., Sorensen, S. A., Wilcox, W. R. & Desnick, R. J. 2009. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrology Dialysis Transplantation,* 24**,** 2102-2111.

Shire 2001. Replagal® (agalsidase alfa). *Summary of product characteristics.*

Smid, B. E., Hoogendijk, S. L., Wijburg, F. A., Hollak, C. E. & Linthorst, G. E. 2013. A revised home treatment algorithm for Fabry disease: influence of antibody formation. *Mol Genet Metab,* 108**,** 132-7.

Smid, B. E., Rombach, S. M., Aerts, J. M., Kuiper, S., Mirzaian, M., Overkleeft, H. S., Poorthuis, B. J., Hollak, C. E., Groener, J. E. & Linthorst, G. E. 2011. Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients. *Orphanet J Rare Dis,* 6**,** 69.

Stalhammar, J., Stern, L., Linder, R., Sherman, S., Parikh, R., Ariely, R. & Wikstrom, G. 2012. Resource utilization and cost of heart failure associated with reduced ejection fraction in Swedish patients. *J Med Econ,* 15**,** 938-46.

Sunder-Plassmann G. 2006. Renal manifestations of Fabry disease. *In:* MEHTA, A., BECK, M. & SUNDER-PLASSMANN, G. (eds.) *Fabry Disease: Perspectives from 5 Years of FOS.* Oxford: Oxford Pharmagenesis.

Sundhedsdatastyrelsen. 2023. *DRG-takster 2023* [Online]. Available: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2023 [Accessed 19 April 2023].

Van Der Veen, S. J., Van Kuilenburg, A. B. P., Hollak, C. E. M., Kaijen, P. H. P., Voorberg, J. & Langeveld, M. 2019. Antibodies against recombinant alpha-galactosidase A in Fabry disease: Subclass analysis and impact on response to treatment. *Mol Genet Metab,* 126**,** 162-168.

Vedder, A. C., Breunig F Fau - Donker-Koopman, W. E., Donker-Koopman We Fau - Mills, K., Mills K Fau - Young, E., Young E Fau - Winchester, B., Winchester B Fau - Ten Berge, I. J. M., Ten Berge Ij Fau - Groener, J. E. M., Groener Je Fau - Aerts, J. M. F. G., Aerts Jm Fau - Wanner, C., Wanner C Fau - Hollak, C. E. M. & Hollak, C. E. 2008. Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3. *Mol Genet Metab,* 94.

Vedder, A. C., Linthorst, G. E., Van Breemen, M. J., Groener, J. E., Bemelman, F. J., Strijland, A., Mannens, M. M., Aerts, J. M. & Hollak, C. E. 2007. The Dutch Fabry cohort: diversity of clinical manifestations and Gb3 levels. *J Inherit Metab Dis,* 30**,** 68-78.

Waldek, S., Patel, M. R., Banikazemi, M., Lemay, R. & Lee, P. 2009. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. *Genet Med,* 11**,** 790-6.

Wallace, E., Goker-Alpan, O. & Alon, S. 2022. Safety and Efficacy of Pegunigalsidase Alfa vs Agalsidase Beta on Renal Function in Fabry Disease: 24-Month Results from the Phase III Randomized, Double-blind, BALANCE Study. *Data on file*.

Wanner, C., Arad, M., Baron, R., Burlina, A., Elliott, P. M., Feldt-Rasmussen, U., Fomin, V. V., Germain, D. P., Hughes, D. A., Jovanovic, A., Kantola, I., Linhart, A., Mignani, R., Monserrat, L., Namdar, M., Nowak, A., Oliveira, J. P., Ortiz, A., Pieroni, M., Spada, M., Tylki-Szymanska, A., Tondel, C., Viana-Baptista, M., Weidemann, F. & Hilz, M. J. 2018. European expert consensus statement on therapeutic goals in Fabry disease. *Mol Genet Metab,* 124**,** 189-203.

Wilcox, W. R., Linthorst, G. E., Germain, D. P., Feldt-Rasmussen, U., Waldek, S., Richards, S. M., Beitner-Johnson, D., Cizmarik, M., Cole, J. A., Kingma, W. & Warnock, D. G. 2012. Anti-α-galactosidase A antibody response to agalsidase beta treatment: data from the Fabry Registry. *Mol Genet Metab,* 105**,** 443-9.

Wolk, M. J., Bailey, S. R., Doherty, J. U., Douglas, P. S., Hendel, R. C., Kramer, C. M., Min, J. K., Patel, M. R., Rosenbaum, L., Shaw, L. J., Stainback, R. F., Allen, J. M. & American College of Cardiology Foundation Appropriate Use Criteria Task, F. 2014. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task For ce, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol,* 63**,** 380-406.

Wyatt, K., Henley, W., Anderson, L., Anderson, R., Nikolaou, V., Stein, K., Klinger, L., Hughes, D., Waldek, S., Lachmann, R., Mehta, A., Vellodi, A. & Logan, S. 2012. The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: A longitudinal cohort study of people with lysosomal storage disorders. *Health Technology Assessment,* 16**,** 1-566.

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

No description of the literature search is necessary due to the presence of a head-to-head clinical trial.

Appendix B Main characteristics of included studies

Phase III BALANCE study (PB-102-F20)

Table 36: BALANCE (PB-102-F20)

BALANCE (PB-102-F20)	NCT02795676
Objective	To assess the efficacy and safety of pegunigalsidase alfa compared with agalsidase beta in adult Fabry disease patients experiencing significant kidney function deterioration while receiving treatment with agalsidase beta for at least 1 year (and received a stable dose for at least 6 months).
Publications – title, author, journal, year	An abstract of the BALANE study was presented at WORLD symposia 2023 (Wallace E., et al 2022). Estimated publication date of full results is Q3-Q4 2023.
Study type and design	A Phase III, randomized, double-blind, multinational, active-controlled study. A fixed block randomization list (52 blocks of 3 per stratum), stratified at baseline by UPCR (less than vs. equal to or greater than 1 gr/gr), was generated with a 2:1 randomization (pegunigalsidase alfa: agalsidase beta) and incorporated into the Target e*CRF system. Once patient eligibility was confirmed by the sponsor's Medical Monitor, the system generated a subject randomization ID number. The study sample size was planned to demonstrate non-inferiority after 1 year of treatment (interim analysis) and non-inferiority after 2 years of treatment (final analysis). To allow for a dropout rate as high as 15%, it was planned for approximately 78 patients to be randomized: approximately 52 patients to the pegunigalsidase alfa arm and approximately 26 to the agalsidase beta arm. With these assumptions, power for showing non-inferiority would be at least 90%. Since pegunigalsidase alfa and agalsidase beta differ in appearance and packaging, the individual doses for infusion were prepared by an unblinded pharmacist or nurse at the site, resulting in identical infusion bag appearance and blinded labelling prior to administration. Both the patients and the staff members administering the treatments were blinded as to what the infusion bag contained. Participants that successfully completed the study were invited to the open-label extension study PB-102-F60.
Sample size (n)	N=78 (53 assigned to pegunigalsidase alfa, 25 to agalsidase beta)
Main inclusion and exclusion criteria	**Inclusion criteria:** • Symptomatic adult Fabry patients aged 18 to 60 years • Males: plasma and/or leukocyte α-galactosidase activity (by activity assay) <30% mean normal levels and one or more of the characteristic features of Fabry disease: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations, a first-degree male

	relative with Fabry disease, and one or more of the characteristic features of Fabry disease: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • eGFR at screening of ≥40 – ≤120 ml/min/1.73 m^2 by CKD-EPI equation • Linear negative slope of eGFR of ≥2 mL/min/1.73 m^2/year based on at least three serum creatinine values over approximately 1 year (range of 9 to 18 months, including the value obtained at the screening visit) • Treatment with a dose of 1 mg/kg agalsidase beta per infusion E2W for at least 1 year and at least 80% of 13 (10.4) mg/kg total dose over the last 6 months • Patients whose partners are of child-bearing potential who agree to use medically accepted methods of contraception, not including the rhythm method **Exclusion criteria:** • History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa • Known non-pathogenic Fabry mutations (polymorphism) • History of renal dialysis or transplantation • History of acute kidney injury in the 12 months before screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischaemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotaemia, and acute postrenal obstructive nephropathy) • ACE inhibitor or ARB therapy initiated, or dose changed in the 4 weeks before screening • eGFR at screening of ≥91 – ≤120 ml/min/1.73 m^2, having a historical eGFR value of >120 ml/min/1.73 m^2 (during the 9 to 18 months before screening) • UPCR >0.5 g/g and not treated with an ACE inhibitor or ARB • Known history of hypersensitivity to a gadolinium-based contrast agent that is not managed with the use of premedication • Females who are pregnant, planning to become pregnant during the study, or are breastfeeding • Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before screening • Congestive heart failure NYHA Class IV • Cerebrovascular event (stroke, transient ischaemic attack) in the 6-month period before screening • Patients with any medical, emotional, behavioural, or psychological condition that may interfere with the patient's compliance to adhere to study requirements (as determined by the investigator and/or medical director)
Intervention	Pegunigalsidase alfa (pegunigalsidase alfa) 1.0 mg/kg E2W (n=53)
Comparator(s)	Agalsidase beta 1.0 mg/kg E2W (n=25)
Follow-up time	24 months

Is the study used in the health economic model?	No The study showed non-inferiority of pegunigalsidase alfa vs agalsidase alfa, hence a cost-minimization approach was chosen
Primary, secondary, and exploratory endpoints	**Efficacy measures:** • Annualized change (slope) in $eGFR_{CKD\text{-}EPI\ 2009}$ (primary endpoint) • LVMi (g/m^2) by MRI • Plasma lyso-Gb_3 • Plasma Gb_3 • Urine lyso-Gb_3 • UPCR – spot urine test • Frequency of pain medication use • Exercise tolerance (stress test) • Short form BPI • MSSI • 5-level EQ-5D® (EQ-5D-5L) **Pharmacokinetic parameters in a subset of 30 patients:** • C_{max} • T_{max} • $T_{1/2}$ • AUC (area under the curve)$_{0\text{-}\infty}$ **Safety measures:** • Frequency, severity, and duration of TEAEs • Clinically significant laboratory abnormalities, specifically: – Haematology: total white blood cell count, haemoglobin, and platelets – Coagulation profile: PT and PTT – Biochemistry: sodium, potassium, glucose, blood urea nitrogen, creatinine, cystatin C, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, and creatine phosphokinase – Vitamin D – Urinalysis: dipstick for the presence of blood, glucose, ketones, and protein • ECG changes from baseline • Physical examination findings • Injection site reactions following study drug administration • Anti-pegunigalsidase alfa antibodies were assessed before dosing with pegunigalsidase alfa at baseline (Visit 1), 2 and 4 weeks after first infusion, and then every month for the first 6 months, and every 3 months until study end – Anti-pegunigalsidase alfa IgG antibodies also assessed for patients continuing treatment in an extension study – For patients who discontinue treatment with pegunigalsidase alfa, anti-pegunigalsidase alfa antibodies were assessed at 1 and 3 months after their last infusion • Anti-pegunigalsidase alfa IgE antibodies were assessed in events of hypersensitivity reaction following sponsor request • Ability to taper off infusion premedication at the start of the study (throughout the first 3 months of the study)

	• Requirement for premedication use overall to manage infusion reactions.
Method of analysis	The primary endpoint – the comparison of the median annualized change (slope) in $eGFR_{CKD-EPI}$ equation 2009 between treatment groups using a 2-stage model with quantile regression. The primary analysis was performed on the ITT population. Analyses were also made on the PP and Safety populations. The prespecified non-inferiority margin for primary endpoint is -3.0 mL/min/1.73m^2/year.
Subgroup analyses	For the primary endpoint and for selected additional efficacy and safety endpoints, prespecified subgroup analyses were performed for • Gender (male/female) • ADA status at baseline (positive/negative) • FD classification (classic/non-classic) • Baseline eGFR category (≤60, >60 ≤90, >90) • Baseline eGFR slope category (≤-5; >-5) • ACEi or ARB treatment at baseline (yes/no) • Region (US/ex-US) • UPCR category at baseline (≤0.5, >0.5 <1, ≥1)
Other relevant information	The primary analysis and the sensitivity analyses assume that the missing data were Missing At Random (MAR). Multiple Imputation (MI) was used to assess the impact of missing data. To this end MI under the MAR assumption was conducted for patients who early terminated. Missing data were imputed within each treatment arm.

Key: ACE, angiotensin converting enzyme; ADAs, anti-drug antibodies; ARB, angiotensin receptor blocker; BPI, Brief Pain Inventory; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQoL-5 Dimension-3 level; FD, Fabry Disease; Gb_3, globotriaosylceramide; IgE, immunoglobulin E; IgG, immunoglobulin G; LLN, lower limit of normal; LVMi, left ventricular mass index; lyso-Gb_3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; NYHA, New York Heart Association; PT, prothrombin time; PTT, partial thromboplastin time; TEAEs, treatment-emergent adverse events; UPCR, urine protein/creatine ratio.

Source: BALANCE study protocol 2017 (Chiesi 2017e)

Phase III BRIDGE study (PB-102-F30)

Table 37: BRIDGE (PB-102-F30)

BRIDGE (PB-102-F30)	NCT03018730
Objective	The BRIDGE study (PB-102-F30; NCT03018730) was designed to assess the safety and efficacy of pegunigalsidase alfa in adults with Fabry disease who were previously treated with agalsidase alfa for at least 2 years
Publications – title, author, journal, year	An abstract of the BRIDGE study was presented at WORLD symposia 2021 (Linhart et al. 2021). Estimated publication date of full results is Q3 2023.
Study type and design	The BRIDGE trial is a Phase III, open-label, multinational, switchover study. After a 3-month screening period, eligible patients were switched from their current agalsidase alfa treatment to receive IV infusions of pegunigalsidase alfa 1 mg/kg E2W for 12 months. Of note, female patients could only contribute 25% of the total trial

	population. After completion, patients were offered enrolment in the open-label extension study, PB-102-F60
Sample size (n)	22 patients (15 males, 7 females)
Main inclusion and exclusion criteria	**Inclusion criteria:** • Symptomatic adult Fabry patients aged 18 to 60 years • Males: plasma and/or leukocyte α-galactosidase activity (by activity assay) <LLN according to laboratory range and one or more of the characteristic features of Fabry disease: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations, a first-degree male relative with Fabry disease and one or more of the characteristic features of Fabry disease: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • Treatment with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months • eGFR ≥ 40 ml/min/1.73 m^2 by CKD-EPI equation • Availability of at least two historical serum creatinine evaluations since starting agalsidase alfa treatment and for not more than 2 years • Patients whose partners are of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method **Exclusion criteria:** • History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa • History of renal dialysis or transplantation • History of acute kidney injury in the 12 months before screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischaemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotaemia, and acute postrenal obstructive nephropathy) • ACE inhibitor or ARB therapy initiated, or dose changed in the 4 weeks before screening • UPCR >0.5 g/g and not treated with an ACE inhibitor or ARB • Known history of hypersensitivity to a gadolinium-based contrast agent that is not managed with the use of premedication • Females who are pregnant, planning to become pregnant during the study, or are breastfeeding • Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before screening • Congestive heart failure NYHA Class IV • Cerebrovascular event (stroke, transient ischaemic attack) in the 6-month period before screening • Presence of any medical, emotional, behavioural, psychological condition that, in the judgement of the Investigator and/or

	Medical Monitor would interfere with the patient´s compliance with the requirements of the study
Intervention	All patients received IV infusions of pegunigalsidase alfa 1 mg/kg E2W
Comparator(s)	N/A
Follow-up time	12 months
Is the study used in the health economic model?	No, a cost-minimization approach was chosen
Primary, secondary, and exploratory endpoints	**Primary outcome measure:** • Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 (time frame: 12 months) **Efficacy measures:** • Mean annualized change in $eGFR_{CKD-EPI}$ • LVMi (g/m^2) preferably by MRI (echocardiogram can be used as an alternative) • Plasma lyso-Gb_3 • Plasma Gb_3 • Urine lyso-Gb_3 • UPCR (spot urine test) • Frequency of pain medication use • Exercise tolerance (stress test) • Short form BPI • MSSI • 5-level EQ-5D® (EQ-5D-5L) **Safety measures:** • Frequency, severity, and duration of TEAEs • Clinically significant laboratory abnormalities, specifically: – Haematology: total white blood cell count, haemoglobin, and platelets – Coagulation profile: PT and PTT – Biochemistry: sodium, potassium, glucose, blood urea nitrogen, creatinine, cystatin C, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, and creatine phosphokinase – Vitamin D – Urinalysis: dipstick for presence of blood, glucose, ketones, and protein • ECG changes from baseline • Physical examination findings • Injection site reactions following study drug administration • Anti-pegunigalsidase alfa antibodies were assessed before dosing with pegunigalsidase alfa at baseline (Visit 1), every month for the first 6 months, and every 3 months until study end – Anti-pegunigalsidase alfa antibodies also assessed for patients continuing treatment in an extension study – For patients who discontinue treatment with pegunigalsidase alfa, anti-pegunigalsidase alfa antibodies were assessed at 1 and 3 months after their last infusion

	• Anti-pegunigalsidase alfa IgE antibodies assessed in the event of a hypersensitivity reaction following a sponsor request • Ability to taper off infusion premedication at the start of the study • Requirement for premedication use overall to manage infusion reactions.
Method of analysis	Safety analysis was based on the Safety Population which included all 22 patients who received any dose of pegunigalsidase alfa in the study. The efficacy analysis was based on the Efficacy Population (EP) which included the 20 patients who had at least one visit with an efficacy evaluation after the first pegunigalsidase alfa infusion; the PPE population included 20 patients, that was defined as all patients who completed the 12-month treatment period with efficacy data available and with no major protocol violations, this population ended up to be identical with the EP.
Subgroup analyses	Subgroup analyses by gender and by treatment-emergent immunogenicity status were performed for the efficacy and safety endpoints.
Other relevant information	There was no imputation for missing efficacy and safety data, except for data associated to AE reporting. Missing data associated with AE reporting were treated as missing except for causality, severity (intensity), and outcome of an AE, for which a "worst case" approach was taken. Thus, if causality was missing, the AE was considered as related to PRX-102; if the severity was missing, the AE was considered as severe; and if the outcome was missing and the stop date not reported, the AE outcome was considered as not-recovered.

Key: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BPI, Brief Pain Inventory; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQoL-5 Dimension-5 level; Gb_3, globotriaosylceramide; IgE, immunoglobulin E; LLN, lower limit of normal; LVMi, left ventricular mass index; lyso-Gb_3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; NYHA, New York Heart Association; PPE, per protocol efficacy; PT, prothrombin time; PTT, partial thromboplastin time; TEAEs, treatment-emergent adverse events; UPCR, urine protein/creatine ratio.

Source: BRIDGE CSR 2020 (Chiesi 2022c)

Phase III BRIGHT study (PB-102-F50)

Table 38: BRIGHT (PB-102-F50)

BRIGHT (PB-102-F50)	NCT03180840
Objective	The BRIGHT study was designed to assess pharmacokinetics, safety, and efficacy of pegunigalsidase alfa in adults with Fabry disease who have been previously treated with either agalsidase alfa or agalsidase beta for at least 3 years, and on a stable dose (>80% labelled dose/kg) for at least 6 months.
Publications – title, author, journal, year	An abstract of the BRIGHT study was presented at the WORLD symposia 2022 (Holida et al. 2022).

	Estimated publication date is Q4 2023.
Study type and design	BRIGHT is a Phase III, open-label, multinational, switch-over study
Sample size (n)	30 patients (24 males, 6 females)
Main inclusion and exclusion criteria	**Inclusion criteria:** • Patients aged 18 to 60 years with a documented diagnosis of Fabry disease • Males: plasma and/or leukocyte α-galactosidase A activity (by activity assay) less than the lower limit of normal per laboratory reference range and one or more of the characteristic features of Fabry disease: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • Females: historical genetic test results consistent with Fabry mutations, or in the case of novel mutations, a first-degree male relative with Fabry disease, and one or more of the characteristic features of Fabry disease: – Neuropathic pain – Cornea verticillate – Clustered angiokeratoma • Treatment with agalsidase alfa or agalsidase beta for at least 3 years and on a stable dose (>80% labelled dose/kg) for at least the last 6 months • eGFR ≥30 mL/min/1.73 m^2 by CKD-EPI equation at screening visit • Availability of at least three historical serum creatinine evaluations since starting agalsidase alfa or agalsidase beta treatment and not more than 2 years • Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically accepted, highly effective method of contraception, including: combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence • Patients whose clinical condition, in the opinion of the Investigator, are suitable for treatment with ERT E4W **Exclusion criteria:** • History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa or agalsidase beta • History of renal dialysis or transplantation • Linear negative slope of eGFR of ≥2 mL/min/1.73 m^2 based on at least four serum creatinine values over approximately 2 years (including the value obtained at the screening visit) • History of acute kidney injury in the 12 months before screening, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischaemia, toxic injury);

	as well as extrarenal pathology (e.g., prerenal azotaemia, and acute post renal obstructive nephropathy) • ACE inhibitor or ARB therapy initiated, or dose changed in the 4 weeks before screening • UPCR at screening >0.5 g/g or mg/mg or 500 mg/g and not treated with an ACE inhibitor or ARB • Females who are pregnant, planning to become pregnant during the study, or are breastfeeding • Cardiovascular event (myocardial infarction, unstable angina) in the 6-month period before screening • Cerebrovascular event (stroke, transient ischaemic attack) in the 6-month period before screening • Presence of any medical, emotional, behavioural, 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
Intervention	Eligible patients were switched from their current ERT to receive IV infusions of pegunigalsidase alfa 2 mg/kg E4W for 12 months (or 14 infusions).
Comparator(s)	N/A
Follow-up time	52 weeks
Is the study used in the health economic model?	No, a cost-minimization approach was chosen
Primary, secondary, and exploratory endpoints	**Primary endpoint:** • Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 (Time frame: throughout the 52-week study) **Efficacy measures:** • $eGFR_{CKD-EPI}$ • LVMi (g/m^2) by echocardiogram • Plasma lyso-Gb_3 levels • Plasma Gb_3 levels • Urine lyso-Gb_3 • UPCR (spot urine test) • Exercise tolerance (stress test) • Short form BPI • MSSI • EQ-5D-3L • Pharmacokinetic parameters: • C_{max} • T_{max} • $T_{1/2}$ • AUC_{0-t} • $AUC_{0-\infty}$ **Safety measures:** • Changes from baseline in: o Clinical laboratory tests o Physical examination o Assessment of the injection site

	○ Electrocardiogram ○ TEAEs ○ Ability to taper off infusion premedication throughout the first 2 months of the study ○ Requirement for premedication use overall to manage infusion reactions ○ The presence of ADAs
Method of analysis	Efficacy analyses were made on the PPE population, whereas safety analyses were made on the safety population.
Subgroup analyses	Subgroup analyses were conducted based on baseline characteristics and demographics for selected efficacy and safety endpoints, chosen from the following list: gender, ADA status, Fabry disease classification, eGFR, previous ERT treatment, use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and hyperfiltration status (this last subgroup was added as a post-hoc analysis).
Other relevant information	The following rules were followed regarding imputations of incomplete or missing dates: • For calculation of age when Fabry therapy was first started, no imputation was done in case the year was missing, and for missing day and month of start of treatment of previous Fabry disease: o If only the day was missing, the middle of the month (i.e., 15th) was used; If both day and month were missing, the middle of the year (i.e., July 1st) was used; • For start dates of AKIs: o If month and year were available and day was missing, the 1st of the month was imputed; if the event was reported during the month of the first infusion, it was imputed to the date of the first infusion; o If the month was missing and year was available, then if the year was the same as the year of the first infusion, the date was considered as the date of the first infusion; otherwise, the date was set to January 1st; o If the year was missing, the date was imputed to the date of the first infusion; • For end dates of AKIs: o If month and year were available and day was missing, the last day of the month was imputed; if the event was reported during the month of the last infusion, it was imputed to the date of end-of-study; o If the month was missing and year was available, then if the year was the same as the year of the last infusion, the date was considered as the last day in the study; otherwise, the date was set to December 31st;

	o If the year was missing, the date was imputed to the last day in the study. Of note, serum creatinine during episodes of AKI were excluded from the eGFR slope calculation and summary tables and considered to be missing. For Aes, if the date of onset was completely unknown, the AE was classified as a TEAE. If the date of onset was partially known and the month of onset of the AE was earlier than the month of the first infusion, the AE was classified as a pre-treatment AE. Missing values associated with TEAEs were treated as missing except for causality, intensity (severity) and outcome of a TEAE, in which case a 'worst case' approach was taken in the analysis. Thus, if causality was missing, the TEAE was regarded as related to PRX-102; if intensity (severity) was missing, the AE was regarded as severe; and if outcome was missing and the stop date was not provided, the TEAE was regarded as 'ongoing'. If seriousness of a TEAE was missing, all efforts were made prior to database lock to make sure that this information was available; if still missing, the worst-case scenario was assumed. No other imputations were made for missing safety or efficacy endpoints.

Key: ACE, angiotensin converting enzyme; ADAs, anti-drug antibodies; ARB, angiotensin receptor blocker; BPI, Brief Pain Inventory; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; EQ-5D-3L, EuroQoL-5 Dimension-3 level; Gb_3, globotriaosylceramide; LVMi, left ventricular mass index; lyso-Gb_3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; TEAEs, treatment-emergent adverse events; UPCR, urine protein/creatine ratio.

Source: BRIGHT protocol 2017 (Chiesi 2017f)

Phase I/II PB-102-F01, PB-102-F02 and PB-102-F03 studies

Table 39: PB-102-F01, PB-102-F02 and PB-102-F03

PB-102-F01, PB-102-F02, PB-102-F03	NCT01678898, NCT01769001, NCT01981720
Objective	To evaluate the pharmacokinetics of pegunigalsidase alfa and assess the efficacy, safety, and tolerability. PB-102-F01 and PB-102-F02 were dose-ranging studies (3 and 9 months respectively), PB-102-F03 was a long-term follow-up study (up to 60 months)
Publications – title, author, journal, year	PB-102_F01 and F02: (Schiffmann et al. 2019) An abstract of study PB-102-F03 was presented at WORLD symposia 2022 (Hughes et al. 2022). Estimated publication date is Q3 2023.
Study type and design	Open label, single arm, dose-ranging study
Sample size (n)	18

Main inclusion and exclusion criteria	**PB-102-F01 & PB-102-F02** Symptomatic adult Fabry patients who were treatment naïve or had not received ERT in the last 6 months **Inclusion criteria:** • Symptomatic adult Fabry patients (≥18 yrs) • Males: plasma and/or leucocyte alpha galactosidase activity (by activity assay) less than lower limit of normal (LLN in plasma=3.2 nmol/hr/ml, LLN in leucocytes=32 nmol/hr/mg/protein) • Females: historical genetic test results consistent with Fabry mutations • Globotriaosylceramide (Gb_3) concentration in urine > 1.5 times upper normal limit • Patients who have never received enzyme replacement therapy (ERT) in the past, or patients who have not received ERT in the past 6 months and have a negative anti alpha galactosidase antibody test • eGFR ≥ 60 mL/min/1.73m2 • The patient signs informed consent • Female patients and male patients whose co-partners are of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method **Exclusion criteria:** • Participation in any trial of an investigational drug within 30 days prior to study screening • Chronic kidney disease stages 3-5 (CKD 3-5) • History of dialysis or renal transplantation • Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening • Severe myocardial fibrosis by MRI (≥2 late-enhancement [LE] positive left ventricular segments) (Weidemann et al. 2009) • History of clinical stroke • Pregnant or nursing • Presence of HIV and/or HBsAg and/or Hepatitis C infections • Known allergies to ERT • Known allergy to Gadolinium based contrast agents • Presence of any medical, emotional, behavioural, 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 **PB-102-F03** **Inclusion criteria:** • Completion of study PB-102-F02 • The patient signs informed consent

	• Female patients of child-bearing potential agree to use a medically acceptable method of contraception, not including the rhythm method. Acceptable methods of contraception include hormonal products, intrauterine device, or male or female condoms. Contraception should be used throughout the duration of the study and for 3 months after termination of treatment. **Exclusion criteria:** • Pregnant or nursing • Presence of any medical, emotional, behavioural, 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
Intervention	Pegunigalsidase alfa
Comparator(s)	N/A
Follow-up time	60 months (PB-102-F03)
Is the study used in the health economic model?	No, a cost-minimization approach was chosen
Primary, secondary, and exploratory endpoints	**PB-102-F01 & PB-102-F02** **Primary outcome:** • Adverse events (time frame: 12 months) **Other outcome measures:** • Plasma Gb_3 concentration • Kidney function – change in eGFR • Plasma lyso-Gb_3 levels • Change in kidney Gb_3 accumulation • Cardiac fibrosis per MRI • Cardiac MRI – ejection fraction • Cardiac MRI – LVM • Cardiac MRI – LVMI • Pharmacokinetics – AUC • Pharmacokinetics – Terminal half life • Pharmacokinetics – clearance of drug • Pharmacokinetics – volume of distribution • Pharmacokinetics – Cmax • Number of participants with ADA • Change in Short Form BPI • Urine creatinine level • Urine Protein/Creatinine ratio • Total urine protein level • Brain MRI • Change in Mainz Severity Score Index (MSSI) • Gastrointestinal Symptom Questionnaire – Severity of abdominal pain • Gastrointestinal Symptoms Questionnaire – Frequency of abdominal pain • Gastrointestinal Symptoms Questionnaire – Frequency of Diarrhoea

	PB-102-F03 • Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 (time frame: every two weeks for 60 months) • Plasma Lyso-GB3 Concentration • Kidney function – change in eGFR
Method of analysis	The following populations were considered for analysis: • Safety population defined as all patients who received any dose (partial or complete) of study treatment as part of study PB-102-F03; • Efficacy population defined as all patients who received at least one complete dose of the study treatment as part of study PB-102-F03; All safety endpoints were analysed in the Safety population. All exploratory efficacy endpoints were analysed in the Efficacy population.
Subgroup analyses	Subgroup analyses were conducted based on baseline characteristics and demographics for selected efficacy and safety endpoints, chosen from the following list: gender, ADA status, Fabry disease classification, eGFR, previous ERT treatment, use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and hyperfiltration status (this last subgroup was added as a post-hoc analysis). Subgroup analyses were made for male/female patients.
Other relevant information	There was no imputation for missing exploratory efficacy and safety data, except for data associated to TEAE reporting for which handling of missing data is described below. Missing values associated with TEAEs were treated as missing except for causality, intensity, and outcome of a TEAE: for these variables a "worst case" approach was taken in the analysis. Thus: • If the causality was missing, the TEAE was regarded as related to the treatment • If the intensity was missing, the intensity of the AE was regarded as severe • If the outcome was missing and the stop date was not provided, the outcome was regarded as "ongoing". • If the seriousness was missing, all efforts were to be made prior to database lock to make sure that this information was available, if still missing, the worst-case scenario was assumed.

Key: ADA, anti-drug antibody; BPI, Brief Pain Inventory; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; EQ-5D-5L, EuroQoL-5 Dimension-5 level; Gb_3, globotriaosylceramide; GSA, Gastrointestinal Symptoms Assessment; HBsAg, Hepatitis B surface antigen; HIV, human immunodeficiency virus IgG, immunoglobulin G; LVM, left ventricular mass; LVMi, left ventricular mass index; lyso-Gb_3, globotriaosylsphingosine; MRI, magnetic resonance imaging; MSSI, Mainz Severity Score Index; TEAEs, treatment-emergent adverse events; UPCR, urine protein/creatine ratio

Source: (Schiffmann et al. 2019); PB-102-F01/PB-102-F02 CSR, 2017 (Chiesi 2017d); PB-102-F03 CSR, 2020 (Chiesi 2020a)

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

A summary of the baseline characteristics of the included studies is presented in Table 40: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Table 40: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	BALANCE		***BRIDGE*** ***(safety population)***	***BRIGHT*** ***(safety population)***	***F01-F02*** ***(safety population, 1.0 mg/kg)***	***F03*** ***(overall population)***
Treatment arm	Pegunigalsidase alfa	Agalsidase beta	Pegunigalsidase alfa	Pegunigalsidase alfa	Pegunigalsidase alfa	Pegunigalsidase alfa
N	52	25	22	30	8	15
Median age, years (range)	44.0 (20, 60)	48.0 (18, 58)	44.5 (24–60)	40.5 (19–58)	30.0 (17–52])	32.0 (17[a] ; 54)
Mean weight, kg	78.89		74.75	82.40	-	-
Gender, n (%)						
Male	29 (55.8)	18 (72.0)	15 (68.2)	24 (80.0)	6 (75.0)	8 (53.3)
Female	23 (44.2)	7 (28.0)	7 (31.8[f])	6 (20.0)	2 (25.0)	7 (46.7)
Race, n (%)						
Asian	2 (3.8)	0				
Black or African American	1 (1.9)	2 (8.0)			2 (25.0)	3 (20.0)
White	49 (94.2)	23 (92.0)	22 (100)	30 (100)	6 (75.0)	11 (73.3)
Other[e]						1 (6.7)
Type of Fabry disease, n (%)						
Classic[b]	27 (51.9%)	14 (56.0%)			6 (75.0)	8 (53.3)
Non-classic	25 (48.1%)	11 (44.0%)			2 (25.0)	7 (46.7)
Kidney parameters						

eGFR (mL/min/1.73 m²)						
Mean (SD/SE)	73.46 (SD 20.21)	74.16 (SD 20.97)	82.5 (SD 23.4)	99.9 (SD 22.1)		112.2 (SE 5.5)
Median (Min, Max)	73.45 (30.2, 125.9)	74.85 (34.1, 107.6)				
eGFR Category (mL/min/1.73 m²), n (%)						
≤60	13 (25.0%)	8 (32.0%)				
60 < and ≤90	28 (53.8%)	11 (44.0%)				
>90	11 (21.2%)	6 (24.0%)				
eGFR slope (mL/min/1.73 m²/year)						
Mean (SD)	-8.03 (6.60)	-8.25 (4.27)	-5.3 (6.3)	-1.8 (3.7)		
Median (Min, Max)	-6.70 (-30.5, 6.3)	-7.84 (-20.3, -2.8)				
eGFR slope categories (mL/min/1.73 m²/year), n (%)						
≤-5	33 (63.5%)	19 (76.0%)				
>-5	19 (36.5%)	6 (24.0%)				
UPCR categories at baseline, n (%)						
UPCR ≤0.5 gr/gr	36 (69.2%)	20 (80.0%)				
0.5 <UPCR <1 gr/gr	9 (17.3%)	2 (8.0%)				
1 ≤UPCR gr/gr	7 (13.5%)	3 (12.0%)				
UPCR category[c], n (%)						
Normal to mildly increased						10 (66.7%)
Moderately increased						5 (33.3%)

Severely increased						0 (0.0%)
Presence of proteinuria (UPCR ≥ 0.5 g/g), n (%)						
Yes			4 (18.2)	2 (6.7)		
No			18 (81.8)	28 (93.3)		
Biomarkers						
Residual enzyme activity in leukocytes, mean % (SD)			12.2 (12.5)	13.7 (16.4)		
α-galactosidase A activity in leukocytes, mean nmol/hr/mg protein (range)						
Male					2.67 (0–7.8)	
Female					69.5 (67–72)	
Residual enzyme activity in plasma, mean % (SD)			10.6 (14.5)	113.4 (356.0)		
α-galactosidase A activity in plasma, mean nmol/hr/mL protein (range)						
Male					0.28 (0.05–0.44)	
Female					6.8 (5.8–7.8)	
Baseline plasma lyso-Gb_3 (nmol/L), mean (SD)			38.3 (41.2)	19.4 (18.1)		
Plasma lyso-Gb_3 (ng/mL), mean (range)					67.6 (5.1–193.4)	70.8 (20.4)
Baseline plasma Gb_3 (nmol/L), mean (SD)			6036.0 (2016.9)			

Plasma Gb_3 concentration (µg/mL), mean (SE)						10.4 (1.5)
Cardiac parameters						
LVMi (g/m²), mean (SE)						52.7 (3.7)
Left ventricular ejection fraction (%), mean (SE)						59.9 (2.2)
Prior treatment						
Median age started ERT, years (range)			38.0 (12-53)	34.5 (7-51)		
Previous ERT, n (%)						
Agalsidase alfa				7 (23.3%)		
Agalsidase beta				23 (76.7%)		
Duration of the last continuous agalsidase-beta treatment (months)[d]						
Mean (SD)	65.03 (47.98)	77.34 (41.25)				
Median (Min, Max)	51.53 (12.6, 236.9)	67.84 (27.6, 168.3)				
Premedication use for agalsidase beta Infusion prior to enrolment, n (%)						
Yes	20 (38.5%)	15 (60.0%)				
No	32 (61.5%)	10 (40.0%)				
Treatment with ACEIs or ARBs, n (%)						
Yes	26 (50.0%)	16 (64.0%)	12 (54.5)	10 (33.3)		
No	26 (50.0%)	9 (36.0%)	10 (45.5)	20 (66.7)		

Anti-drug antibodies						
Baseline immunogenicity status to agalsidase alfa, n (%)						
Positive			1 (4.5)	0/7 (0.0)		
Negative			21 (95.5)	7/7 (100.0)		
Baseline immunogenicity status to agalsidase beta, n (%)						
Positive		8 (32.0%)		11/23 (47.8)		
Negative		17 (69.0%)		12/23 (52.2)		
Baseline immunogenicity status to pegunigalsidase alfa, n (%)						
Positive	18 (34.6%)		2 (9.1)	10/30 (33.3)		
Negative	34 (65.4%)		20 (90.9)	20/30 (66.7)		

Key: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gb3, globotriaosylceramide; LVMi, left ventricular mass index; lyso-Gb3, globotriaosylsphingosine; PPE, per protocol efficacy; SD, standard deviation; SE, standard error ; UPCR, urine protein/creatine ratio.

Notes: [a], Age limit of 18 years was waived for one patient; [b], classic phenotypic Fabry disease was defined as patients with low (<30% of the normal mean) values of α-galactosidase A activity and at least one Fabry-specific symptom such as neuropathic pain, cornea verticillata or clustered angiokeratoma; [c], Normal to Mildly increased: UPCR <150 mg/g; Moderately Increased: UPCR ≥150 mg/g and <500 mg/g; Severely Increased: UPCR ≥500 mg/g; [d], "Last" treatment refers to patients who had several periods of treatment with agalsidase beta in the past; [e], May include Asians; [f], Of note, it had been planned to include a maximum of 25% of female patients in the study, this proportion was slightly exceeded due to the long screening process.

Source: BALANCE CSR 2022 (Chiesi 2022d), BRIDGE CSR 2020 (Chiesi 2020c), BRIGHT CSR, 2021(Chiesi 2021), (Schiffmann et al. 2019), PB-102-F03 CSR 2020 (Chiesi 2020a)

Phase III BALANCE study

Baseline characteristics of the population in the BALANCE study are presented in Table 41 and Table 42 (Chiesi 2022c).

Table 41: Baseline characteristics of patients in the BALANCE study (ITT population)

	Pegunigalsidase alfa (n = 52)	**Agalsidase beta** (n = 25)	**Total** (n = 77)
Median age, years (range)	44.0 (20, 60)	48.0 (18, 58)	46.0 (18, 60)
Gender, n (%)			
Male	29 (55.8)	18 (72.0)	47 (61.0)
Female	23 (44.2)	7 (28.0)	30 (39.0)
Race, n (%)			
Asian	2 (3.8)	0	2 (2.6)
Black or African American	1 (1.9)	2 (8.0)	3 (3.9)
White	49 (94.2)	23 (92.0)	72 (93.5)
Type of Fabry disease, n (%)			
Classic	27 (51.9%)	15 (66.7%)	41 (53.2%)
Non-classic	25 (48.1%)	10 (33.3%)	36 (46.8%)
eGFR (mL/min/1.73 m^2)			
Mean (SD)	73.46 (20.21)	74.16 (20.97)	73.69 (20.32)
Median (Min, Max)	73.45 (30.2, 125.9)	74.85 (34.1, 107.6)	74.51 (30.2, 125.9)
eGFR Category (mL/min/1.73 m^2), n (%)			
≤60	13 (25.0%)	8 (32.0%)	21 (27.3%)
60 < and ≤90	28 (53.8%)	11 (44.0%)	39 (50.6%)
>90	11 (21.2%)	6 (24.0%)	17 (22.1%)
eGFR slope (mL/min/1.73 m^2/year)			
Mean (SD)	-8.03 (6.60)	-8.25 (4.27)	-8.10 (5.92)
Median (Min, Max)	-6.70 (-30.5, 6.3)	-7.84 (-20.3, -2.8)	-7.25 (-30.5, 6.3)
eGFR slope categories (mL/min/1.73 m^2/year), n (%)			
≤-5	33 (63.5%)	20 (80.0%)	52 (67.5%)
>-5	19 (36.5%)	5 (20.0%)	25 (32.5%)
UPCR categories at baseline, n (%)			
UPCR ≤0.5 gr/gr	36 (69.2%)	20 (80.0%)	56 (72.7%)
0.5 <UPCR <1 gr/gr	9 (17.3%)	2 (8.0%)	11 (14.3%)
1 ≤UPCR gr/gr	7 (13.5%)	3 (12.0%)	10 (13.0%)

Treatment with ACEIs or ARBs, n (%)			
Yes	26 (50.0%)	16 (64.0%)	42 (54.5%)
No	26 (50.0%)	9 (36.0%)	35 (45.5%)
Duration of the last continuous agalsidase-beta treatment (months)[a]			
Mean (SD)	65.03 (47.98)	77.34 (41.25)	69.03 (46.00)
Median (Min, Max)	51.53 (12.6, 236.9)	67.84 (27.6, 168.3)	57.43 (12.6, 236.9)
Premedication use for agalsidase beta Infusion prior to enrolment, n (%)			
Yes	20 (38.5%)	15 (60.0%)	35 (45.5%)
No	32 (61.5%)	10 (40.0%)	42 (54.5%)
ADA status for:			
Positive	18 (34.6%)	8 (32.0%)	-
Negative	34 (65.4%)	17 (69.0%)	-

Key: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; SD, standard deviation; UPCR, urine protein/creatine ratio.

Notes: [a], "Last" treatment refers to patients who had several periods of treatment with agalsidase beta in the past

Source: BALANCE CSR 2022 (Chiesi 2022c)

Table 42: Other baseline measures by gender in the BALANCE study (ITT population)

	Pegunigalsidase alfa		Agalsidase beta	
	Male (n = 29)	Female (n = 23)	Male (n = 18)	Female (n = 7)
% residual enzyme activity in leukocytes[a]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
% residual enzyme activity in plasma[b]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Plasma lyso-Gb_3 (nM)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]

Key: lyso-Gb_3, globotriaosylsphingosine; SD, standard deviation.

Notes: [a], Defined as the value in leukocyte × 100/83.5, where 83.5 nmol/hr/mg protein is the mean between min and max of the lab normal reference range; [b], Defined as the value in plasma ×100/12.95, where 12.95 nmol/hr/mL is the mean of the lab normal reference range.

Source: BALANCE CSR 2022 (Chiesi 2022c).

Phase III BRIDGE study

Table 43 presents a summary of the baseline characteristics of patients in the PPE and safety populations.

Table 43: Baseline characteristics of patients in the BRIDGE (PB-102-F30) study

	Safety population			PPE population		
	Male (n = 15)	Female (n = 7)	Total (n = 22)	Male (n = 13)	Female (n = 7)	Total (n = 20)
Median age, years (range)	[redacted]	[redacted]	[redacted] (24–60)	[redacted]	[redacted]	[redacted]
Race, n						
White	15	7	22	13	7	20
Other	0	0	0	0	0	0
Median age started ERT, years (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Residual enzyme activity in leukocytes, mean % (SD)	4.8 [redacted]	27.9 [redacted]	12.2 [redacted]	[redacted]	[redacted]	[redacted]
Residual enzyme activity in plasma, mean % (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline eGFR (mL/min/1.73 m^2), mean (SD)	80.8 [redacted]	86.1 [redacted]	82.5 [redacted]	75.9 [redacted]	86.1 [redacted]	79.5 [redacted]
Baseline annualized eGFR slope (mL/min/1.73 m^2/year), mean (SD)	-5.4 [redacted]	-5.0 [redacted]	-5.3 [redacted]	-6.3 [redacted]	-5.0 [redacted]	-5.9 [redacted]
Baseline plasma lyso-Gb_3 (nmol/L), mean (SD)	49.7 [redacted]	13.8 [redacted]	38.3 [redacted]	51.8 [redacted]	13.8 [redacted]	38.5 [redacted]
Baseline plasma Gb_3 (nmol/L), mean (SD)	[redacted]	[redacted]	[redacted]	6403.2 [redacted]	5468.3 [redacted]	6076.0 [redacted]
Presence of proteinuria (UPCR ≥ 0.5 g/g), n (%)						
Yes	[redacted]	[redacted]	[redacted]	4 (30.8)	0 (0.0)	4 (20.0)
No[a]				9 (69.2)	7 (100.0)	16 (80.0)
Treatment with ACEIs or ARBs, n (%)						
Yes	[redacted]	[redacted]	[redacted]	7 [redacted]	4 [redacted]	11 [redacted]
No				6 [redacted]	3 [redacted]	9 [redacted]
Baseline immunogenicity status to agalsidase alfa, n (%)						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative						
Baseline immunogenicity status to pegunigalsidase alfa, n (%)						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative						

Key: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gb_3, globotriaosylceramide; lyso-Gb_3, globotriaosylsphingosine; PPE, per protocol efficacy; SD, standard deviation; SE, standard error; UPCR, urine protein/creatine ratio.

Note: [a], Includes patients with a UPCR between level of quantification and 0.5 g/g, and patients with a urine protein level below the threshold of methodological detection

Source: BRIDGE CSR 2020 (Chiesi 2020c)

Phase III BRIGHT study

Baseline characteristics of the safety population in the BRIGHT study are presented in Table 44.

Table 44: Baseline characteristics of patients in the BRIGHT (PB-102-F50) study: safety population

	Safety population		
	Male (n = 24)	Female (n = 6)	Total (n = 30)
Median age, years (range)	[redacted]	[redacted]	40.5 (19–58)
Race, n			
White	24	6	30
Other	0	0	0
Previous ERT, n (%)			
Agalsidase alfa	[redacted]	[redacted]	[redacted]
Agalsidase beta	[redacted]	[redacted]	[redacted]
Median age started ERT, years (range)	[redacted]	[redacted]	[redacted]
Residual enzyme activity in leukocytes, mean % (SD)	[redacted]	[redacted]	[redacted]
Residual enzyme activity in plasma, mean % (SD)	[redacted]	[redacted]	[redacted]
Baseline eGFR (mL/min/1.73 m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Baseline annualized eGFR slope (mL/min/1.73 m^2/year), mean (SD)	[redacted]	[redacted]	[redacted]
Baseline plasma lyso-Gb_3 (nmol/L), mean (SD)	[redacted]	[redacted]	[redacted]
Presence of proteinuria (UPCR ≥0.5 g/g), n (%)			
Yes	2 (8.3)	0 (0.0)	2 (6.7)
No	22 (91.7)	6 (100.0)	28 (93.3)
Treatment with ACEIs or ARBs, n (%)			
Yes	9 (37.5)	1 (16.7)	10 (33.3)
No	15 (62.5)	5 (83.3)	20 (66.7)
Baseline immunogenicity status to agalsidase alfa, n (%)			
N	5	2	7
Positive	0 (0.0)	0 (0.0)	0 (0.0)
Negative	5 (100.0)	2 (100.0)	7 (100.0)
Baseline immunogenicity status to agalsidase beta, n (%)			
N	19	4	23
Positive	11 (57.9)	0 (0.0)	11 (47.8)
Negative	8 (42.1)	4 (100.0)	12 (52.2)
Baseline immunogenicity status to pegunigalsidase alfa, n (%)			
N	24	6	30
Positive	10 (41.7)	0 (0.0)	10 (33.3)
Negative	14 (58.3)	6 (100.0)	20 (66.7)

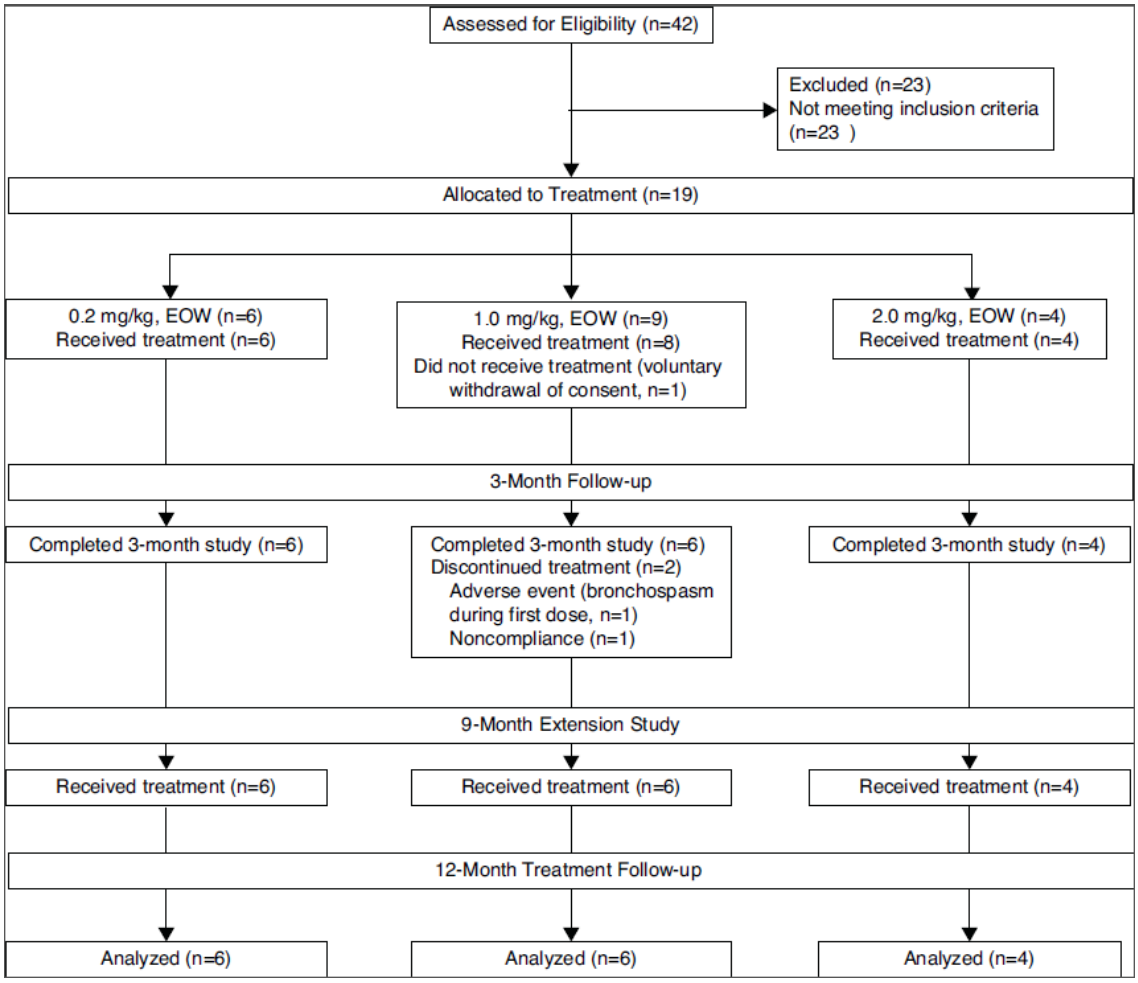
Key: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; lyso-Gb_3, globotriaosylsphingosine; PPE, per protocol efficacy; SD, standard deviation; SE, standard error; UPCR, urine protein/creatine ratio.

Source: BRIGHT CSR, 2021(Chiesi 2021)

Phase I/II PB-102-F01 and PB-102-F02

Figure 8 presents a CONSORT diagram of patient flow during the PB-102-F01 and PB-102-F02 studies.

Figure 8: CONSORT diagram of patient flow during study PB-102-F01 and PB-102-F02



Key: EOW, every other week.

Source: (Schiffmann et al. 2019)

Table 45 presents a summary of the baseline characteristics of patients in the safety population.

Table 45: Baseline characteristics of patients in the PB-102-F01 and PB-102-F02 studies: Safety population

	Safety population (N = 18)		
	0.2 mg/kg (n = 6)	1.0 mg/kg (n = 8)	2.0 mg/kg (n = 4)
Median age, years (range)	[redacted]	[redacted]	[redacted]
Sex, n (male: female)	4:2	6:2	1:3
Race, n			
Caucasian	4	6	4
African American	1	2	0
Other	1	0	0
Ethnicity, n			
Hispanic or Latino	2	0	1

	Safety population (N = 18)		
	0.2 mg/kg (n = 6)	1.0 mg/kg (n = 8)	2.0 mg/kg (n = 4)
Neither Hispanic nor Latino	4	8	3
α-galactosidase A activity in leukocytes, mean nmol/hr/mg protein (range)			
Male	3.15 (1.6–5)	2.67 (0–7.8)	0.56
Female	27.5 (15–40)	69.5 (67–72)	42.7 (33–53)
α-galactosidase A activity in plasma, mean nmol/hr/mL protein (range)			
Male	0.22 (0–0.4)	0.28 (0.05–0.44)	0.4
Female	3.15 (2–4.3)	6.8 (5.8–7.8)	4.8 (2.52–7.8)
Classic disease characterization[a], n	5	6	1
Plasma lyso-Gb_3 (ng/mL), mean (range)	93.9 (7.5–272.9)	67.6 (5.1–193.4)	20.2 (3.4–61.8)

Key: lyso-Gb_3, globotriaosylsphingosine.

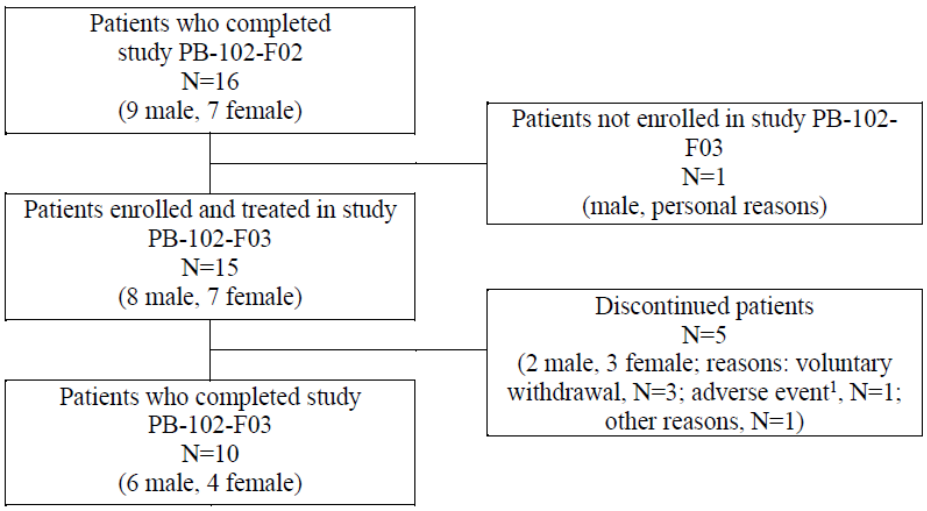
Notes: [a], classic phenotypic Fabry disease was defined as patients with low (<30% of the normal mean) values of α-galactosidase A activity and at least one Fabry-specific symptom such as neuropathic pain, cornea verticillata or clustered angiokeratoma.

Source: (Schiffmann et al. 2019)

Phase I/II PB-102-F03 study

Figure 9 presents a CONSORT diagram of patient flow during study PB-102-F03. Of note, all completers of the PB-102-F03 study (N = 10) moved to the PB-102-F60 extension study and are continuing to be treated.

Figure 9: CONSORT diagram of patient flow during study PB-102-F03



[1] Fatal TEAE of COPD

Key: COPD, chronic obstructive pulmonary disease.

Source: PB-102-F03 CSR 2020 (Chiesi 2020a)

Table 46 presents a summary of the baseline characteristics for patients in the complete population.

Table 46: Baseline characteristics of patients in study PB-102-F03: Safety/Efficacy population

	Male/Classic patients (n = 8)	Female/Non-classic patients (n = 7)	Treated ≥5 years (n = 10)	Overall (n = 15)
Median age, years (range)	[redacted]	[redacted]	[redacted]	32.0 (17[a] ; 54)
Gender, n (%)				
Male (all classic)	8 (100)	0 (0)	6 (60.0)	8 (53.3)
Female (all non-classic)	0 (0)	7 (100)	4 (40.0)	7 (46.7)
Race, n (%)				
African American	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)				
Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]
Plasma concentration, GB3 & lyso-GB3				
Plasma lyso-Gb_3 concentration (ng/mL), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Plasma Gb_3 concentration (µg/mL), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
UPCR category[b], n (%)				
Normal to mildly increased	[redacted]	[redacted]	[redacted]	[redacted]
Moderately increased	[redacted]	[redacted]	[redacted]	[redacted]
Severely increased	[redacted]	[redacted]	[redacted]	[redacted]
eGFR (mL/min/1.73 m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LVMi (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Left ventricular ejection fraction (%), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Key: eGFR, estimated glomerular filtration rate; Gb_3, globotriaosylceramide; LVMi, left ventricular mass index; lyso-Gb_3, globotriaosylsphingosine; SE, standard error; UPCR, urine protein/creatine ratio.

Notes: [a], Age limit of 18 years was waived for one patient; [b], Normal to Mildly increased: UPCR <150 mg/g; Moderately Increased: UPCR ≥150 mg/g and <500 mg/g; Severely Increased:

UPCR ≥500 mg/g

Source: PB-102-F03 CSR 2020 (Chiesi 2020a)

Comparability of the study populations with country specific patients eligible for treatment

According to clinical experts, the baseline characteristics of the study patient populations are comparable to the current Danish Fabry disease population eligible for treatment with ERTs (Chiesi 2023b).

Appendix D Efficacy and safety results per study

Definition, validity, and clinical relevance of included outcome measures

The definition of each included outcome measure is provided in Table 47 below.

Table 47: Definitions of outcomes used in the clinical trial programme

Outcome measure	Definition	Validity	Clinical relevance
Annualized change (slope) in estimated glomerular filtration rate ($eGFR_{CKD-EPI}$)	The eGFR measure was derived based on the level of serum creatinine using the CKD-EPI formula: eGFR (mL/min/1.73 m^2) = 141 × min(Scr/κ,1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black / African American] where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Age is the actual age when the patient's serum creatinine was collected. At the first stage, the individual annualized mean change (slope) in eGFR was estimated for each patient using the following linear regression model: eGFR = α + β × [time in year]. The slope β (mL/min/1.73 m^2 / year) is an estimate of the individual patient's annualized change in eGFR. At the 2nd stage, the annualized mean change (slope) of the eGFR between the two treatment arms was compared using quantile regression estimating the median slopes. Non-inferiority was declared if the lower bound of the confidence interval for the treatment difference (pegunigalsidase alfa minus agalsidase beta) was greater or	(Levey et al. 2009)	Fabry disease is associated with renal symptoms, which manifest as proteinuria and reduced glomerular filtration rate (GFR), which ultimately leads to renal insufficiency and end-stage renal disease. Measuring the effects on treatments on GFR decline, which ultimately leads to kidney failure is one strategy that has been commonly utilized to study and estimate the early benefit of treatment on kidney function As no previously established clinically relevant NI margin is available, the NI margin in this study was identified using the combined knowledge on the natural history of the disease and the data published on the effect of available treatments on renal function deterioration in Fabry Disease patients.

	equal to -3.0 mL/min/1.73 m^2/year (Chiesi 2022c).		
Left Ventricular Mass Index (LVMi)	LVMi was measured by cardiac MRI at baseline and every 12 months. Analyses were performed separately for patients who had hypertrophy at baseline, patients that did not have it, and patients whose hypertrophy at baseline were missing (in case the cardiac MRI was not performed at baseline or was not evaluable). Hypertrophy was defined as LVMi above 91 g/m^2 for males and above 77 g/m^2 for females (Chiesi 2022c)		Cardiac complications of Fabry disease may include a thickening of the left ventricular wall, which is assessed by the LVMI.
Cardiac Stress Test	An exercise stress test was performed at baseline and every 12 months based on Bruce protocol. Qualitative evaluation (yes/no) of symptoms (chest pain, shortness of breath, dizziness, palpitations, and other) and the overall impression: normal stress test (yes/no) is summarized by number (%) of patients by visit and treatment group (Chiesi 2022c).	(Garner et al. 2017, Wolk et al. 2014)	FD is a multisystemic disease and impact the heart. Cardiac stress tests assess a patient's functional capacity, as well as the probability and extent of coronary artery disease. It also assesses the risks, prognosis, and effects of therapy.
Echocardiography	The number (%) of patients with the qualitative assessment (Normal/Other) for aortic, mitral, tricuspid, and pulmonic function is presented in a shift table from baseline to Week 52 and Week 104 by treatment group (Chiesi 2022c).		FD is a multisystemic disease and impact the heart. Echocardiography can detect cardiomyopathy (thickening of the walls) as well as heart failure.
Concentrations of plasma Gb3 and Lyso-Gb3	Quantification was done centrally at baseline, 6 weeks every 3 months up to a year, and then every 6 months. The analysis included lipid extraction from the matrix (plasma/urine) followed by ultra-performance liquid chromatography-tandem mass spectrometry. A Mixed Model Repeated Measure (MMRM) approach was used to model the change from baseline of log of plasma lyso-Gb3. The dependent variable was the		Gb3 and lyso-Gb3 are biomarkers of FD. The levels of Gb3 and lyso-Gb3 can be used to assess the global burden or activity of the disease.

	change from baseline of log of lyso-Gb3 to each post baseline visit. The variables to be included in the model were log plasma lyso-Gb3 at baseline visit (class variable), treatment (class variable), and visit by treatment interaction term. The first choice for the within-patient correlations was an unstructured covariance structure. If the model did not converge, the heterogeneous Toeplitz structure was used, followed by a homogeneous Toeplitz structure, and then a compound symmetry structure until a stable model was achieved. Only data at scheduled visits were used for this analysis. Missing data were not imputed. The Kenward-Roger degrees of freedom approximation was used (Chiesi 2022c).		
Mainz Severity Score Index (MSSI)	Total scores and change from baseline of each of the domains (general, neurological, cardiovascular, renal dysfunction, and an overall score that is the sum of these four scores). A total MSSI score < 20 is considered as mild, 20 ≤ and ≤ 40 is considered moderate, and > 40 is considered severe. The MSSI was administrated by the Investigator at baseline and every 6 months (Chiesi 2022c)	(Beck 2006)	MSSI can support in assessing the burden of FD.
Urine protein/creatinine ratio (UPCR) category by a spot urine test	Patients provided spot urine samples for assessment of UPCR at screening, baseline, and then every 3 months. Analyses were performed centrally. The findings were classified into three categories based on the Kidney Disease Improving Global Outcomes guidelines (2012): - Normal to mildly increased: UPCR < 0.15 gr/gr - Moderately increased: UPCR ≥ 0.15 gr/gr but ≤ 0.5 gr/gr - Severely increased: UPCR > 0.5 gr/gr (Chiesi 2022c)	(Kidney Disease: Improving Global Outcomes 2012)	UPCR can support assessment of kidney function.

Short form Brief Pain Inventory (BPI)	The BPI or a validated translated version was self-completed by patients at screening, baseline, and then every 3 months. Rate the severity of various aspects of pain on a scale of 0 to 10 (no pain / pain as bad as you can imagine), and to indicate on a scale of 0 to 10 (does not interfere / completely interferes) how this pain impacts their general activity, mood, walking, working, sleeping, relations with other people, and enjoyment of life. The BPI yields scores for "Pain at Its Worst in Last 24 Hours", "Pain at Its Least in Last 24 Hours", "Pain Right Now", and "Pain on Average". The scales are scored from 1 to 10, with a score of 1–4 points indicating mild pain, 5–6 indicating moderate, and 7–10 indicating severe. Descriptive statistics of the qualitative assessments and change from baseline for pain severity domains and pain interference domains were summarized by visit and treatment group. A 95% CI based on the t-distribution for a paired sample, for the change from baseline, was presented. A 95% CI of the change from baseline to 12 months and to 24 months between the two treatment groups using t-distribution for two samples was presented (Chiesi 2022c).		Pain is in general one of the first symptoms that patients with FD experience and it is one of the characteristic symptoms of FD used to diagnose the disease. BPI can support in assessing the severity of pain.
Quality of life (EQ-5D-5L)	The EQ-5D-5L questionnaire, developed by the EuroQol Group was completed at baseline and then every 6 months. Descriptive statistics of the qualitative assessments regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are summarized by visit and by treatment group. The number (%) of patients with no change or improvement (difference from baseline is ≥ 0) and the		EQ-5D-5L can support in assessing the burden of FD

	number and proportion with a worse score (difference from baseline is < 0) are summarized by visit (Chiesi 2022c).		

Results per study

Efficacy results from the Phase III BALANCE study (PB-102-F20)

Efficacy results are presented for the ITT population, which comprised 77 patients who completed 24 months of treatment (Chiesi 2022c).

Table 48: Results of BALANCE (NCT02795676)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods for estimation	References
Outcome	**Study arm**	**N**	**Results (mean [95% CI]) except for eGFR slope which is: Results (median [95% CI])**	**Difference**	**95% CI**	**P-value**	**Difference**	**95% CI**	**P-value**		
eGFR slope (mL/min/1.73 m^2/year; ITT population)	Pegunigalsidase alfa	51	-2.51 (-3.79; -1.24)	-0.359	-2.444 – 1.726	NS**	N/A	N/A	N/A	Non-inferiority margin was -3.0	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	25	-2.16(-3.81; -0.51)								
eGFR slope (mL/min/1.73 m^2/year; PP population)	Pegunigalsidase alfa	48*	-2.52 (-3.67; -1.36)	-0.118	-2.450 – 2.213	NS**	N/A	N/A	N/A	Non-inferiority margin was -3.0	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	24	-2.40 (-4.34; -0.46)								
Plasma lyso-Gb_3	Pegunigalsidase alfa	51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	BALANCE CSR 2022 (Chiesi 2022c)

Change from baseline at w 104 (nM), ITT	Agalsidase beta	25	xxx (xxxxx)								
Plasma Gb_3, change from baseline at week 104 (nM), ITT	Pegunigalsidase alfa	46	138.0 (-282.2; 558.2)	219.8	-549.3; 988.9	NS	N/A	N/A	N/A	Difference in means using a t-distribution for 2 independent samples	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	22	-81.8 (-698.6; 535.0)								
Urine lyso-Gb_3 concentrations Change in baseline at w 104 (pM/mM creatinine), ITT population	Pegunigalsidase alfa	37	7.0 (-8.09; 22.09)	18.1	0.1; 36.1		N/A	N/A	N/A	Difference in means using a t-distribution for 2 independent samples	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	19	-11.2 (-20.41; -1.99)								

Short form BPI, change from baseline at week 104, ITT population	Pegunigalsidase alfa	45	0.4 (-0.3; 1.0)	0.2	-0.9; 1.2	NS	N/A	N/A	N/A	The Short Form BPI is designed to rapidly assess the severity of pain and its impact on functioning. It yields scores for "Pain at Its Worst in Last 24 Hours", "Pain at Its Least in Last 24 Hours", "Pain Right Now", and "Pain on Average". The scales are scored from 1 to 10, with a score of 1–4 points indicating mild pain, 5–6 indicating moderate, and 7–10 indicating severe.	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	22	0.2 (-0.6; 1.0)								
Mainz Severity Score Index (MSSI), change from baseline at week 104	Pegunigalsidase alfa	46	-2.07 (-3.62; -0.52)	-4.11	-6.8; -1.4		N/A	N/A	N/A	The Mainz Severity Score Index (MSSI) yields scores for general, neurological, cardiovascular, renal, and overall assessments. An overall score of less than 20 points is considered mild, 20 to 40 is considered moderate, and greater than 40 is considered severe signs and symptoms of Fabry disease.	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	23	2.04 (-0.24; 4.33)								

5-level EQ-5D (EQ-5D-5L), overall health score, change from baseline at week 104, ITT population	Pegunigalsidase alfa	46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The overall health score (from 0 to 100) is summarized by visit and by treatment group using descriptive statistics together with the change from baseline. A statistical comparison in the change from baseline to Week 104 between the two treatment groups is made.	BALANCE CSR 2022 (Chiesi 2022c)
	Agalsidase beta	22	[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	BALANCE CSR 2022 (Chiesi 2022c)
	[redacted]	[redacted]	[redacted]								

[redacted]	[redacted]	[redacted]	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)		BALANCE CSR 2022 (Chiesi 2022c)
	[redacted]	[redacted]	xxx (xxxxx)								
[redacted]	[redacted]	[redacted]	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	BALANCE CSR 2022 (Chiesi 2022c)
	[redacted]	[redacted]	xxx (xxxxx)								
[redacted]	[redacted]	[redacted]	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)	xxx (xxxxx)		BALANCE CSR 2022 (Chiesi 2022c)
	[redacted]	[redacted]	xxx (xxxxx)								

Key: BPI, Brief Pain Inventory; eGFR, estimated glomerular filtration rate; Gb_3, globotriaosylceramide; LVMi, left ventricular mass index; lyso-Gb_3, globotriaosylsphingosine; SE, standard error; MMRM, Mixed model repeated measures; UPCR, urine protein/creatine ratio

Notes: *52 patients had baseline values and are included in the intention-to-treat population, 48 patients had values at week 104 and are included in the per protocol population; **NS: a pre-defined non-inferiority margin of -3.0 was set.

Source: BALANCE CSR 2022 (Chiesi 2022c)

Primary efficacy endpoint

Renal outcomes (eGFR slope)

The primary endpoint was the annualized change in eGFR (slope), which is derived from eGFR assessments over time. The objective of the primary analysis was to assess whether pegunigalsidase alfa was non-inferior to agalsidase beta for this endpoint, based on the data obtained from 24 months of treatment using 2-stage quantile regression (Chiesi 2022c).

A summary of eGFR values at each visit for the ITT and PP populations is provided in Table 49 (Chiesi 2022c). At Week 104, values for the ITT and PP populations, were identical. Mean values were slightly lower in both treatment arms. A tendency for higher decreases over time in glomerular filtration in ADA positive patients compared with ADA-negative patients was seen in both treatment arms. For the pegunigalsidase alfa arm, the n was 51 since one subject had fewer than four eGFR observations, which was deemed minimum to perform the analysis of the change in slope.

Table 49: Summary of eGFR (mL/min/1.73 m2) values

	ITT set		PP set	
	Pegunigalsidase alfa N = 52	Agalsidase beta N = 25	Pegunigalsidase alfa N = 4 8	Agalsidase beta N = 24
Baseline				
n	51	25	48	24
Mean (SE)	73.46 [redacted]	74.16 [redacted]	[redacted]	[redacted]
Median	73.45	74.85	[redacted]	[redacted]
Min; Max	30.2–125.9	34.1–107.6	[redacted]	[redacted]
Week 104				
n	47	24	47	24
Mean (SE)	70.53 [redacted]	72.05 [redacted]	[redacted]	[redacted]
Mean change from baseline	-3.60	-1.97	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]

Key: SE: standard error

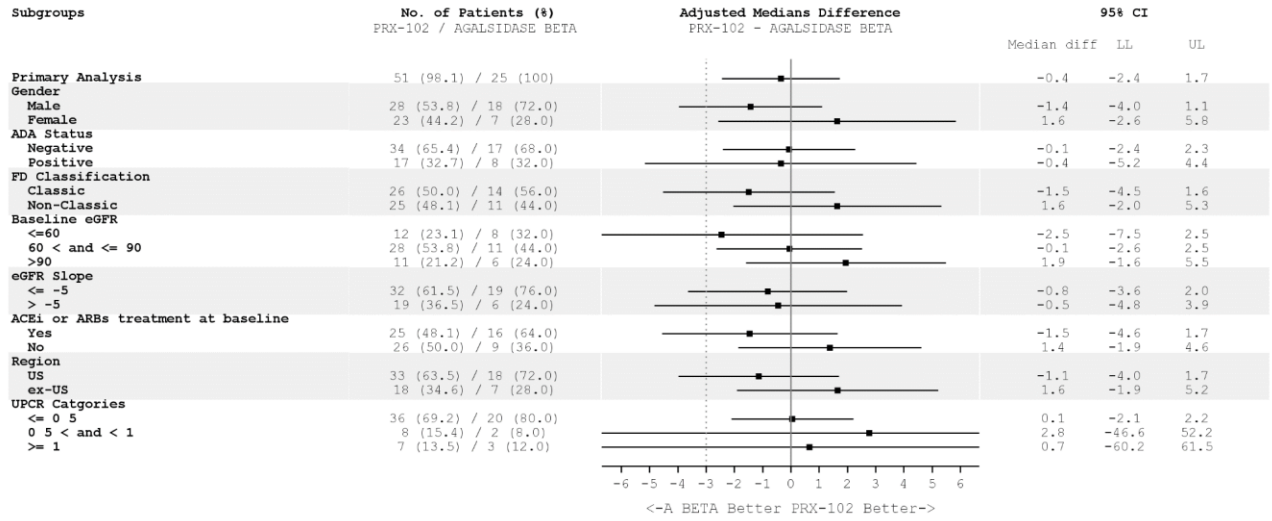
Source: BALANCE CSR 2022 (Chiesi 2022c)

Regarding the impact of ADA status, a tendency for higher decreases over time in glomerular filtration in ADA positive patients compared with ADA-negative patients was seen in both treatment arms.

Sensitivity and supportive analysis

Further sensitivity and supportive analyses (Figure 10) confirmed non-inferiority of pegunigalsidase alfa to agalsidase beta, including the important stratification factor, UPCR, as covariate yielded a between treatment difference of 0.282 (95% CI: -1.789; 2.353)(Chiesi 2022c). Post-hoc analyses were performed to investigate the observed imbalances between treatment arms with regards to gender distribution, Fabry disease classification, and ADA status at baseline by including these factors as covariates in the model. In all cases, no influence of the covariate was seen, as results were similar to the primary analyses.

Figure 10: Forest plot of eGFR differences in slopes – subgroups within the ITT set



Key: FD, Fabry Disease; UPCR, urinary protein to creatinine ratio; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LL, lower Limit; UL, upper Limit, ADA, anti-drug antibody, eGFR, estimated glomerular filtration rate
Note: Vertical dotted line drawn at the prespecified non-inferiority margin of -3.0 ml/min/1.73 m^2/year
Source: BALANCE CSR 2022 (Chiesi 2022c)

Overall results

In summary, the results indicate that pegunigalsidase alfa is not inferior to agalsidase beta with regards to the primary endpoint. The robustness of the finding that pegunigalsidase alfa was non-inferior to agalsidase beta was confirmed in a wide variety of sensitivity and supportive analyses (Chiesi 2022c).

Secondary efficacy endpoints

Pharmacodynamics

Plasma lyso-Gb_3 concentrations

At baseline, median values for plasma Lyso-Gb_3 levels at baseline were 15.2 (nM) in the pegunigalsidase alfa arm and 17.6 (nM) in the agalsidase beta arms (Chiesi 2022c). At Week 104, the change from baseline, in median values, was 1.15 in the pegunigalsidase alfa arm and -1.50 in the agalsidase beta arm. In mean values, the mean plasma lyso-Gb_3 concentration was similar between the pegunigalsidase alfa and agalsidase beta arms (26.2 nM and 32.1 nM, respectively). At Week 104, the concentration of lyso-Gb_3 had increased slightly (3.30 nM) in the pegunigalsidase alfa arm and decreased slightly (8.74 nM) in the agalsidase beta arm (Table 50).

These results indicate stability in both arms, and these changes were not reflected in the eGFR slopes of each treatment arm (Chiesi 2022c).

Table 50: Summary of change in plasma lyso-Gb_3 concentrations from baseline to Week 104 – ITT population

	Pegunigalsidase alfa (n = 52)	Agalsidase beta (n = 25)
Baseline		
n	52	25
Mean (SE)	26.22 (3.78)	32.14 (7.08)
Median	15.20	17.60

Min; Max	0.8 ; 143.9	2.1 ; 142.0
Change from baseline at Week 104 (nM)		
n	46	22
Mean (SE)	3.30 (1.38)	-8.74 (4.85)
Median	1.15	-1.5
Min; Max	[redacted]	[redacted]
Percent (%) change from baseline at Week 104		
Mean (SE)	10.34 (3.80)	-12.69 (4.60)
Median	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Key: lyso-Gb_3, globotriaosylsphingosine; SD, standard deviation; SE, standard error.

Source: BALANCE CSR 2022 (Chiesi 2022c)

As expected, a gender difference was noted in lyso-Gb_3 levels. Female patients had very low levels at baseline ([redacted] nM in the pegunigalsidase alfa and agalsidase beta arms, respectively) and showed hardly any change during the study ([redacted] at Week 104, respectively), while median values in male patients at baseline were [redacted] respectively, and the trends for changes seen in male patients ([redacted], respectively at Week 104) were similar to the changes seen in the overall population (Chiesi 2022c).

Notably, ADA-positive patients at baseline showed higher mean baseline values ([redacted] in the pegunigalsidase alfa and agalsidase beta arms, respectively) than those ADA-negative patients ([redacted], respectively) (Chiesi 2022c).

The results of an analysis of the changes in plasma lyso-Gb_3 are presented in Table 51 (Chiesi 2022c) Although the p-value was [redacted], the difference is not considered meaningful based on clinical judgement

Table 51: Change from baseline in mean plasma lyso-Gb_3 concentrations, MMRM – ITT population

	Value	95% confidence interval	p-value
Number of subjects considered in the model			
Pegunigalsidase alfa	51		
Agalsidase beta	25		
Adjusted means in change of log (plasma Lyso-Gb_3) at Week 104			
Pegunigalsidase alfa	[redacted]	[redacted]	
Agalsidase beta	[redacted]	[redacted]	
Adjusted means difference in change of log (plasma Lyso-Gb_3) at Week 104			
Pegunigalsidase alfa – Agalsidase beta	[redacted]	[redacted]	[redacted]

Key: lyso-Gb_3, globotriaosylsphingosine; SE, standard error; MMRM, Mixed model repeated measures

Source: BALANCE CSR 2022 (Chiesi 2022c)

Urine lyso-Gb_3 concentrations

At baseline, the mean urine lyso-Gb_3 concentrations were similar in the pegunigalsidase and agalsidase beta arms (48.1 and 44.5 pM/mM creatinine, respectively) (Chiesi 2022c). At Week 104, the concentration had increased slightly (by 7.0 pM/mM creatinine) in the pegunigalsidase alfa arm and decreased (-11.2 pM/mM creatinine) in the agalsidase beta arm. Since the confidence intervals contained 0, this suggests no difference between the two arms, and changes in both treatment arms for both variables were not considered clinically significant.

Plasma Gb_3 concentrations

At baseline, the mean Gb_3 plasma concentration was higher in the pegunigalsidase alfa arm than in the agalsidase beta arm: 5087.7 nM vs. 4695.4 nM (Chiesi 2022c). In the pegunigalsidase alfa arm, there was a mean increase from baseline of 138.0 nM, while in the agalsidase beta arm, there was a mean decrease of -81.8 nM. Since the confidence intervals contained 0, this suggests no difference between the two arms, and changes in both treatment arms for both variables were not considered clinically significant.

Renal outcomes

Urine Protein/Creatinine Ratio:

The majority of patients had mild proteinuria (UPCR ≤0.5 gr/gr) throughout the study (Chiesi 2022c). At baseline, more patients in the pegunigalsidase alfa arm compared with the agalsidase beta arm had moderate levels (17.3% vs 8.0%). In the pegunigalsidase alfa arm, the number of patients categorized as having severe impairment (UPCR ≥1 gr/gr) was 7/52 (13.5%) at baseline and 6/45 (13.3%) at Week 104, while in the agalsidase beta arm, these numbers were 3/25 (12.0%) and 4/24 (16.7%), respectively. [redacted]

Cardiac outcomes

LVMi

In male patients 20 to 60 years of age, the normal range for LVMi is 57 to 91 g/m^2, in female patients 20 to 60 years of age the normal range is 47 to 77 g/m^2 (Kawel-Boehm et al. 2015).

LVMi results are shown in Table 52 (Chiesi 2022c). For each timepoint, was mean values for males in each treatment arm were compared against the males in the other treatment arm, and females were compared against females. Among those who had hypertrophy at baseline, mean LVMi values slightly decreased over 2 years of treatment in the pegunigalsidase alfa arm (-2.4 and -6.5 in males and females), while a modest overall increase in mean LVMi was observed in the agalsidase beta arm (5.0 and -4.0 in males and females). Among patients without hypertrophy, both groups showed very little change from baseline (range: -3.7, 1.0). Of note, there were missing data for some patients since cardiac MRI could not be performed due to COVID-19 restrictions at the hospital.

When interpreting data, it has to be considered that variability was high as indicated by the large confidence intervals and sample sizes in the subgroups were low. All confidence intervals contained 0, which suggests no statistically significant differences between the treatments for both genders.

Table 52: Summary of LVMi (g/m^2) by gender and hypertrophy status – ITT population

	Pegunigalsidase alfa		Agalsidase beta	
	Males (n = 29)	Females (n = 23)	Males (n = 18)	Females (n = 7)
LVMi for patients with hypertrophy at baseline				
Baseline				
N	8	4	7	2
Mean (SE)	111.548 (6.101)	122.145 (22.841)	115.753 (8.436)	81.285 (2.375)
Change from baseline at Week 104				

N	5	4	5	2
Mean (SE)	-2.410 (8.511)	-6.523 (8.557)	5.000 (13.274)	-4.040 (11.090)
Pegunigalsidase alfa – agalsidase beta: 95% CI for difference in means, males: -44.904, 30.084				
Pegunigalsidase alfa – agalsidase beta: 95% CI for difference in means, females: -56.257, 51.292				
LVMi for patients without hypertrophy at baseline				
Baseline				
N	15	13	8	5
Mean (SE)	67.171 (3.899)	50.021 (2.435)	73.861 (4.005)	49.010 (6.011)
Change from baseline at Week 104				
N	8	11	7	5
Mean (SE)	-1.344 (5.768)	2.820 (3.025)	0.987 (2.740)	-3.682 (4.716)
Pegunigalsidase alfa – agalsidase beta: 95% CI for difference in means, males: -16.573, 11.912				
Pegunigalsidase alfa – agalsidase beta: 95% CI for difference in means, females: -6.582, 19.586				

Key: CI, confidence interval; LVMi, left ventricular mass index; SE, standard error
Source: BALANCE CSR 2022 (Chiesi 2022c)

Stress test

For many patients, data were missing for this measure. In the pegunigalsidase alfa arm, the percentage of patients with normal findings was 62.1% (18/29 patients) at baseline and 57.9% (22/38 patients) at Week 104. In the agalsidase beta arm, the percentage of patients with normal findings was 50.0% (6/12 patients) at baseline and 64.7% (11/17 patients) at Week 104 (Chiesi 2022c). There was no trend of either an increase or a decrease in either treatment arm. However, the high number of patients with missing data makes the results difficult to interpret.

Echocardiogram

Patients underwent an echocardiogram for the assessment of aortic, mitral, pulmonic, and tricuspid function. The majority of patients had normal assessments throughout the study for all parameters. It is important to note that the echocardiogram procedure was not standardized across sites thus, the results are difficult to interpret (Chiesi 2022c).

Incidence of Fabry clinical events

In the pegunigalsidase alfa arm, 17.3% of patients experienced a total of 11 events during the study: seven were cardiac, three cerebrovascular, and one renal. In the agalsidase alfa arm, 8.0% of patients experienced two events: both were cardiac. Of note, all patients reporting Fabry clinical events had either suffered with a similar event when untreated or under treatment with agalsidase beta before the study or had signs/symptoms of organ damage at study start. These results reflects pre-existing organ involvement in ERT-experienced patients and do not allow to draw any conclusion on the effect of change to a new ERT (Chiesi 2022c).

Pharmacokinetics

[redacted]

[redacted] Results also indicated an important impact of the presence of ADAs. In patients who were negative for ADA at baseline, pegunigalsidase alfa had a half-life between 100 and 106 hours over up to two years of treatment, and AUC was generally consistent across visits. On the contrary, patients who were ADA positive at baseline had low concentrations of pegunigalsidase alfa with a half-life of <10 hours across visits up to one year of treatment (Chiesi 2022c).

Pain medication use

A total of [redacted] in the pegunigalsidase arm and 22 patients (88.0%) in the agalsidase arm used pain medication at some point during the study (Chiesi 2022c). The most common medications were paracetamol and ibuprofen, taken orally. For the majority of patients, pain medication used did not change during the study.

Short form Brief Pain Inventory

[redacted]

Mainz Severity Score Index

For the MSSI, an overall score of less than 20 points is considered mild, and greater than 40 is considered severe (Chiesi 2022c). At baseline, a mean of 23.18 points and 25.16 points were observed in the pegunigalsidase alfa arm and agalsidase beta arm, respectively. Scores remained stable during the study, with a minor mean decrease (improvement by -2.1 points) seen in the pegunigalsidase alfa arm and a minor increase in the agalsidase beta arms (+2.0 points). The confidence intervals of the difference in mean changes did not contain 0, which suggests a difference between the two arms in favour of pegunigalsidase alfa. The findings for the scores on the individual scales were similar.

EQ-5D-5L

In both groups, for each domain, the majority of patients reported improvement or no change (Table 53) (Chiesi 2022c).

Table 53: Summary of EQ-5D-5L domain changes at Week 104

		Pegunigalsidase alfa N = 52		Agalsidase beta N = 25	
Number of patients with data at Week 104		N = 46		N = 22	
Mobility	Improvement or no change	41	(89.1%)	19	(86.4%)
	Worsening	5	(10.9%)	3	(13.6%)
Self-care	Improvement or no change	41	(89.1%)	20	(90.9%)
	Worsening	5	(10.9%)	2	(9.1%)
Usual activities	Improvement or no change	36	(78.3%)	20	(90.9%)
	Worsening	10	(21.7%)	2	(9.1%)
Pain/Discomfort	Improvement or no change	38	(82.6%)	16	(72.7%)
	Worsening	8	(17.4%)	6	(27.3%)
Anxiety/Depression	Improvement or no change	39	(84.8%)	20	(90.9%)

	Worsening	7	(15.2%)	2	(9.1%)

Source: Chiesi BALANCE CSR 2022 (Chiesi 2022c)

Efficacy results from the Phase III BRIDGE study (PB-102-F30)

Of note, BRIDGE is a single-arm study, therefore no table similar to Table 48 has been completed for BRIDGE since the table is designed specifically for comparative studies. The results from BRIDGE are presented below.

Clinical efficacy outcomes

Efficacy results are presented for the PPE population, which comprised all patients who had completed 12 months of study treatment (n = 20).

Pharmacodynamics

Plasma lyso-Gb_3 concentrations

At baseline, mean plasma lyso-Gb_3 concentrations were 38.5 nM (51.8 and 13.8 for male and female patients, respectively), and decreased by 31.5% after 12 months, with reductions observed in both male and female patients (32.4% and 29.8%; Table 54) (Chiesi 2020b). For most patients, a continuous reduction in plasma lyso-Gb_3 concentrations was observed until 9 months and these levels were maintained for 12 months (Figure 11).

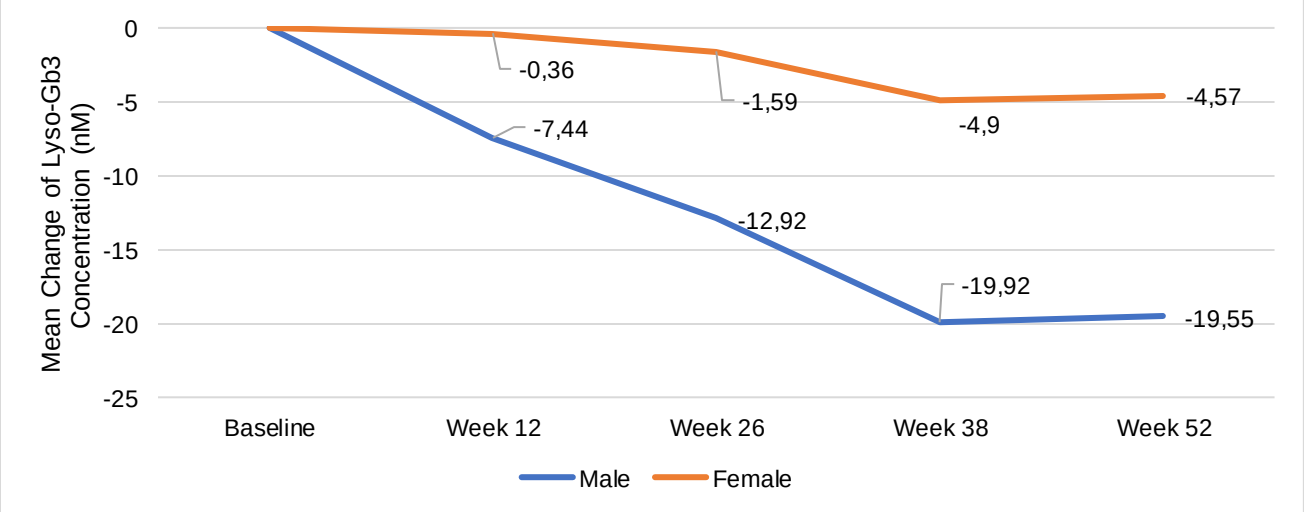
Table 54: Summary of change in plasma lyso-Gb_3 concentrations from baseline to 12 months

	Male (n = 13)	Female (n = 7)	Total (n = 20)
Plasma lyso-Gb_3 concentration (nM), mean (SE)			
Baseline	51.8 (13.6)	13.8 (2.3)	38.5 (9.7)
Month 12	32.3 (6.9)	9.2 (1.1)	24.2 (5.1)
Change in plasma lyso-Gb_3 concentrations from baseline to 12 months			
Mean (SE)	-19.55 (7.6)	-4.6 (1.4)	-14.3 (5.1)
% change in plasma lyso-Gb_3 concentrations from baseline to 12 months			
Mean (SE)	-32.4 (4.8)	-29.8 (4.7)	-31.5 (3.4)

Key: lyso-Gb_3, globotriaosylsphingosine; SE, standard error

Source: BRIDGE CSR 2020 (Chiesi 2020c)

Figure 11: Plasma lyso-Gb_3 concentrations over time (by gender)



Key: Lyso-Gb_3, globotriaosylsphingosine; SE, standard error

Source: BRIDGE CSR, 2020 (Chiesi 2020c)

Urine lyso-Gb_3 concentrations

At baseline, mean urine lyso-Gb_3 concentrations were 58.4 pM/mM (males: 66.0 pM/mM, females: 45.4 pM/mM), and decreased to [redacted] pM/mM after 12 months (-[redacted]%), with reductions observed in both male and female patients (decreasing to 41.2 pM/mM [-[redacted] %] and [redacted] pM/mM [redacted] %], respectively) (Chiesi 2020c).

Plasma Gb_3 concentrations

At baseline, mean plasma Gb_3 concentrations were [redacted] nM, decreasing to [redacted] nM after 12 months (-[redacted] %) (Chiesi 2020c). While absolute values were higher in male patients than in female patients, percent changes from baseline were similar (-[redacted] % and -[redacted] %, respectively).

Renal outcomes

Change in $eGFR_{CKD\text{-}EPI}$ and annualized eGFR slope

At baseline (pre-switch), the total mean eGFR was 79.5 mL/min/1.73 m^2, decreasing slightly to 76.9 mL/min/1.73 m^2 after 12 months (Chiesi 2020c). At baseline (pre-switch), the total annualized eGFR slope was -5.9 mL/min/1.73 m^2/year, and this was improved with pegunigalsidase alfa to -1.2 mL/min/1.73 m^2/year. For male and female patients, annualized eGFR slopes were similar at baseline, and the mean changes in the annualized eGFR slope from baseline to 12 months were consistent in male and female patients (both improving by 4.7). Table 55 presents a summary of the change in the eGFR and eGFR slope from baseline to 12 months.

Table 55: Summary of change in the eGFR and eGFR slope from baseline to 12 months

	Male (n = 13)	Female (n = 7)	Total (n = 20)
eGFR (mL/min/1.73 m^2), mean (SE)			
Baseline	[redacted]	[redacted]	79.5 (4.9)
Month 12	[redacted]	[redacted]	76.9 (5.2)
Change in eGFR from baseline (pre-switch) to 12 months (post-switch)			
Mean (SE)	[redacted]	[redacted]	-2.6 (2.1)
eGFR slope (mL/min/1.73 m^2/year), mean (SE)			
Baseline	-6.3 [redacted]	-5.03 [redacted]	-5.9 (1.3)
Month 12	-1.7 [redacted]	-0.21 [redacted]	-1.2 (1.8)
Change in the eGFR slope from baseline (pre-switch) to 12 months (post-switch)			
Mean (SE)	+4.6 [redacted]	+4.83 [redacted]	+4.7 [redacted]
P-value[a]	[redacted]	[redacted]	[redacted]

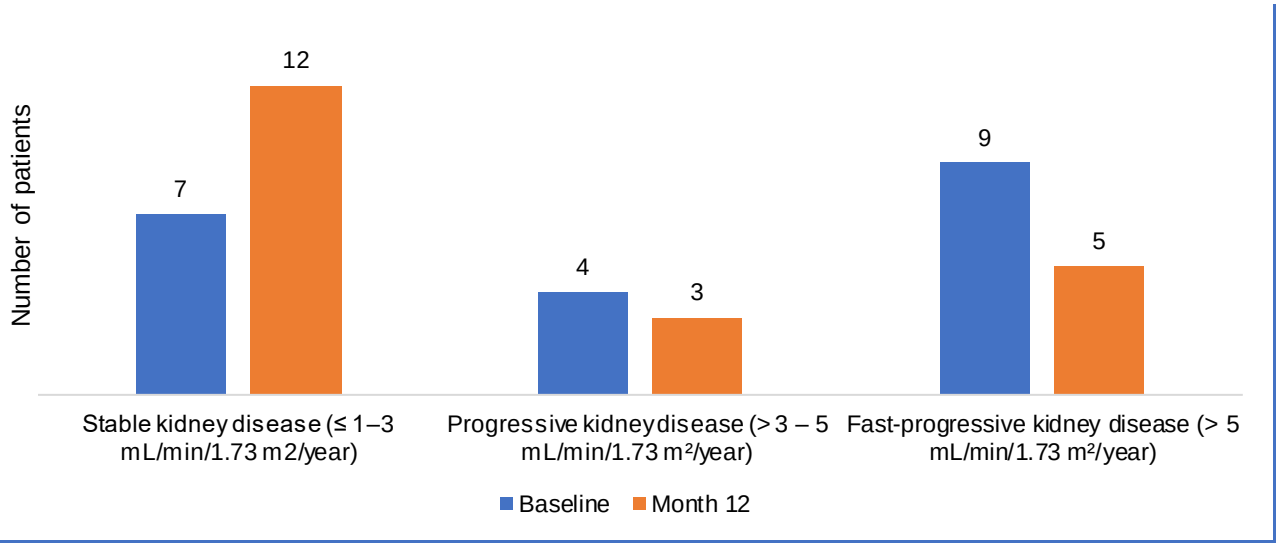
Key: eGFR, estimated glomerular filtration rate; NR, not reported; SE, standard error.

Notes: [a], p-value for change from baseline between pre- and post-switch, calculated using a paired t-test.

Source: BRIDGE CSR 2020 (Chiesi 2020c)

Figure 12 presents a summary of the change in kidney disease status following the switch to pegunigalsidase alfa. After patients were switched to pegunigalsidase alfa, the number of patients with stable kidney disease (slopes ≥-3 mL/min/1.73 m^2/year) increased from seven (35.0%) to twelve (60.0%) patients, and the number of patients with progressive (slope between ≥-5 to <-3 mL/min/1.73 m^2/year) and fast-progressive kidney disease (slopes <-5 mL/min/1.73 m^2/year) decreased from four to three, and from nine to five, respectively (Chiesi 2020c).

Figure 12: Change in annualized eGFR following the switch to pegunigalsidase alfa



Key: eGFR, estimated glomerular filtration rate.

Source: BRIDGE CSR 2020 (Chiesi 2020c)

Proteinuria: Urine protein/creatinine ratio (spot urine test)

Exact UPCR values could be determined in ten out of 20 (50%) patients at baseline, and in 11 out of 20 (55%) patients at 12 months. This was because urine protein concentrations were below the level of detection (<4 mg/dL) at a number of sampling time points (Chiesi 2020c). Due to the afore-mentioned limitations, no statistical analyses were conducted (Chiesi 2020c). As such, the shifts of UPCR classification based on Kidney Disease: Improving Global Outcomes (KDIGO) categories (KDIGO 2012) were used to assess the treatment effect on proteinuria throughout the study.

At baseline, a total of three (15%) patients had normal to mildly increased UPCR (<0.15 g/g), three (15%) patients had moderately increased UPCR (≥0.15 to ≤0.5 g/g), four (20%) patients had severely increased UPCR (>0.5 g/g), and the UPCR category for ten (50%) patients could not be determined (Chiesi 2020c). At 12 months, there was little change in the distribution of patients between KDIGO and UPCR categories.

Of note, the [redacted] patients with proteinuria (KDIGO classification of 'severely increased') at 12 months were all receiving ACEIs or ARBs at baseline (Chiesi 2020c).

Cardiac outcomes: Echocardiography results

LVMi

In male patients 20 to 60 years of age, the normal range for LVMi is 57 to 91 g/m^2, in female patients 20 to 60 years of age the normal range is 47 to 77 g/m^2 (Kawel-Boehm et al. 2015).

LVMi was determined based on cardiac MRI data. Mean LVMi was 86.9 g/m^2 at baseline and 89.4 g/m^2 at Month 12 (Chiesi 2020c). [redacted] ([redacted] %) patients had a normal LVMi at baseline, [redacted] had elevated levels, and [redacted] showed a low value. For [redacted] patient, a deterioration between baseline and Month

12 was noted (from normal to elevated LVMi), while for [redacted] patients, improvements in the category were recorded (from low or high to normal).

The normal range for left ventricular ejection fraction (LVEF) is [redacted] to [redacted] % regardless of gender. The LVEF increased by a mean of [redacted] % over the treatment period ([redacted] % at baseline to [redacted] % at Month 12).

Exercise tolerance (stress test)

Stress test results were unavailable for two patients at 12 months. At baseline, seven (35.0%) patients had an abnormal stress test, increasing to eight (42.1%) patients at 12 months (Chiesi 2020c).

Fabry clinical events

In the safety population, only two Fabry clinical events were reported, and both events occurred in one (4.5%) patient (Chiesi 2020c). The two events were:

- One moderate cerebrovascular event (TEAE of 'transient ischemic attack'), which occurred after Visit 1 and was not related to study treatment. The event led to study drug interruption (infusion deferred) and resolved with sequela. The patient had a previous medical history of transient ischemic attack in 2010.
- One moderate cardiac event (new complete right bundle branch block reported as a TEAE of 'ECG change') on the day of the last visit, which was considered unlikely to be related to study treatment. The event did not result in a study drug dose change. The patient had a previous medical history of arrythmias, cardiomyopathy, conduction defects, hypertension, and valvular insufficiency.

No renal Fabry clinical events were reported during the study.

Humanistic outcomes

Humanistic outcomes data were presented for the PPE population.

Pain medication use

A total of 16 patients (80.0%) used pain medication at some point during the study. Patients often used one (six patients) or two (five patients) pain medications during the study, and a maximum of five pain medications were taken by one patient (Chiesi 2020c).

Short form Brief Pain Inventory

Overall, there were no major changes in short form BPI results, where zero (0) is no pain or interference. The BPI results showed a mean change in the pain severity mean severity score from a baseline value of 1.43 to Month 12 of 0.23 ([redacted] in male patients and [redacted] in female patients) (Chiesi 2020c).

Mainz Severity Score Index

From baseline to 12 months, MSSI scores were stable over the treatment period or showed slight improvements (Chiesi 2020c). Mean overall MSSI scores improved slightly from [redacted] at baseline to [redacted] at 12 months. The neurological score also improved from [redacted] at baseline to [redacted] at 12 months.

In males and females, mean overall MSSI scores improved from [redacted] at baseline to [redacted] at 12 months, and from [redacted] at baseline to [redacted] at 12 months, respectively.

EQ-5D-5L

Overall, there were no major changes in the short form EQ-5D-5L results from baseline to 12 months, indicating that treatment with pegunigalsidase alfa had no detrimental impact on patient QoL (Table 56) (Chiesi 2020c).

Table 56: Summary of EQ-5D-5L domain changes from baseline to 12 months

Timepoint	No problem	Slight problem	Moderate problem	Severe problem
Mobility, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Self-care, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Pain or discomfort, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety or depression, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: BRIDGE CSR 2020 (Chiesi 2020c)

At baseline, the median EQ VAS score was [redacted] (range: [redacted]), which improved slightly after 12 months to [redacted] (range: [redacted]) (Chiesi 2020c). Males had lower baseline EQ VAS scores than females ([redacted] [range: [redacted]] versus [redacted] [range: [redacted]]) and at 12 months ([redacted] [range: [redacted]] versus [redacted] [range: [redacted]]). Of note, all [redacted] patients with severe problems at 12 months were male.

Efficacy results from the Phase III BRIGHT study

Of note, BRIGHT is a single-arm study, therefore no table similar to Table 48 has been completed for BRIGHT since the table is designed specifically for comparative studies. The results from BRIGHT are presented below.

Clinical efficacy outcomes

Efficacy results are presented for the PPE population, which comprised 29 patients who had completed 12 months of study treatment.

Pharmacodynamics

Plasma lyso-Gb_3 concentrations

At baseline, mean plasma lyso-Gb_3 concentration was 19.4 nM (23.3 nM and 4.4 nM for male and female patients, respectively) (Chiesi 2021). After 12 months, the mean plasma lyso-Gb_3 concentration was increased to 22.2 nM. This effect was mainly driven by male patients, with a mean increase from baseline to Month 12 of 3.8 nM; plasma lyso-Gb_3 levels remained stable in female patients (Table 57).

Table 57: Summary of change in plasma lyso-Gb_3 concentrations from baseline to 12 months

	Male (n = 23)	Female (n = 6)	Total (n = 29)
Plasma lyso-Gb3 concentration (nM), mean (SE)			
Baseline	23.3 [redacted]	4.4 [redacted]	19.4 (3.4)
Month 12	[redacted]	[redacted]	22.2 (3.6)
Change in plasma lyso-Gb_3 concentrations from baseline to 12 months			
Mean (SE)	[redacted]	[redacted]	[redacted]
% change in plasma lyso-Gb_3 concentrations from baseline to 12 months			
Mean (SE)	[redacted]	[redacted]	[redacted]

Key: lyso-Gb_3, globotriaosylsphingosine; SE, standard error.

Source: BRIGHT CSR 2021 (Chiesi 2021)

Urine lyso-Gb3 concentrations

Overall, urine lyso-Gb_3 concentrations were relatively stable with a slight decrease from [redacted] pM/mM at baseline to [redacted] pM/mM at Month 12 (Chiesi 2021).

Plasma Gb3 concentrations

At baseline, mean plasma Gb_3 concentrations were [redacted] nM, slightly increasing to [redacted] nM after 12 months (Chiesi 2021). Gb_3 concentration tended to increase in [redacted] patients (mean increase of [redacted] nM) and decrease in [redacted] patients (mean decrease of -[redacted] nM) during this period.

Renal outcomes

Change in $eGFR_{CKD\text{-}EPI}$ and annualized eGFR slope

Mean absolute eGFR values remained relatively stable over time. At baseline, the total mean eGFR was 99.4 mL/min/1.73 m^2, slightly increasing to 100.7 mL/min/1.73 m^2 after 12 months (Chiesi 2021). However, a status of kidney hyperfiltration (eGFR value >120 mL/min/1.73 m^2) at baseline was present in 5/29 patients in the PPE population ([redacted] patients with a positive ADA status). When considering those patients with a status of hyperfiltration at baseline (n = 5), a pronounced decrease in eGFR from baseline to Week 52 of [redacted] mL/min/1.73 m^2 was observed. For the remaining population, eGFR was relatively stable with a change of [redacted] mL/min/1.73 m^2.

The total annualized eGFR slope was -1.8 mL/min/1.73 m^2/year at baseline, and -2.9 mL/min/1.73 m^2 at Month 12 (Chiesi 2021). In patients who had a status of hyperfiltration at baseline (n = 5), a greater mean decline in eGFR slope (from -1.3 to -5.4 mL/min/1.73 m^2/year) was observed compared with the remaining 24 patients who were non-hyperfiltrating (from -1.9 to -2.4 mL/min/1.73 m^2/year). The greater rate of decline observed in patients with kidney hyperfiltration may indicate filtration rate normalization in these patients.

As for previous ERT subpopulations, mean absolute eGFR values were similar for patients previously treated with agalsidase alfa and agalsidase beta.

Table 58 presents a summary of the change in eGFR and eGFR slope from baseline to Month 12. Figure 13 shows the mean eGFR change over time.

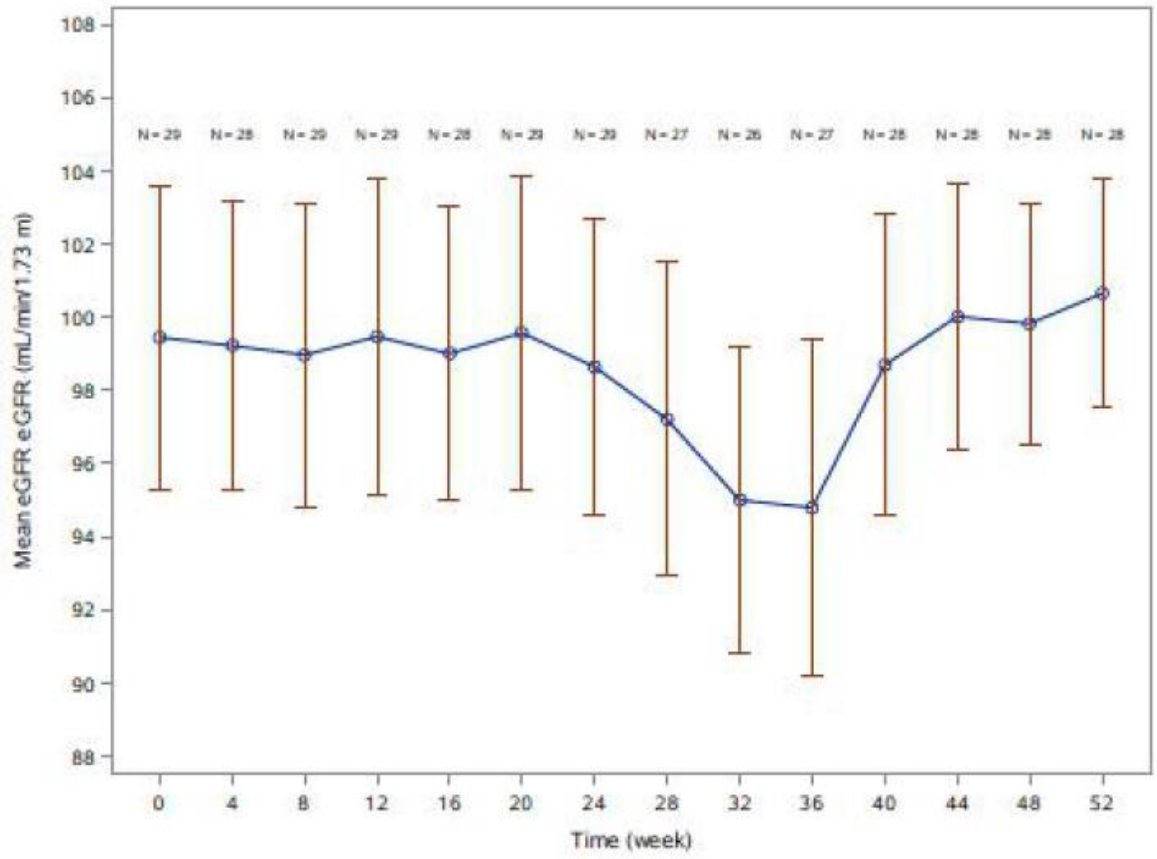
Table 58: Summary of change in eGFR and eGFR slope from baseline to 12 months

	Male (n = 23)	Female (n = 6)	Total (n = 29)
eGFR (mL/min/1.73 m²), mean (SE)			
Baseline	[redacted]	[redacted]	99.4 (5.2)
Month 12	[redacted]	[redacted]	100.6 (3.1)
Change in eGFR from baseline (pre-switch) to 12 months (post-switch)			
Mean (SE)	-0.6 (1.6)	-3.5 (3.1)	-1.3 (1.4)
eGFR slope (mL/min/1.73 m²/year), mean (SE)			
Baseline	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]

Key: eGFR, estimated glomerular filtration rate; SE, standard error.

Source: BRIGHT CSR 2021 (Chiesi 2021)

Figure 13: Mean (SE) eGFR over time



Source: BRIGHT CSR 2021 (Chiesi 2021)

Proteinuria: Urine protein/creatinine ratio (spot urine test)

Exact UPCR values could be determined in some patients at many sample points because urine protein concentrations were below the level of detection (<4 mg/dL) at a number of sampling time points (Chiesi 2021).

[redacted] ([redacted]%) patients had normal to mildly increased UPCR at baseline regardless of gender. [redacted] ([redacted]%) patients had moderately increased UPCR, and severely increased UPCR was reported

in [redacted] ([redacted] %) patients who were both male, with a positive ADA status and non-classic Fabry disease and who had been previously treated with agalsidase beta. [redacted] patients showed an overall shift during the study to severely increased UPCR.

Cardiac outcomes: Echocardiography results and Stress Test

In this study, the echocardiograms were not performed in a standardized manner and/or read centrally and therefore, data for quantitative echocardiography evaluations were only presented by patient. Echocardiography assessments regarding aortic, mitral, pulmonic and tricuspid valves showed stability in the proportion of patients with normal/other results throughout the study (Chiesi 2021).

- Aortic valves: [redacted] patients had normal results during the study, including [redacted] patients at baseline and [redacted] patients at Week 52
- Mitral valves: approximately [redacted] of the patients had normal results during the study, [redacted] patients at baseline and [redacted] patients at Week 52
- Pulmonic valves: [redacted] patients had normal results at baseline and [redacted] patients had normal results at Week 52
- Tricuspid valves: [redacted] patients had normal results at baseline and [redacted] patients had normal results at Week 52

The cardiac stress test results generally showed an improvement or remained stable during treatment; a normal overall impression was recorded in 67.9% of patients at baseline and 87.5% of patients at Week 52.

Fabry clinical events

No Fabry clinical events were identified in this study (Chiesi 2021).

Pharmacokinetic analyses

The PK results (Table 59) indicate that pegunigalsidase alfa, administered at a dose of 2 mg/kg E4W, is rapidly available and has a $t_{1/2}$ ranging from [redacted] hours (Chiesi 2021). In addition, the mean concentrations of pegunigalsidase alfa at the end of each dosing interval (i.e., 4 weeks post-dose) were significantly above the lower limit of quantification ([redacted] ng/mL) and ranged from [redacted] to [redacted] ng/mL, further supporting the use of a 4-week dosing interval. All observations regarding the PK parameters indicate a consistent PK profile throughout the 12-month study.

Table 59: Pharmacokinetic properties of pegunigalsidase alfa (2 mg/kg E4W)

Pharmacokinetic parameter (mean)	Baseline	Month 12	CV across visits
Mean infusion length, hours	[redacted]	[redacted]	[redacted]
AUC-∞, ng•hr/mL	[redacted]	[redacted]	[redacted]
C_{max}, µg/mL	[redacted]	[redacted]	[redacted]
T_{max}, hours	[redacted]	[redacted]	[redacted]
Half-life ($T_{1/2}$), hours	[redacted]	[redacted]	[redacted]

Clearance, mL/hour	[redacted]	[redacted]	[redacted]
Volume of distribution, mL	[redacted]	[redacted]	[redacted]
C_{24hr}, ng/mL	[redacted]	[redacted]	[redacted]
C_{2wk}, ng/mL	[redacted]	[redacted]	[redacted]
C_{4wk}, ng/mL	[redacted]	[redacted]	[redacted]

Key: AUC, area under the curve; CV, coefficient of variation; E4W, every 4 weeks.

Source: BRIGHT CSR, 2021 (Chiesi 2021)

There were [redacted] patients who were ADA positive at baseline; they have a lower area under the curve (AUC) and shorter $t_{1/2}$, but a comparable C_{max}. Results showed that there was no noticeable difference in PK parameters between patients who had a body weight >100 kg and <100 kg or between genders.

Humanistic outcomes

Humanistic outcomes were presented for the PPE population.

Pain medication use

Pain medication use at some point during the study was reported for a total of [redacted] %) patients. Patients often received [redacted] ([redacted] patients), [redacted] ([redacted] patients) or [redacted] ([redacted] patients) pain medications during the study. The use of four, five, and seven pain medications were reported in [redacted] patient (Chiesi 2021).

Short form Brief Pain Inventory

No major changes were observed from baseline to Month 12, indicating no changes in pain perception over the treatment period (Chiesi 2021). Compared with baseline, [redacted] of patients ([redacted] %) had an improvement or no change in average pain severity at Week 24 and Month 12 ([redacted] %] and [redacted] %] patients, respectively), and [redacted] patients had a deterioration at Week 24 ([redacted] %) and Week 52 ([redacted] %).

Mainz Severity Score Index

The MSSI scores were generally stable or showed a slight improvement from baseline to Month 12 (Chiesi 2021). Mean overall MSSI scores improved from [redacted] at baseline to [redacted] at 12 months, neurological score improved from [redacted] at baseline to [redacted] at 12 months and cardiovascular score improved from [redacted] at baseline to [redacted] at 12 months. [redacted] of patients had an MSSI overall score classified as mild or moderate at baseline ([redacted] % and [redacted] %, respectively), while [redacted] ([redacted] %) patient had a score classified as severe.

EQ-5D-5L

The overall health score was relatively stable or showed a slight improvement during the study, with mean values of [redacted] and [redacted] at baseline and at Month 12, respectively (Table 60) (Chiesi 2021). The [redacted] of patients had no problems for each of the five score dimensions.

Table 60: Summary of EQ-5D-5L domain changes from baseline to 12 months

Timepoint	No problem	Slight problem	Moderate problem	Severe problem
Mobility, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Self-care, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Pain or discomfort, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety or depression, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a],one patient had extreme anxiety/depression at baseline and Month 12

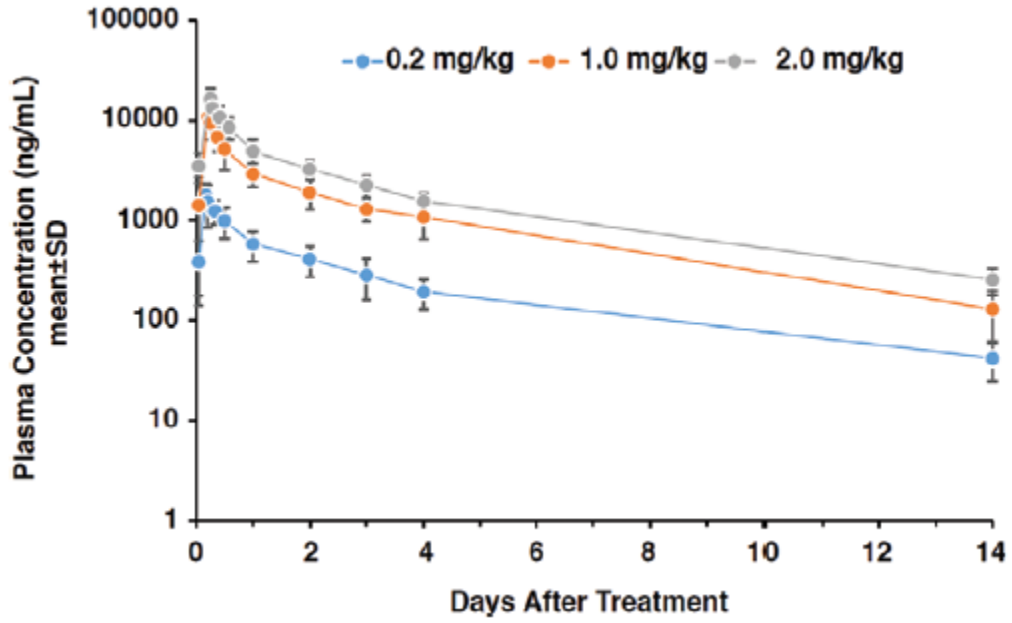
Source: BRIGHT CSR 2021 (Chiesi 2021)

Efficacy results from the Phase I/II PB-102-F01 and PB-102-F02 studies

Pharmacokinetic analyses

A range of pharmacokinetic analyses were conducted to determine the appropriate dose for subsequent clinical studies. Measurable concentrations of pegunigalsidase alfa were present throughout the entire 2-week dosing interval for each dose group (Figure 14). Specifically, pegunigalsidase alfa 1.0 mg/kg dose had enhanced pharmacokinetic properties, including a plasma half-life of approximately 80 hours, and a substantially higher $AUC_{0-\infty}$ of 390,896 ng•hr/mL.

Figure 14: Summary of pegunigalsidase alfa plasma levels throughout the 14-day dosing interval



Key: SD, standard deviation.

Source: (Schiffmann et al. 2019)

Pharmacodynamics

This section reports plasma Gb_3 and lyso-Gb_3 concentrations, as well as kidney Gb_3 concentrations (obtained through kidney biopsy analyses) for patients in the PB-102-F01 and PB-102-F02 studies. Of note, one male patient in the 0.2 mg/kg treatment group had no recorded baseline plasma Gb_3 concentration, and therefore, was not included in the analysis with respect to the change from baseline.

Plasma Gb_3 concentrations

Table 61 presents the changes in mean plasma Gb_3 concentrations from baseline to 6 and 12 months by treatment group. As expected, male patients had a higher mean concentration of plasma Gb_3 at baseline than female patients in all cohorts (Chiesi 2017d). At both 6 and 12 months, reductions in mean plasma Gb_3 concentrations were observed in both men and women across all treatment groups. The greatest reductions in mean plasma Gb_3 concentrations were observed for patients in the 1.0 mg/kg dose group, reducing by [redacted] % and [redacted] % in males and females, respectively.

Table 61: Plasma Gb_3 concentrations by dose group and gender

Gb_3 (ug/ml)	0.2 mg/kg (n = 6)		1.0 mg/kg (n = 6)		2.0 mg/kg (n = 6)	
	Male (n = 4)	Female (n = 2)	Male (n = 4)	Female (n = 2)	Male (n = 1)	Female (n = 3)
Baseline, mean (SE)	14.0 [redacted]	5.8 [redacted]	13.3 [redacted]	6.5 [redacted]	12.7 [redacted]	5.8 [redacted]
6 months, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gb_3 (ug/ml)	0.2 mg/kg (n = 6)		1.0 mg/kg (n = 6)		2.0 mg/kg (n = 6)	
	Male (n = 4)	Female (n = 2)	Male (n = 4)	Female (n = 2)	Male (n = 1)	Female (n = 3)
12 months, mean (SE)	[redacted]					
Mean % change from baseline to 12 months	[redacted]					

Key: Gb_3, globotriaosylceramide; N/A, not applicable; SE, standard error.

Source: PB-102-F01 and PB-102-F02 CSR, 2017 (Chiesi 2017d)

Note that for the [redacted] patients with classic Fabry disease, a total mean reduction from baseline in plasma Gb_3 concentration was observed at both 6 and 12 months, decreasing by 30.4% ([redacted]%) and 33.3% ([redacted]%), respectively (Chiesi 2017d).

Plasma lyso-Gb_3 concentrations

Reductions in mean plasma lyso-Gb_3 levels were also observed throughout the study for the entire study population. Table 62 presents the changes in mean plasma lyso-Gb_3 concentrations from baseline to 6 and 12 months by dose group. Male patients had a higher mean concentration of plasma lyso-Gb_3 at baseline than female patients in all cohorts (Chiesi 2017d). At both 6 and 12 months, reductions in plasma lyso-Gb_3 concentrations were observed in both males and females across all treatment groups. Again, the greatest reductions in mean plasma lyso-Gb_3 concentrations were observed for patients in the 1.0 mg/kg dose group, reducing by 67.7% and 44.5% in males and females, respectively.

Table 62: Plasma lyso-Gb_3 concentrations by dose group and gender

Lyso-Gb_3 (ug/mL)	0.2 mg/kg (n = 6)		1.0 mg/kg (n = 6)		2.0 mg/kg (n = 6)	
	Male (n = 4)	Female (n = 2)	Male (n = 4)	Female (n = 2)	Male (n = 1)	Female (n = 3)
Baseline, mean (SE)	134.2 (47.2)	13.4 (5.9)	100.6 (39.4)	10.6 (3.8)	61.8 (N/A)	6.4 (2.3)
6 months, mean (SE)	[redacted]					
Mean % change from baseline to 6 months	[redacted]					
12 months, mean (SE)	45.1 [redacted]	12.4 [redacted]	25.6 [redacted]	5.7 [redacted]	30.8 [redacted]	4.0 [redacted]
Mean % change from baseline to 12 months	-61.8 (5.9)	-6.6 (1.2)	-67.7 (7.7)	-44.5 (6.2)	-50.2 (N/A)	-37.2 (9.5)

Key: Lyso-Gb_3, globotriaosylsphingosine; N/A, not applicable; SE, standard error.

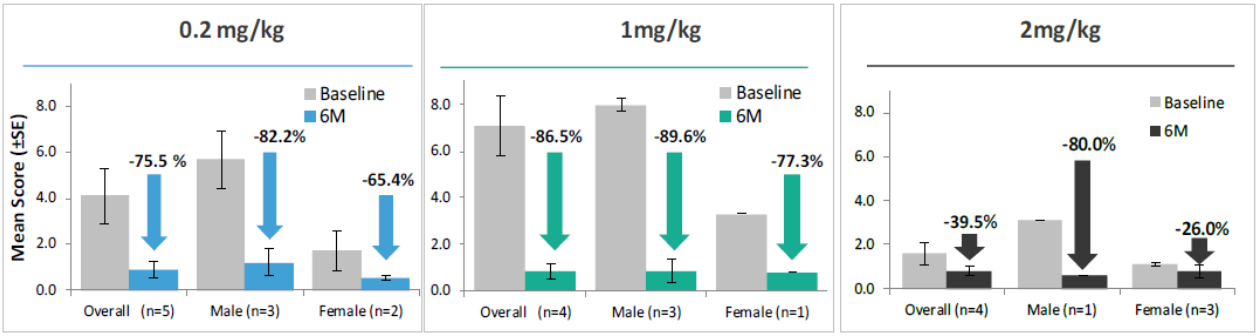
Source: PB-102-F01 and PB-102-F02 CSR, 2017 (Chiesi 2017d)

For the [redacted] patients with classic Fabry disease, a total mean reduction from baseline in plasma lyso-Gb_3 concentration was observed at both 6 and 12 months, decreasing by [redacted]% ([redacted]%) and [redacted]% ([redacted]%), respectively (Chiesi 2017d).

Gb_3 deposition in the kidney

Kidney biopsies analysing Gb_3 deposition in kidney peritubular capillaries were performed at baseline and following 6 months of treatment with pegunigalsidase alfa; data were available from 13 patients. From baseline to 6 months, the total mean Barisoni Lipid Inclusion Scoring System (BLISS) score decreased by 67.8% (SE 8.9%), reducing from 4.26 to 0.83 (Schiffmann et al. 2019, Chiesi 2017d). Mean improvements in the BLISS score were observed in males and females across all three treatment groups, with the largest reductions in the 1.0 mg/kg treatment group (-89.6% and -77.3%, respectively; Figure 15). Furthermore, 11 patients demonstrated more than a 50% reduction in the number of Gb_3 inclusions at 6 months (≥50% reduction in BLISS score). The eight patients with classic Fabry disease had a greater mean decrease in the BLISS score compared with that of the total study population (-84.1% versus -67.8%; Figure 16). Approximately, 80% of the overall population had lowered BLISS scores by >50% at Month 6, which is favourable compared with migalastat (52% with >50% reduction for migalastat versus 45% for placebo) (KDIGO 2012). Of note, the reductions in Gb_3 deposition in kidney peritubular capillaries were highly correlated with sustained reductions in plasma lyso-Gb_3 concentrations.

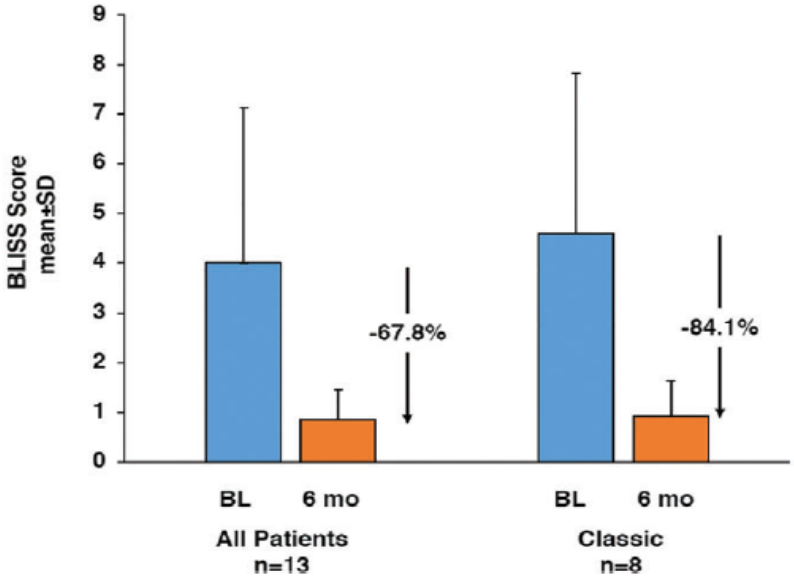
Figure 15: Reduction of Gb_3 deposition in kidney peritubular capillaries following 6 months of pegunigalsidase alfa treatment (by dose group and gender)



Key: 6M, 6 months; Gb_3, globotriaosylceramide; SE, standard error.

Source: PB-102-F01 and PB-102-F02 CSR (Chiesi 2017d)

Figure 16: Reduction of Gb_3 deposition in kidney peritubular capillaries following 6 months of pegunigalsidase alfa treatment (classic versus total population)



Key: BL, baseline; BLISS, Barisoni Lipid Inclusion Scoring System; Gb_3, globotriaosylceramide; mo, months; SD, standard deviation.

Notes: The three dosing groups were combined for this analysis.

Source: (Schiffmann et al. 2019)

Renal outcomes

Change in eGFR

Overall, the eGFR results indicate stability in kidney function after 12 months of treatment with pegunigalsidase alfa (Schiffmann et al. 2019, Chiesi 2017d). For the total population, mean eGFR at baseline was 111.2 (SE 20.9) mL/min/1.73 m^2 (range: 78–156 mL/min/1.73 m^2), decreasing to 110.2 (SE 21.1) mL/min/1.73 m^2 (range: 72–151 mL/min/1.73 m^2) after 6 months, and 110.5 (SE 23.4) mL/min/1.73 m^2 (range: 68–152 mL/min/1.73 m^2) after 12 months; a mean decrease of [redacted] and -0.8 mL/min/1.73 m^2, respectively (Chiesi 2017a, Schiffmann et al. 2019).

Table 63 presents the changes in eGFR from baseline to 6 and 12 months for each individual patient. For [redacted] patients, there was little change in eGFR from baseline to 12 months; [redacted] patients had a decrease in eGFR, and [redacted] patients had an increase (Chiesi 2017d). The proportion of patients with an eGFR within normal range (90–120 ml/min/1.73 m^2) (Wanner et al. 2018) [redacted] from baseline to 12 months (44%).

In the 1.0 mg/kg dose group, [redacted] experienced a decrease in eGFR (Chiesi 2017d). [redacted] patients ([redacted]) had slight decreases in eGFR, but [redacted] patients retained eGFR values >[redacted] mL/min/1.73 m^2 (Table 63). [redacted] patient had a decrease in eGFR that resulted in a change, indicating mild to moderate kidney function impairment (60–90 ml/min/1.73 m^2)(Wanner et al. 2018); however, [redacted] was suspected to be influenced by intermittent treatment with doxycycline, which is known to transiently exacerbate renal disease.

Table 63: Change in eGFR from baseline to 6 and 12 months by individual patient

Dose	Gender	eGFR at baseline[a] (ml/min/1.73 m^2)	eGFR at 6 months (ml/min/1.73 m^2)	Mean % change from baseline to 6 months	eGFR at 12 months (ml/min/1.73 m^2)	Mean % change from baseline to 12 months
0.2 mg/kg	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.0 mg/kg	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.0 mg/kg	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: eGFR, estimated glomerular filtration rate.

Notes: [a], 12-month data not reported for this female patient, therefore eGFR value at 38 weeks was used in supplement.

Source: PB-102-F01 and PB-102-F02 CSR (Chiesi 2017d)

For the [redacted] patients with classic Fabry disease, eGFR remained stable throughout the study, with a mean eGFR of [redacted] ml/min/1.73 m^2 at both baseline and 12 months (Chiesi 2017b).

Annualized eGFR slope

Table 64 presents a summary of the annualized eGFR slopes for all patients. Overall, [redacted] patients ([redacted]%) had a positive eGFR slope and [redacted] patients ([redacted]) had a [redacted] eGFR slope (Chiesi 2017d). Of the [redacted] patients with [redacted] eGFR slopes, [redacted] were considered to have stable renal function, [redacted] had progressive renal disease, and [redacted] had fast-progressive renal disease.

The [redacted] patients in the 1.0 mg/kg dose group had positive annualized eGFR slopes; however, [redacted] patient had a negative eGFR slope of -[redacted] (i.e. progressive renal disease), and [redacted] patient had a negative eGFR slope of -[redacted] (i.e. fast-progressive renal disease) (Chiesi 2017d). Note that [redacted] patient was suspected to be influenced by intermittent treatment with doxycycline, which is known to transiently exacerbate renal disease.

Table 64: Annualized eGFR slope per patient

Dose	Gender (patient number)	eGFR at baseline	eGFR at 12 months	Slope[c]
0.2 mg/kg	Male (F103)	[redacted]	[redacted]	[redacted]
	Male (F106)			
	Male (F105)			
	Male (F104)			
	Female (F101)			
	Female (F102)			
1.0 mg/kg	Male (F112)			
	Male (F113)			
	Male (F108)			
	Male (F114)			
	Female (F107)			
	Female (F115)			
2.0 mg/kg	Male (F119)			
	Female (F116)			
	Female (F117)			
	Female (F118)			

Key: eGFR, estimated glomerular filtration rate.

Notes: [a], 12-month data not reported for this female patient, therefore eGFR value at 38 weeks was used in supplement; [b], this patient was suspected to be influenced by intermittent treatment with doxycycline, used to treat a series of adverse events. Doxycycline may transiently exacerbate renal disease; [c] Slope loss ≤ 1–3 mL/min/1.7 3m^2/year = stable renal function; Slope loss >3 mL/min/1.73 m^2/year = progressive renal disease; slope loss >5 mL/min/1.73 m^2/year = fast-progressive renal disease.

Source: PB-102-F01 and PB-102-F02 CSR (Chiesi 2017d)

For the 10 patients with classic Fabry disease, the mean annualized eGFR slope was -1.8 mL/min/1.73 m^2/year (range: -18.18–6.35 mL/min/1.73 m^2/year) (Chiesi 2017d). On excluding the male patient who was treated with doxycycline, the remaining nine patients demonstrated a positive mean eGFR slope of 0.01 mL/min/1.73 m^2/year (range: -6.35–6.35 mL/min/1.73 m^2/year).

Proteinuria: Urine protein/creatinine ratio (spot urine test)

At baseline, 12 patients had a normal urine protein/creatine ratio (UPCR) and four had a UPCR above normal (>200 mg/g) (Schiffmann et al. 2019). After 12 months of pegunigalsidase alfa treatment, only

two patients had an abnormal UPCR; however, it should be noted that these patients had the highest UPCR at baseline, and both demonstrated a decrease in UPCR during treatment.

Table 65 presents the changes in mean UPCR from baseline to 6 and 12 months by treatment group.

Table 65: Change in UPCR from baseline to 6 and 12 months by dose group and gender

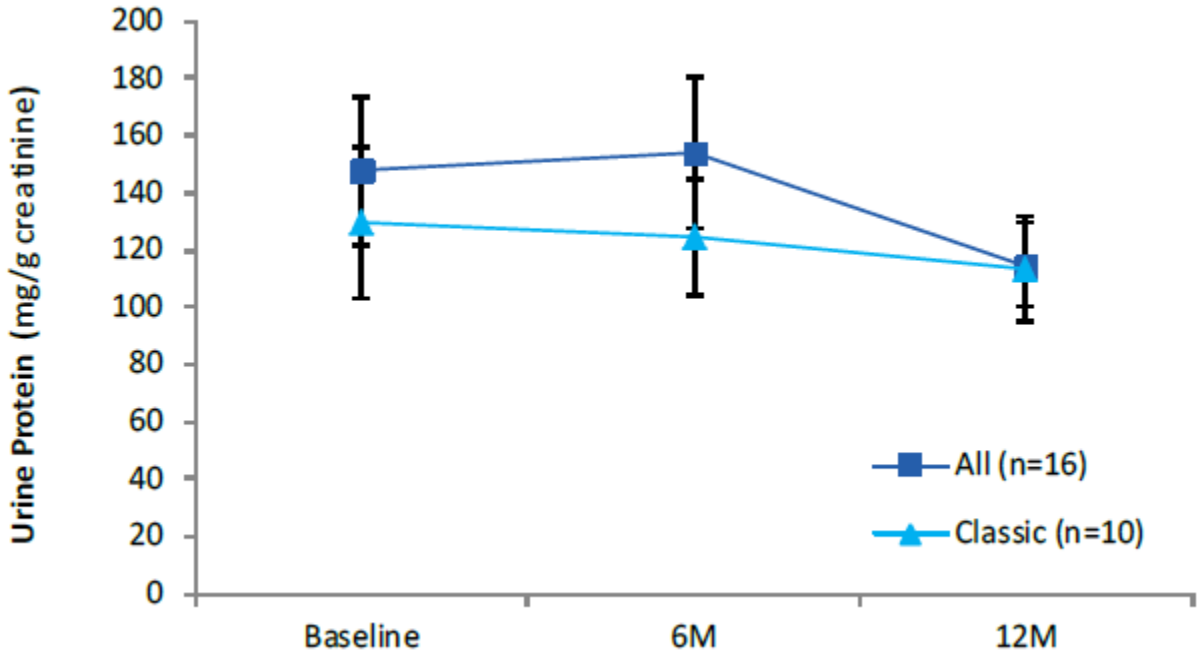
UPCR (mg/g)	0.2 mg/kg (n = 6)		1.0 mg/kg (n = 6)		2.0 mg/kg (n = 6)	
	Male (n = 4)	Female (n = 2)	Male (n = 4)	Female (n = 2)	Male (n = 1)	Female (n = 3)
Baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline to 6 months (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline to 12 months (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: N/A, not applicable; SE, standard error; UPCR, urine protein/creatine ratio.

Source: PB-102-F01 and PB-102-F02 CSR, 2017 (Chiesi 2017a)

Figure 17 presents a summary of UPCR for all patients versus those with classic Fabry disease. At baseline, patients with classic Fabry disease had a mean UPCR of [redacted] (SE [redacted]) mg/g and [redacted] of the [redacted] classic Fabry patients had a UPCR >200 mg/g (Schiffmann et al. 2019, Chiesi 2017a). After 12 months, the mean UPCR decreased to [redacted] (SE [redacted]) mg/g, a mean decrease of [redacted] mg/g (Chiesi 2017a)

Figure 17: Urine protein/creatinine ratio levels (All versus Classic Fabry patients)



Key: M, month.

Source: PB-102-F01 and PB-102-F02 CSR (Chiesi 2017d)

Cardiac outcomes: MRI results

LVM, LVMi and ejection fraction

For all patients at baseline, mean LVM, left ventricular mass index (LVMi) and ejection fraction were within the normal range, and no cardiac fibrosis was present (Schiffmann et al. 2019). Cardiac MRI results showed that the majority of patients maintained cardiac parameters (LVM, LVMi and ejection fraction) within the normal ranges throughout the 12-month study period.

In male patients, 20 to 60 years of age, the normal range for LVMi is 57 – 91 g/m^2, in female patients, 20 to 60 years of age, the normal range is 47 – 77 g/m^2 (Kawel-Boehm et al. 2015).

It should also be noted that no cardiac fibrosis was observed after 12 months. Table 66 presents the change from baseline to 6 and 12 months in LVM, LVMi and ejection fraction.

Table 66: Change in LVM, LVMi and ejection fraction from baseline to 6 and 12 months by dose group and gender

	0.2 mg/kg (n = 6)		1.0 mg/kg (n = 6)		2.0 mg/kg (n = 6)	
	Male (n = 4)	Female (n = 2)	Male (n = 4)	Female (n = 2)	Male (n = 1)	Female (n = 3)
LVM (g)[a]						
Baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	0.2 mg/kg (n = 6)		1.0 mg/kg (n = 6)		2.0 mg/kg (n = 6)	
	Male (n = 4)	Female (n = 2)	Male (n = 4)	Female (n = 2)	Male (n = 1)	Female (n = 3)
Mean % change from baseline to 12 months	[redacted]					
LVMi (g/m^2)[b]						
Baseline, mean (SE)	[redacted]					
6 months, mean (SE)	[redacted]					
Mean % change from baseline to 6 months	[redacted]					
12 months, mean (SE)	[redacted]					
Mean % change from baseline to 12 months	[redacted]					
Ejection fraction (%)[c]						
Baseline, mean (SE)	[redacted]					
6 months, mean (SE)	[redacted]					
Mean % change from baseline to 6 months	[redacted]					
12 months, mean (SE)	[redacted]					
Mean % change from baseline to 12 months	[redacted]					

Key: LVM, left ventricular mass; LVMi, left ventricular mass index; SE, standard error.
Notes: [a], normal range for males and females: 85–181 g and 66–115 g, respectively; [b], normal range for males and females: 46–84 g/m^2 and 37–67 g/m^2, respectively; [c], normal range for males and females 55–74%.
Source: PB-102-F01 and PB-102-F02 CSR, 2017 (Chiesi 2017d, Chiesi 2017c)

For the total population, the mean LVM at baseline was [redacted]) g, and the mean LVMi was [redacted] (SE [redacted]) g/m^2 (Chiesi 2017d, Chiesi 2017c). Mean LVM decreased to [redacted]) g after 6 months, and [redacted]) g after 12 months, a mean decrease of [redacted] and [redacted] g, respectively. Similarly, mean LVMi decreased to [redacted] (SE [redacted]) g/m2 after 6 months, and [redacted] (SE [redacted]) g/m2 after 12 months, a mean decrease of [redacted] and [redacted] g/m2, respectively. The mean ejection fraction at baseline was [redacted]% (SE [redacted]%), decreasing to [redacted]% ([redacted]%) at 6 months, and [redacted]% (SE [redacted]%) at 12 months, a mean decrease of [redacted]% and [redacted]%, respectively (Chiesi 2017c).

Throughout the 12-month treatment period, mean LVM, LVMi and ejection fraction values for males and females in the 1.0 mg/kg dose group remained within the normal range (Table 66) (Chiesi 2017d, Chiesi 2017c).

For the 10 patients with classic Fabry disease, mean LVM decreased slightly from baseline to 12 months. Decreasing from light decreases from baseline were observed in both mean LVM (-4.6 g [-2.6%]) and mean LVMi (-2.7 g/m^2 [-3.1%]), and slight decreases from baseline in mean ejection fraction (-4.7% [-7.3% change]) were also observed after 12 months (Chiesi 2017d).

Cerebrovascular outcomes

Brain MRI results

For all patients, [redacted] evidence of stroke was detected at baseline or following 12 months of pegunigalsidase alfa treatment (Chiesi 2017d).

Humanistic outcomes

Mainz Severity Score Index

For the total population, improvements in MSSI score were observed across all subscales. Table 67 presents a summary of the changes in the number of patients reporting MSSI subscale symptoms from baseline to 12 months. Treatment with pegunigalsidase alfa led to a reduction in the number of patients reporting any of the symptoms represented on the MSSI.

The total mean general score decreased from 6.6 at baseline to 4.8 at 12 months, a change largely driven by improvements in abdominal pain, diarrhoea and constipation, and musculoskeletal symptoms (Chiesi 2017d, Chiesi 2017c). Total mean neurological score decreased from 7.8 at baseline to 5.2 at 12 months, an improvement largely driven by a reduction in the number of patients with neuropathic pain, tinnitus, and vertigo. The total mean cardiovascular score decreased from 3.7 at baseline to 2.9 at 12 months, an improvement largely driven by reductions in the number of patients with cardiac structural/functional and ECG abnormalities. The total mean renal score decreased from 2.5 at baseline to 1.5 at 12 months, resulting from a reduction in the number of patients with proteinuria.

Table 67: Improvements in MSSI subscale symptoms from baseline to 12 months

MSSI subscale	Total population (n = 16)	
	Baseline, n (%)	12 months, n (%)
General score		
Abdominal pain	[redacted]	[redacted]
NYHA classification (I–II)	[redacted]	[redacted]
Diarrhoea/constipation	[redacted]	[redacted]
Musculoskeletal symptoms	[redacted]	[redacted]
Neurological score		
Neuropathic pain	[redacted]	[redacted]
Tinnitus	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Cardiovascular score		
Structural/functional abnormalities[a]	[redacted]	[redacted]
ECG abnormalities	[redacted]	[redacted]
Renal score		
Proteinuria	[redacted]	[redacted]

Key: ECG, electrocardiogram; NYHA, New York Heart Association; MSSI, Mainz Severity Score Index.

Notes: [a], including thickening of wall/septum, left ventricular hypertrophy (as seen on ECG), and cardiomyopathy.

Source: PB-102-F01 and PB-102-F02 CSR, 2017 (Chiesi 2017c)

Short form Brief Pain Inventory

For the total population, mean changes from baseline to 12 months in pain severity score (-[redacted]) were observed, including mean decreases in worst pain (-[redacted]), least pain (-[redacted]), pain on average (-[redacted]) and pain right now (-[redacted]). Similarly, mean changes in pain interference score (-[redacted]) were also observed, including mean decreases in pain interfering with: general activity (-[redacted]), mood (-[redacted]), walking (-[redacted]),

working (-[redacted]), sleeping (-[redacted]), enjoyment of life (-[redacted]), and enjoyment with other people (-[redacted]). Similar improvements were also observed in the 10 classic Fabry patients, with mean reductions in both severity and interference score (-[redacted] for both).

Gastrointestinal Symptoms Assessment questionnaire

For the total population, improvements from baseline to 12 months in GSA score were observed. At baseline, 50% of patients had no or mild abdominal pain, 31% never or rarely had abdominal pain, and 59% never or rarely had diarrhoea; however, after 12 months, 63% of patients had no or mild abdominal pain, 44% never or rarely had abdominal pain, and 69% never or rarely had diarrhoea.

Similar improvements from baseline to 12 months were observed for the 10 patients with Classic Fabry disease. Indeed, the proportion of classic Fabry patients with no or mild abdominal pain increased from 60% to 70%, those never or rarely having abdominal pain increased from 30% to 50%, and those never or rarely having diarrhoea increased from 30% to 60%.

Efficacy results from the Phase I/II PB-102-F03 study

Unless stated otherwise, baseline values were those from baseline (i.e., Visit 1) in study PB-102-F01 and the presented timepoints correspond to an overall maximum treatment period of 72 months (i.e., 3 months in study PB-102-F01, 9 months in study PB-102-F02 and up to 60 months in study PB-102-F03). As only a small number of patients were treated for more than 60 months, efficacy data presented do not exceed Month 60 data (Chiesi 2020a).

Pharmacodynamics

Plasma lyso-Gb_3 concentrations

A continuous strong reduction in the total mean plasma lyso-Gb_3 concentration was observed from baseline (Visit 1 of study PB-102-F01) up to approximately Month 24, followed by a stabilization at approximately [redacted]% reduction for males and [redacted]% reduction for females throughout the remainder of the study. The mean reduction from baseline was [redacted] ng/mL ([redacted]% reduction from baseline) at Month 12 and 68.4 ng/mL ([redacted]% reduction from baseline) at Month 60 (Chiesi 2020a). Of note, [redacted] patients reached a reduction of ≥50% by Month 24. The number (%) of patients with a reduction from baseline of ≥[redacted]% in plasma lyso-Gb_3 concentration increased over the 60-month treatment period, from two patients at Month 12 to >[redacted]% of patients starting at Month 24 (Table 68).

Table 68: Summary of the change in plasma lyso-Gb_3 concentration from baseline in PB-102-F01 to 60 months in PB-102-F03

Plasma lyso-Gb_3 concentration	Male/Classic patients (n = 8)	Female/Non-classic patients (n = 7)	Treated ≥5 years (n = 10)	Overall (n = 15)
Baseline				
Absolute value (ng/mL), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 (Visit 27)				
Absolute value (ng/mL), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 (Visit 54)				

Absolute value (ng/mL), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 48 (Visit 106)				
Absolute value (ng/mL), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean % change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 60 (Visit 132)				
Absolute value (ng/mL), mean (SE)	[redacted]	[redacted]	6.4 (1.5)	6.4 (1.5)
Mean change from baseline (SE)	-111 (31.0)	-4.6 (0.9)	-68.4 (25.0)	-68.4 (25.0)
Mean % change from baseline (SE)	[redacted]	[redacted]	-83.3 (4.0)	-83.3 (4.0)

Key: lyso-Gb_3, globotriaosylsphingosine; SE, standard error.

Source: PB-102-F03 CSR 2020 (Chiesi 2020a)

There was a high correlation (R = 0.963) between the absolute change from baseline to Month 6 in kidney Gb_3, evaluated by BLISS. The correlation of kidney deposits (BLISS) with plasma lyso-Gb_3, which is a reliable biomarker for improvement in organ involvement and function (Chiesi 2020a).

Plasma Gb_3 concentrations

A reduction in the total mean plasma lyso-Gb_3 concentration was observed from baseline following treatment with pegunigalsidase alfa, decreasing by 3.4 µg/mL (22.9% reduction from baseline) at 12 months and a similar reduction was maintained up to 48 months of treatment. At Month 60, a smaller mean reduction of -2.8 µg/mL (-8.5%) was observed due to an increase in values in female patients at that timepoint (Chiesi 2020a).

Renal outcomes Change in eGFR

A relatively stable eGFR was observed over the 60-month treatment period. At baseline, the mean eGFR was 111.7 mL/min/1.73 m^2 (range: [redacted] mL/min/1.73 m^2), slightly decreasing by -0.4 mL/min/1.73 m^2 at Month 24 and by -10.9 mL/min/1.73 m^2 at Month 60. Long-term treated subjects (≥5 years) showed a development of eGFR values over time similar to the overall population (Chiesi 2020a).

Annualized eGFR slope

The mean annualized eGFR slope was -1.6 mL/min/1.73 m^2/year (range: [redacted] mL/min/m^2/year) (Table 69). The mean annualized eGFR slopes were more negative (indicating a higher decrease in eGFR over time) in male versus female patients and in long-term treated patients compared with the overall population (Chiesi 2020a).

Table 69: Annualized eGFR slope – Efficacy population

eGFR slope (mL/min/1.73 m^2/year)	Male/Classic patients (n = 8)	Female/Non-classic patients (n = 7)	Treated ≥5 years (n = 10)	Overall (n = 15)
Mean (SE)	[redacted]	[redacted]	[redacted]	-1.6 (0.8)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]

Key: eGFR, estimated glomerular filtration rate; SE, standard error.

Source: PB-102-F03 CSR, 2020 (Chiesi 2020a)

Proteinuria: Urine protein/creatinine ratio (spot urine test)

The [redacted] of patients ([redacted]%) had normal or mildly increased UPCR [redacted]% had moderately increased UPCR at baseline. [redacted] patient had severely increased UPCR at any time during the study (Chiesi 2020a). Shifts from normal or mildly increased UPCR at baseline to moderately increased UPCR were observed in [redacted] patients ([redacted]%) at Month 12, in [redacted] patients ([redacted]%) at Month 24, in [redacted] patients ([redacted]%) at Month 48, and in [redacted] patients ([redacted]%) at Month 60. Shifts from moderately increased UPCR at baseline to normal or mildly increased UPCR were observed in [redacted] patients ([redacted]%) at Month 12, in [redacted] patients ([redacted]%) at Month 24, in [redacted] patients ([redacted]%) at Month 48, and in [redacted] patient ([redacted]%) at Month 60.

Cardiac outcomes

Cardiac MRI results showed stability in LVM, LVMi and EF, with limited mean changes within normal ranges overall and per gender (Chiesi 2020a).

LVM

In male patients 20 to 60 years of age, the normal range for LVM is 107-187 g, in female patients 20 to 60 years of age, the normal range is 70 -142 g (Kawel-Boehm et al. 2015).

The mean LVM absolute value at baseline was 115.6 g for male patients and 70.8 for female patients and considered within normal ranges. At Month 24, cardiac MRI showed a mean slight increase among female patients (18.1 g), whereas in male patients, there was a slight mean decrease of 4.6 g. At Month 60, the mean increase observed in both subgroups was more pronounced in female patients (23.1 g) compared with male patients (14.1 g) (Chiesi 2020a). Although an increase from baseline was observed for male and female patients, the mean absolute LVM values remained normal at Month 24 and Month 60.

LVMi

In male patients 20 to 60 years of age, the normal range for LVMi is 57 – 91 g/m^2, in female patients 20 to 60 years of age, the normal range is 47 – 77 g/m^2 (Kawel-Boehm et al. 2015).

The mean (SE) LVMi absolute value was [redacted] g/m^2 ([redacted]) for male patients and [redacted] g/m^2 ([redacted]) for female patients and considered to be within normal ranges for male patients and below normal for female patients (Chiesi 2020a). A slow increase in mean LVMi was observed in both subgroups, with larger increases in female patients (Table 70).

Table 70: Change in LVMi from baseline in PB-102-F01 to 60 months in PB-102-F03

LVMi	Male/Classic patients (n = 8)	Female/Non-classic patients (n = 7)	Treated ≥5 years (n = 10)	Overall (n = 15)
Baseline				
Absolute value (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 (Visit 27)				
Absolute value (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 (Visit 54)				
Absolute value (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 48 (Visit 106)				
Absolute value (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Month 60 (Visit 132)				
Absolute value (g/m^2), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	5.7 (2.2)	13.6 (5.3)	[redacted]	[redacted]

Key: LVM, left ventricular mass; LVMi, left ventricular mass index; SE, standard error.

Source: PB-102-F03 CSR 2020 (Chiesi 2020a)

Cardiac hypertrophy was defined as LVMi above 91 g/m^2 for male patients and LVMi above 77 g/m^2 for female patients. [redacted] patients had hypertrophy at baseline or up to Month 48. At Month 48 and Month 60, [redacted] female patient was documented with cardiac hypertrophy (LVMi of [redacted] g/m^2 at Month 48 and [redacted] g/m^2 at Month 60, i.e., the index was not increasing over an extended treatment period) (Chiesi 2020a).

Cardiac fibrosis

Cardiac fibrosis was an exclusion criterion at baseline (study PB-102-F01). [redacted] patients developed fibrotic segments. No patients developed fibrosis during the study (Chiesi 2020a).

Ejection Fraction

In male patients 20 to 60 years of age, the normal range for EF is [redacted]%, in female patients 20 to 60 years of age, the normal range is [redacted]% (Kawel-Boehm et al. 2015).

EF was considered stable over 60 months of treatment. The overall mean EF absolute value was [redacted]% and considered to be within normal ranges. At Month 60, cardiac MRI results showed a slight mean decrease from screening of [redacted]%, with a mean absolute value of [redacted] (Chiesi 2020a).

Cardiac function

Overall, there were no relevant changes in echocardiography parameters during the study. Changes from a normal stress test at screening to an abnormal one was seen in one patient at Month 6, [redacted] patients at Month 12, and [redacted] patients each at Month 24 and Month 48. For the [redacted] patients with an

abnormal stress test at Month 48, the test showed normal results at Month 60 (Chiesi 2020a). Most patients had no ST changes, chest pain, dizziness, shortness of breath, or palpitations at screening or post-baseline.

Fabry clinical events

The single Fabry Clinical event in the study was a non-cardiac-related death following a chronic obstructive pulmonary disease (COPD) exacerbation after 39 months of treatment, which was considered unrelated to study treatment (Chiesi 2020a).

Humanistic outcomes

Mainz Severity Score Index

Stability or improvements in disease severity was confirmed by the MSSI. The overall mean score at baseline was [redacted]. Mean change from baseline in the overall score was -7.5 at Month 24 and -3.6 at Month 60. All mean sub-scores showed decreases, i.e. improvements compared with baseline for the vast majority of post-baseline visits (Table 71) (Chiesi 2020a).

Table 71: Improvements in MSSI subscale symptoms from baseline to Month 60 – Efficacy population

MSSI subscales	Baseline, n = 15	Month 12, n = 15	Month 24, n = 11	Month 48, n = 9	Month 60, n = 10
Total general score					
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)					
Total neurological score					
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)					
Total cardiovascular score					
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)					
Total renal score					
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)					

Key: MSSI, Mainz Severity Score Index; NA, not applicable

Source: PB-102-F03 CSR, 2020 (Chiesi 2020a)

Short Form Brief Pain Inventory

Reduction of scores from baseline indicated an improvement in pain severity and pain interference with daily life. The mean (SE; range) baseline average pain severity and general interference scores were [redacted] ([redacted]; range [redacted]) and [redacted] ([redacted]; range [redacted]), respectively. Mean (SE) change in the average pain severity score from baseline to Month 24 was -[redacted] ([redacted]) and to Month 60 was -[redacted] ([redacted]). Mean (SE) change in the general interference score from baseline to Month 24 was -[redacted] ([redacted]) and to Month 60 was -[redacted] ([redacted]) (Chiesi 2020a). Improvement or stability of pain levels in patients was confirmed by the analysis of the percentages of patients with an improvement or no change in average pain. At Month 24, [redacted] patients ([redacted]% of patients with data) and at Month 60, [redacted] patients ([redacted]% of patients with data) showed improvement or no change in the score for average pain.

Gastrointestinal Symptoms Assessment questionnaire

Based on the GSA at baseline, six patients (40%) and two patients (13%) reported moderate or severe abdominal pain, respectively (Chiesi 2020a). Post-baseline evaluations generally showed a reduction in the number of patients with moderate or severe abdominal pain, and an improvement in gastrointestinal symptoms was observed up to Month 24, followed by a stabilization at low levels. Improvements in severity of abdominal pain at Months 12, 24, 48, and 60 were observed for [redacted] patients ([redacted]%), [redacted] patients ([redacted]%), [redacted] patients ([redacted]%), and [redacted] patients ([redacted]%), respectively, compared with a worsening in severity of abdominal pain at Months 12, 24, 48, and 60 in [redacted] patients ([redacted]%), [redacted] patient ([redacted]%), [redacted] patients ([redacted]%), and [redacted] patients ([redacted]%), respectively. Similarly, improvements in frequency of abdominal pain and diarrhoea were more commonly seen during the study than deterioration. Table 72 presents a summary of the shifts in gastrointestinal symptom severity and frequency from baseline to Month 60.

Table 72: Patients with Gastrointestinal Symptoms – Efficacy population

Severity of abdominal pain, n (%)	Baseline, n = 15	Month 12, n = 15	Month 24, n = 11	Month 48, n = 10	Month 60, n = 10
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Frequency of abdominal pain, n (%)	Baseline, n = 15	Month 12, n = 15	Month 24, n = 11	Month 48, n = 10	Month 60, n = 10
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Frequency of diarrhoea, n (%)	Baseline, n = 15	Month 12, n = 15	Month 24, n = 11	Month 48, n = 10	Month 60, n = 10
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PB-102-F03 CSR 2020 (Chiesi 2020a)

Appendix E Safety data for intervention and comparator(s)

Safety results from the Phase III BALANCE study

Exposure

More than [redacted] of the infusions in the pegunigalsidase alfa arm and [redacted] of those in the agalsidase beta arm were administered at home, indicating that the treatment was often considered safe for home infusion especially in the pegunigalsidase alfa group (Chiesi 2022c). In the pegunigalsidase alfa arm, the mean (min; max) duration was reduced from [redacted] ([redacted]) hours at baseline to [redacted] ([redacted]) hours at Week 104. The reduction in infusion duration was less pronounced in the agalsidase beta arm, where the means were [redacted] ([redacted]) hours at baseline and [redacted] ([redacted]) hours at Week 104.

Treatment-emergent anti-pegunigalsidase alfa antibodies

Figure 18 shows the proportion of patients with IgG antibodies from baseline to Week 104 (Chiesi 2022c). The presence of antibodies to pegunigalsidase alfa prior to exposure is explained by strong cross-reactivity to components of pegunigalsidase alfa that are shared with agalsidase beta.

Figure 18: [redacted] BALANCE study

[redacted]

Source: Chiesi BALANCE CSR 2022 (Chiesi 2022c)

Treatment-emergent IgG ADA was observed in six ([redacted]%) patients in the pegunigalsidase alfa arm and in five (20.0%) in the agalsidase beta arm. At the end of the study, higher portion of patients who were positive for ADA at baseline became ADA negative in the pegunigalsidase alfa arm: [redacted] ([redacted]% of the ADA positives) vs. [redacted] ([redacted]% of the ADA positives) from the agalsidase beta arm.

Regarding nAbs, at baseline, 17 (94.4%) of the [redacted] IgG-positive pegunigalsidase alfa patients and seven (87.5%) of the [redacted] IgG-positive agalsidase beta patients were positive for neutralizing antibodies. At Week 104, the percentages were [redacted]% (7/[redacted]) in the pegunigalsidase alfa arm, and [redacted] (6/[redacted]) in the agalsidase beta.

Overall, there was little change in the percentage of patients who were ADA positive, with a trend of reduction observed in the pegunigalsidase alfa arm and stability in the agalsidase beta arm. The low rate of treatment-emergent ADA in the pegunigalsidase alfa arm is highly encouraging, since it might have been expected that a new product would be more likely to induce an immune response compared to one that had been taken for years. The proportion of patients with neutralizing ADA

decreased in the pegunigalsidase alfa arm while it remained stable in the agalsidase beta arm. This finding in favour of pegunigalsidase alfa is important not only from a safety perspective but also with respect to efficacy, since antibodies developed against an ERT product, especially neutralizing antibodies, may reduce the bioavailability of the enzyme and potentially have an impact on the clinical outcome.

Summary of treatment-emergent adverse events

47 (90.4%) patients in the pegunigalsidase alfa arm and 24 (96.0%) in the agalsidase beta arm reported at least one TEAE (Table 73) (Chiesi 2022c). Rates for severe TEAEs, serious TEAEs, and related TEAEs were also lower in the pegunigalsidase alfa arm. [redacted] ([redacted]%) patients in the pegunigalsidase alfa arm vs. none in the agalsidase beta arm experienced TEAEs that led to withdrawal from the study. No deaths were reported during the study.

Table 73: Summary of treatment-emergent adverse events in BALANCE (NCT02795676)

				Estimated absolute difference in effect (ARR)			Estimated relative difference in effect (RRR)			Description of methods for estimation	References
Outcome	***Study arm***	***N***	***Result***	***Difference***	***95% CI***	***P- value***	***Difference***	***95% CI***	***P- value***		
Any TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	47 (90.4)	[redacted]	[redacted]	0.684	[redacted]	[redacted]	[redacted]	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	24 (96.0)								
Any TEAE Number of events (rate)	Pegunigalsidase alfa	52	561 (572.36)	[redacted]	[redacted]	0.0718	[redacted]	[redacted]	[redacted]	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	406 (816.85)								
Mild or moderate TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	[redacted]	[redacted]	[redacted]	0.684	[redacted]	[redacted]	[redacted]	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	[redacted]								

										maximum likelihood estimation	
Mild or moderate TEAE Number of events (rate)	Pegunigalsidase alfa	52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	387 [redacted]								
Severe TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	15 (28.8)	0.846%	-20.634%, 22.326%	1	OR: 1.042	0.361-3.007	0.939	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	7 (28.0)								
Severe TEAE Number of events (rate)	Pegunigalsidase alfa	52	26 (26.53)	-11.469	-31.368, 8.429	0.39	RRR:0.698	0.496-0.982	0.0366	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	19 (38.23)								

										estimation. The confidence intervals are estimated using normal approximation.	
Serious TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	8 (15.4)	-4.615%	-23.109%, 13.878%	0.856	OR: 0.727	0.211- 2.503	0.856	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	[redacted]								
Serious TEAE Number of events (rate)	Pegunigalsidase alfa	52	14 (14.28)	-7.714	-22.715, 7.286	0.446	RRR:0.6493506	0.4618 - 0.9128	0.0117	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	11 (22.13)								
TEAE leading to withdrawal Patients with at least one event, n (%)	Pegunigalsidase alfa	52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	0 (0.0)								

										maximum likelihood estimation	
TEAE leading to withdrawal Number of events (rate)	Pegunigalsidase alfa	52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	0								
Any related TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	21 (40.4)	-3.615%	-27.205%, 19.974%)	0.956	OR: 0.862	0.329-2.262	0.763	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	11 (44.0)								
Any related TEAE Number of events (rate)	Pegunigalsidase alfa	52	42 (42.85)	-109.143	(-145.691, -72.594)	<0.001	RRR:0.281	0.2005-0.3963	<0.001	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	76 (152.91)								

										estimation. The confidence intervals are estimated using normal approximation.	
Related mild or moderate TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	[redacted]	[redacted]	[redacted]	0. 956	[redacted]	[redacted]	[redacted]	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	[redacted]								
Related mild or moderate TEAE Number of events (rate)	Pegunigalsidase alfa	52	40 (40.81)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	75 (150.90)								
Related severe TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	2 (3.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	1 (4.0)								

										maximum likelihood estimation	
Related severe TEAE Number of events (rate)	Pegunigalsidase alfa	52	2 (2.04)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	1 (2.01)								
Related serious TEAE Patients with at least one event, n (%)	Pegunigalsidase alfa	52	1 (1.9)	xxxxx	xxxxx	xxxxx	xxxxx			P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	0 (0.0)								
Related serious TEAE Number of events (rate)	Pegunigalsidase alfa	52	1 (1.02)	[redacted]	[redacted]	[redacted]	[redacted]			Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	0								

										estimation. The confidence intervals are estimated using normal approximation.	
Related TEAE leading to withdrawal Patients with at least one event, n (%)	Pegunigalsidase alfa	52	1 (1.0)	[redacted]	[redacted]	[redacted]	[redacted]			P-values were calculated with Fisher exact test, and confidence limits and the confidence intervals with Wald maximum likelihood estimation	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	0 (0.0)								
Related TEAE leading to withdrawal Number of events (rate)	Pegunigalsidase alfa	52	1 (1.02)	[redacted]	[redacted]	[redacted]	[redacted]			Rate is calculated as the adjusted number of events per 100 years of exposure The rate ratios are estimated using Wald unconditional maximum likelihood estimation. The confidence intervals are estimated using normal approximation.	BALANCE CSR, 2022 (Chiesi 2022c)
	Agalsidase beta	25	0 (0.0)								

Key: ARR: Absolute risk reduction; OR: Odds ratio; RRR: Relative risk reduction; TEAE: treatment-emergent adverse event.
Note: there were no death in the BALANCE trial, hence no TEAE leading to death is reported

Most common and severe treatment-emergent adverse events

In the pegunigalsidase alfa arm, the most common type of reported TEAEs were nasopharyngitis in [redacted] patients ([redacted]%), headache in [redacted] patients ([redacted]%), diarrhoea in [redacted] patients ([redacted]%), nausea in [redacted] patients ([redacted]%), and fatigue in [redacted] patients ([redacted]%) (Chiesi 2022c). In the agalsidase beta arm, the most common TEAEs were diarrhoea, seen in [redacted] ([redacted]%), and headache, back pain, cough, and bronchitis, each in [redacted] patients ([redacted]%).

Eight patients (15.4%) in the pegunigalsidase alfa arm experienced a total of 14 SAEs, for an exposure-adjusted rate of [redacted] events per 100 patient-years of treatment, and 6 (24.0%) patients in the agalsidase beta arm experienced a total of 11 SAEs, for an adjusted rate of [redacted] events.

Relatedness of AEs

AEs that were considered to be at least possibly related to study drug were identified as adverse drug reactions (ADRs) (Chiesi 2022c). The percentages of patients with ADRs were similar between both arms: 21 (40.4%) in the pegunigalsidase alfa arm and 11 (44.0%) in the agalsidase beta arm, but the percentages of ADR events were more than double in the agalsidase beta arm: 42 (7.5%) of the 561 AEs in the pegunigalsidase alfa arm vs. 76 (18.7%) of the 406 AEs in the agalsidase beta arm. In the pegunigalsidase alfa arm, the most frequently reported ADRs were fatigue (3 patients, 3 events) and nausea (2 patients, 3 events), and in the agalsidase beta arm, they were pruritus (3 patients, 23 events), and fatigue and chest discomfort (2 patients, 3 events each).

Only one SAE in the pegunigalsidase alfa group, which was an event of hypersensitivity, was considered related to study treatment. This event occurred with the first infusion in the study and was defined as an IRR.

Related TEAEs were more likely to occur in ADA positive compared to ADA negative patients. This difference was more pronounced in the agalsidase beta arm (84 vs. 296 events per 100 patient years in ADA-negative and -positive patients, respectively) than the pegunigalsidase alfa arm (20 vs. 87 events, respectively).

Injection-site and infusion-related reactions following drug administration

[redacted] patients ([redacted]%) in the pegunigalsidase alfa arm and [redacted] patients ([redacted]%) in the agalsidase beta arm experienced injection-site reactions, although these are events considered to be related to the procedure rather than to the study drug (Chiesi 2022c).

IRRs were defined as TEAEs that occurred during an infusion or within 2 hours after its completion, and whose causality was assessed as definitely, probably, or possibly related to study treatment. A total of 11 patients (21.2%) experienced 13 IRRs associated with 12 infusions for an adjusted rate of 0.5 events per 100 infusions in the pegunigalsidase alfa arm, whereas this rate was considerable higher in the agalsidase beta arm with 6 (24.0%) patients experiencing a total of 51 IRRs associated with 40 infusions, for an adjusted rate of 3.9 events per 100 infusions (~8-fold lower for pegunigalsidase alfa compared to agalsidase beta). Only one serious IRR was reported (hypersensitivity reaction described above). In the pegunigalsidase alfa arm, reactions of chills, hypersensitivity, infusion related reaction were reported in [redacted] patients each ([redacted]%), with [redacted] events in [redacted] patients in all cases. [redacted] other IRR was reported more than once in the pegunigalsidase alfa arm. In the agalsidase beta arm, pruritus was reported in [redacted] patients (x[redacted]%); this was also the most commonly reported IRR in this treatment arm, with a total of [redacted] events, [redacted] of them in [redacted] patient. The results of IRRs incidence within 24 hours of infusion were similar to those seen for the 2-hour time period, considerably higher in the agalsidase beta arm. In the pegunigalsidase alfa arm, [redacted] patients ([redacted]%) experienced a total of [redacted] IRRs associated with [redacted] infusions, for an adjusted rate of [redacted] events per 100 infusions, while in the agalsidase beta

arm, [redacted] ([redacted] %) patients experienced a total of [redacted] IRRs associated with [redacted] infusions, for an adjusted rate of [redacted] events per 100 infusions. [redacted] IRRs of pruritus were reported in the pegunigalsidase alfa arm. All IRRs were resolved.

Adverse events leading to withdrawal

Two patients in the pegunigalsidase alfa arm withdrew from the study due to AEs; one experienced a serious event of hypersensitivity assessed as an IRR, and the other, who had severely deteriorated kidney function prior to the study, withdrew due to end renal stage disease that was unlikely to be related to treatment (Chiesi 2022c).

Use of premedication

At baseline, 21 (40.4%) patients in the pegunigalsidase alfa arm used infusion premedication compared to 16 (64.0%) in the agalsidase beta arm. At the end of the study, only 3 (6.4%) patients in the pegunigalsidase alfa arm used infusion premedication compared to 3 (12.5%) in the agalsidase beta arm. In the majority of cases, the medication was taken prior to the start of infusion, not during (Chiesi 2022c).

Electrocardiography

Clinically abnormal ECG findings of any type in the pegunigalsidase alfa arm were found in [redacted] patients [redacted] at baseline and [redacted] %) at Week 104. In the agalsidase beta arm, these were found in [redacted] patients ([redacted] %) at baseline and at Week 104 (Chiesi 2022c).

Brain Magnetic Resonance Imaging

Brain MRIs investigated evidence of stroke and other pathologies; there were no notable findings (Chiesi 2022c).

Clinical laboratory abnormalities

There were no notable changes in biochemistry, haematology and urinalysis variables during the study (Chiesi 2022c).

Safety results from the Phase III BRIDGE study

Results were presented for the safety population (n = 22), which included all patients who received at least one dose of pegunigalsidase alfa during the study. However, it should be noted that the results of immunogenicity testing were only available for the PPE population.

Treatment-emergent anti-pegunigalsidase alfa antibodies

Pre-treatment

At baseline, [redacted] patient ([redacted] %) had test results for anti-pegunigalsidase alfa IgE antibodies. Another patient tested positive for anti-agalsidase alfa IgG and anti-pegunigalsidase alfa IgG antibodies, and baseline titers were [redacted] and [redacted] for antibodies against agalsidase alfa and pegunigalsidase alfa, respectively (Chiesi 2020c). [redacted] patient was also positive for nAbs against both agalsidase alfa and pegunigalsidase alfa. Furthermore, it should be noted that this patient had been treated with agalsidase beta before treatment with agalsidase alfa. [redacted] antibodies were detected to the plant glycan and PEG moieties of pegunigalsidase alfa. [redacted] patient tested positive for anti-pegunigalsidase alfa antibodies and for nAbs against pegunigalsidase alfa. [redacted] patients who experienced an immediate hypersensitivity reaction, were found negative for IgG antibodies to agalsidase alfa and pegunigalsidase alfa, but positive for IgE antibodies to pegunigalsidase alfa.

Post-treatment

In the PPE population, seven (32%) patients tested positive for anti-pegunigalsidase alfa IgG antibodies at one or more time points (Chiesi 2020c). Of these patients, four remained positive throughout the 12 months and the other three had transient/sporadic responses. Furthermore, [redacted] of the seven patients had lower post-treatment titers (range: [redacted]) relative to the titers of the [redacted] patients who had pre-existing ADAs and a titer-boosted response (range: [redacted]).

The two patients with [redacted] remained positive throughout the 12-month study period with neutralizing activity, and was therefore considered persistent (Chiesi 2020c). Despite this, the ADA titers of one of these patients decreased after 2 weeks of pegunigalsidase alfa treatment (Figure 19). It should be noted that this patient had the highest plasma lyso-Gb_3 levels at baseline and the greatest decrease in plasma lyso-Gb_3 after 12 months.

Figure 19: [redacted]

Key: [redacted]

Source: BRIDGE CSR (Chiesi 2020c)

Summary of treatment-emergent adverse events

Of note, since BRIDGE is a single-arm trial the summary of treatment-emergent adverse events in the study are presented in Table 74 instead of a table similar to Table 73 for BALANCE which is designed for comparative studies.

Twenty-one (96%) patients reported a total of 127 TEAEs, of which the majority (123; 97%) were considered mild or moderate in severity (Table 74) (Chiesi 2020c). Four TEAEs (3%) were considered severe and occurred in four male patients (18%); note that all severe events were also classified as serious adverse events (SAEs). Of note, almost all TEAEs (90%) were considered unrelated to study treatment. In fact, the incidence of TEAEs considered by the Investigator to be definitely, probably, or possibly related to study treatment was low, with a total of 13 events (10%) in five (23%) male patients. No deaths were reported during the study.

Table 74: Summary of treatment-emergent adverse events in the BRIDGE study

	Male patients (N = 15)		Female patients (N = 7)		Total (N = 22)	
	Patients, n (%)	Events, n (%)	Patients, n (%)	Events, n (%)	Patients, n (%)	Events, n (%)
At least 1 TEAE	[redacted]	[redacted]	[redacted]	[redacted]	21 (95.5)	127
At least 1 mild or moderate TEAE	[redacted]	[redacted]	[redacted]	[redacted]	19 (86.4)	123 (96.9)
At least 1 severe TEAE (also classed as SAEs)	[redacted]	[redacted]	[redacted]	[redacted]	4 (18.2)	4 (3.1)
At least 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least 1 TEAE unrelated or unlikely related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least 1 TEAE possibly, probably, or definitely related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least 1 TEAE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	2 (9.1)	2 (1.6)

Key: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: BRIDGE CSR (Chiesi 2020c)**Most common and severe treatment-emergent adverse events**

The most frequently reported TEAEs were nasopharyngitis in seven patients (32%; [redacted]), headache in five patients (23%; [redacted]), and dyspnoea in three patients (14%; [redacted]). All other TEAEs were reported in two patients or less (Chiesi 2020c). Severe TEAEs included Type I hypersensitivity in two [redacted] patients (9%), infectious mononucleosis in one [redacted] patient (5%), and urinary tract infection in one [redacted] patient (5%). Only the Type I hypersensitivity events were considered related to study treatment and resulted in two patients discontinuing study treatment.

All mild and moderate TEAEs ([redacted]%) were resolved or were resolving, as were all four serious/severe adverse events (Chiesi 2020c). Specifically, the two SAEs considered related to study treatment (Type I hypersensitivity) were resolved within 1 day.

Injection-site and infusion-related reactions following study drug administration

A total of four TEAEs related to injection site reactions were reported in three patients (14%; [redacted]); all were considered non-serious and unrelated to study treatment (Chiesi 2020c). Furthermore, all four events were resolved, and all patients completed the study.

A total of nine TEAEs related to IRRs were reported in five [redacted] patients (23%). Of these, seven occurred in three patients and were considered non-serious (mild in severity), possibly or probably related to study treatment, and were resolved (Chiesi 2020c). As discussed in the previous section, a serious/severe IRR (Type I hypersensitivity) was experienced by two [redacted] patients, but these were resolved within 1 day after the patients discontinued study treatment.

Use of premedication

Of the patients in the study, [redacted] % did not require premedication to manage infusion reactions at any time during the study, including the first administration (Chiesi 2020c). [redacted] ([redacted] %) patient received infusion premedication at baseline, which was tapered off at Visit 14; [redacted] ([redacted] %) patients who did not receive premedication at baseline, received it at several visits during the study. [redacted] of these [redacted] patients was able to taper off the premedication at the end of the study, and [redacted] received it until the last administration.

Clinical laboratory abnormalities

There were no notable changes in biochemistry or haematology variables during the study (Chiesi 2020c).

Physical examination findings

A number of body systems were assessed during the physical examination assessments, including but not limited to abdomen, anorectal, breasts, cardiovascular, head/ears/eyes/nose/throat, lungs, lymph nodes, musculoskeletal, neurologic, skin and urogenital (Chiesi 2020c). Most patients had normal physical examination findings at baseline and throughout the study. However, some shifts from normal at baseline to abnormal during the study were observed, including abnormalities in abdomen in two patients, cardiovascular in one patient, head/ears/eyes/nose/throat in one patient, lymph node in one patient, and musculoskeletal in one patient.

Electrocardiogram changes from baseline

There were no notable changes in the mean heart rate (HR), PR interval, QRS interval, QT interval, or in qualitative ECG parameters (normal sinus rhythm, conduction abnormalities, left ventricular hypertrophy, supraventricular tachycardia, premature atrial contraction, atrial flutter, atrial fibrillation, premature ventricular contraction, ventricular tachycardia, and any clinically significant findings), with the exception of one event of complete right bundle branch block in one male patient (Chiesi 2020c). This ECG change was considered as moderate in severity, non-serious, and unlikely related to study treatment. Furthermore, the patient did not receive an alteration in dose of the study drug.

Safety results from the Phase III BRIGHT study

Results were presented for the safety population (n = 30), which included all patients who received at least one dose of pegunigalsidase alfa during the study. However, it should be noted that the results of immunogenicity testing post-treatment were only available for the PPE population (n = 29).

Length of infusion

The mean infusion duration generally decreased during the study from baseline (4.8 hours) to Month 12 (2.3 hours) (Chiesi 2021). As per the protocol, the initial infusion had a duration of 4 hours for patients ≤100 kg and of 6 hours for patients ≥100 kg. The duration was gradually tapered and by Month 12, the majority of patients had reached the targeted lengths of 2 hours for patients ≤100 kg and of 3 hours for patients ≥100 kg.

Treatment-emergent anti-pegunigalsidase alfa antibodies

Pre-treatment

At baseline, 11 (37%) patients, all male, who had previously been treated with agalsidase beta, were positive for ADAs to agalsidase beta (Chiesi 2021). Of these, ten (30%) patients were also positive for ADAs to pegunigalsidase alfa. [redacted] patients who were previously treated with agalsidase alfa

tested negative for IgG antibodies to both agalsidase alfa and pegunigalsidase alfa. Of note, the patient who withdrew from the study after the baseline visit only had immunogenicity assessed at screening and baseline; the patient was positive pre-existing ADA positive.

Post-treatment

In the PPE population, 19 (66%) patients were negative for ADAs to pegunigalsidase alfa at all timepoints tested (Chiesi 2021). Of the remaining ten (34%) patients who were positive for ADAs to pegunigalsidase alfa at baseline, eight (28%) of them were also ADA positive at one or more timepoints post-treatment. Of these ten patients who were ADA positive at baseline, six remained ADA positive until the end of the study. Only one patient had a titer-boosted ADA response following treatment with pegunigalsidase alfa; this patient also had anti-pegunigalsidase alfa nAb at all visits. Regarding nAbs, all ADA positive patients at any timepoint also had neutralizing activity at most of the timepoints. None of the ADA samples had detectable antibodies to the plant glycans or PEG moieties.

In summary, only patients with pre-existing IgG antibodies were positive for ADAs to pegunigalsidase alfa during the study; no patients developed ADAs de-novo following the switch to pegunigalsidase alfa.

Summary of treatment-emergent adverse events

Of note, since BRIGHT is a single-arm trial the summary of treatment-emergent adverse events in the study are presented shortly in flow-text below instead of a table similar to Table 73 for BALANCE which is designed for comparative studies.

Of the 183 TEAEs that were reported in 27 (90%) patients, the majority of whom were considered mild or moderate in severity (180 TEAEs in 90% of patients), the TEAEs were resolved or resolving at the end of the study (Chiesi 2021). Three TEAEs were considered severe and affected two (6.7%) male patients, and two of these were also a serious TEAE. The majority of TEAEs (70%), including the two serious TEAEs, were considered unrelated to the treatment; the remaining 30% were considered treatment-related and were mild or moderate in severity. No deaths were reported during the study.Safety results from the Phase I/II PB-102-F01 and PB-102-F02 studies

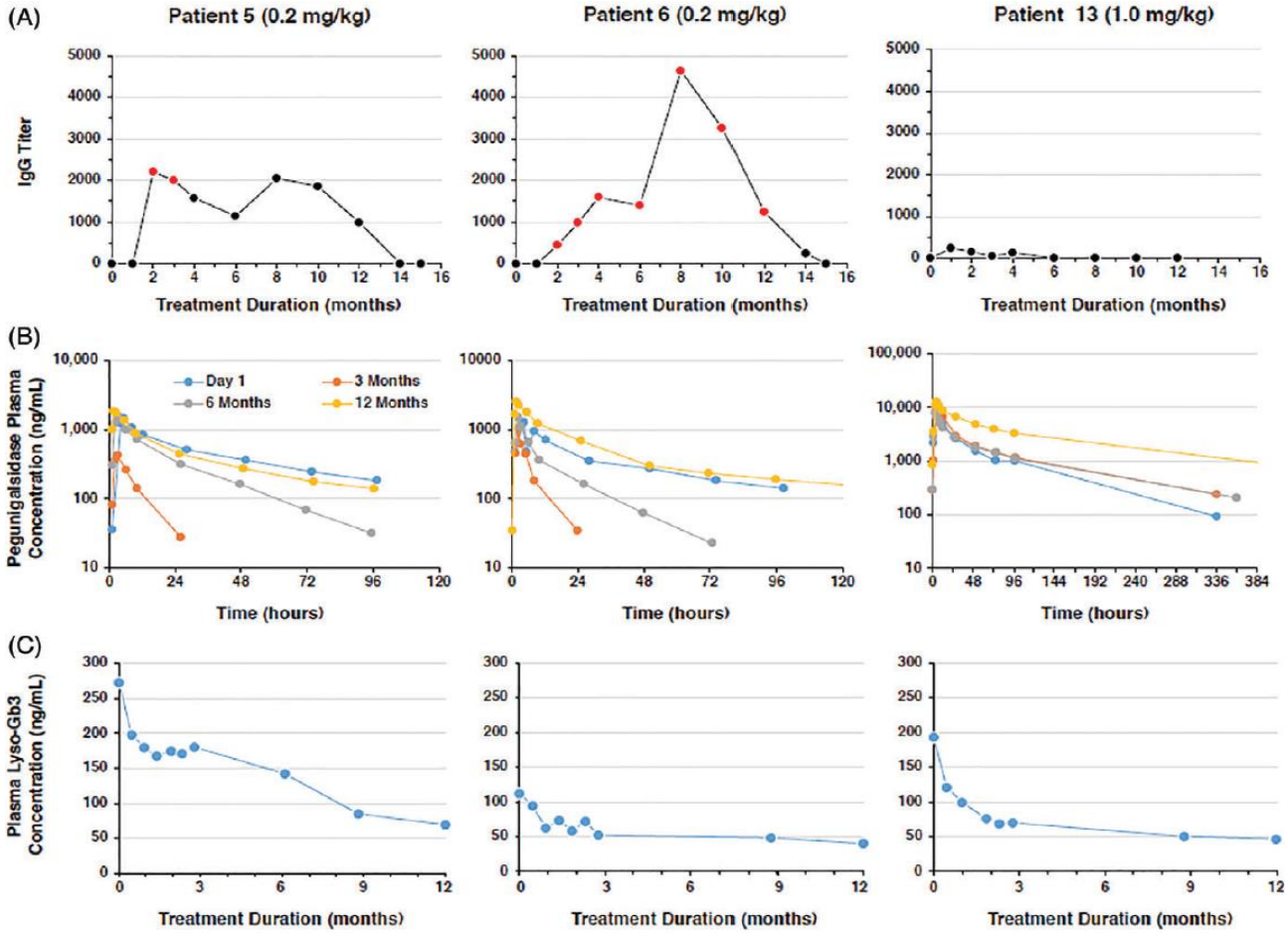
Summary of treatment-emergent adverse events

Immunogenicity

In the safety population, of the 16 patients who completed 12 months of treatment, three male patients (19%) developed treatment-induced IgG antibodies to pegunigalsidase alfa: two (13%) in the 0.2 mg/kg group (maximum titres 2,198 and 4,633) tested positive for nAbs and one (6%) in the 1.0 mg/kg group (titre of ≤ 237), although this patient did not develop nAbs; no patients in the 2.0 mg/kg group developed treatment-induced ADAs (Schiffmann et al. 2019). It should be noted that all three patients became ADA negative after approximately 12 months of treatment, suggesting immune tolerance induction.

Overall, there was no evidence to suggest that the presence of ADAs had influenced the pharmacodynamics, efficacy, or safety profile of pegunigalsidase alfa (Schiffmann et al. 2019). The ADAs in the two patients in the 0.2 mg/kg group were transiently neutralizing, but became non-neutralizing as treatment continued, with transient and reversible effects on pharmacokinetics (i.e. an increase in enzyme clearance and a decrease in $T_{1/2}\gamma$); as the patient in the 1.0 mg/kg treatment group had no nAbs, there was no effect on the pharmacokinetic profile of pegunigalsidase alfa (Figure 20). Plasma lyso-Gb_3 concentrations continued to decline as treatment continued despite the presence of ADAs, suggesting the latter had little effect on the effectiveness of pegunigalsidase alfa.

Figure 20: The effect of ADA positivity on pharmacokinetics and pharmacodynamics of pegunigalsidase alfa



Key: ADA, antidrug antibody; IgG, immunoglobulin G; lyso-Gb_3, globotriaosylsphingosine.

Notes: (A) IgG ADA titre, with red symbols indicating neutralizing antibodies; (B) Pharmacokinetic profiles on Day 1 and at Months 3, 6, and 12; (C) Lyso-Gb_3 levels.

Source: (Schiffmann et al. 2019)

[redacted] patients with pegunigalsidase alfa-induced IgG antibodies did not have any adverse events related to the infusions, and were not treated with premedication during the study (Chiesi 2017d). [redacted] patient experienced nausea at 8 months, which was considered possibly related to treatment. Of note, [redacted] patients in the safety population presented with anti-pegunigalsidase antibodies at baseline: [redacted] patient with IgE antibodies experienced an adverse event leading to study discontinuation; this patient also tested positive for IgG anti-pegunigalsidase antibodies after first infusion), and [redacted] patient experienced abdominal pain during pegunigalsidase alfa infusions, which was considered possibly related to treatment.

Clinical laboratory evaluations

There were no clinically significant changes from baseline in laboratory haematology, biochemistry and urinalysis parameters observed during the study; most parameters remained at normal levels throughout (Chiesi 2017d).

Physical examination findings

For most patients, vital signs (systolic and diastolic blood pressures, pulse rate, temperature, and respiration rate) remained within normal range during the 12 months (Chiesi 2017d). [redacted] patient in the 1.0 mg/kg treatment group experienced [redacted] occurrences of hypotension that were considered possibly or probably related to treatment. These lower systolic (89 mmHg) and diastolic (47 and 49 mmHg) blood pressure results occurred after the start of infusion; however, these reactions were transient and resolved the same day.

At 12 months, the proportion of patients with abnormal physical examinations was similar to that observed at baseline (Chiesi 2017d). The most common abnormal physical examination results at 12 months were in the skin (0.2 mg/kg: 67% of patients; 1.0 mg/kg: 83% of patients; 2.0 mg/kg: 50% of patients) and neurological body systems (0.2 mg/kg: 17% of patients; 1.0 mg/kg: 17% of patients; 2.0 mg/kg: 25.0% of patients).

Electrocardiogram assessments

At 12 months, a total of [redacted] patients ([redacted] %) had ECG abnormalities: [redacted] ([redacted] %) had conduction abnormalities, [redacted] ([redacted] %) had left ventricular hypertrophy, [redacted] ([redacted] %) had abnormal sinus rhythm, and [redacted] ([redacted] %) had premature atrial contraction (Chiesi 2017d). Of these [redacted] patients, [redacted] ([redacted] %) had the same ECG abnormalities at baseline.

[redacted] patients ([redacted] %) experienced clinically significant ECG changes from baseline during the study (Chiesi 2017d):

- [redacted] patient in the 0.2 mg/kg treatment group had non-specific T wave abnormalities at 12 months
- [redacted] patient in the 1.0 mg/kg treatment group with a short QT interval at baseline had voltage criteria for LVH at 3 months and non-specific T wave abnormalities at 12 months

Safety results from the Phase I/II PB-102-F03 study

Infusion-related reactions

A total of [redacted] IRRs ([redacted] % of all TEAEs) were reported in six patients (40.0%) in the overall treatment period (Chiesi 2020a). None of the IRRs were reported as serious, and they were all of mild or moderate in severity. None of these IRRs led to study discontinuation, and all were resolved. [redacted] IRR occurred when infusions were given in the home setting which underlines the appropriateness of measures to decide whether home infusion is a safe option.

Clinical laboratory evaluations

There were no clinically relevant mean % changes from baseline in most parameters assessed for biochemistry, haematology and urinalysis (Chiesi 2020a). Similarly, the majority of patients had negative results in urinalysis parameters such as blood, glucose, and nitrite at Month 60. For protein in urine, the proportion of patients with negative results increased during the course of the studies.

Vital signs

The majority of parameters assessed for vital signs remained within normal ranges (Chiesi 2020a). Of note, one patient (6.7%) experienced two mild, non-serious TEAEs of hypotension considered as possibly (first TEAE) or probably (second TEAE) related to treatment in PB-102-F01 and PB-102-F02,

respectively. Two of these events were reported as occurring during the infusion or within 2 hours of infusion, and one was reported as occurring between 2 to 24 hours after infusion.

Physical examination findings

There were no relevant differences in the proportion of patients presenting with abnormal findings in their physical examination between baseline and post-baseline timepoints (Chiesi 2020a).

Electrocardiogram assessments

Electrocardiogram data showed considerable variation over time (Chiesi 2020a). Results were:

- A slight mean (SE) decrease between baseline and Month 60 in heart rate of - ( ) beats/min from a mean (SE) baseline value of ( ) beats/min;
- PR duration decreased by a mean (SE) of - ( ) msec from a baseline value of ( ) msec.
- QRS duration increased by a mean (SE) of ( ) msec from a baseline value of ( ) msec.
- QT duration increased by a mean (SE) of ( ) msec from a baseline value of ( ) msec.

No relevant differences in the number of patients presenting with abnormal ECG findings between baseline and post-baseline timepoints were observed.

Of note, events of LVH and events of tachycardia were reported in patients each (%) (Chiesi 2020a). Furthermore, TEAE of 'electrocardiogram QRS complex abnormal', of 'electrocardiogram ST segment abnormal' and of 'electrocardiogram ST segment depression' were reported in patient (%); TEAEs of 'electrocardiogram T wave abnormal', and t of 'heart rate irregular' were also reported in patients (%). None of these events led to study discontinuation.

Cerebrovascular disease

evidence of stroke was found in any patient in the safety population during the treatment period (Chiesi 2020a).

Immunogenicity

In the safety population, two patients (13.3%) were positive at baseline for anti-pegunigalsidase alfa IgG ADAs (Chiesi 2020a). One of these patients was negative for all post-baseline timepoints and can be considered as ADA negative post-treatment.

In the overall treatment period (up to 72 months), four patients (26.7%) were positive for anti-pegunigalsidase alfa IgG ADAs at one or more post-treatment timepoints and were considered as treatment-induced or titer-boosted ADAs (Chiesi 2020a). None of the other patients tested positive throughout the treatment period. One patient was positive for anti-pegunigalsidase alfa IgG at the end of the overall treatment period.

Concomitant medications

In the overall treatment period, the most commonly used concomitant medications were as follows (Chiesi 2020a):

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Appendix F Comparative analysis of efficacy and safety

Not relevant as head-to-head data is presented.

Appendix G Extrapolation

Not applicable as no extrapolations were made.

Appendix H Literature search for HRQoL data

Not relevant as a cost-minimization model was used.

Appendix I Mapping of HRQoL data

Not relevant as a cost-minimization model was used.

Appendix J Probabilistic sensitivity analyses

Not relevant as a cost-minimization model was used.