29 January 2026
EMA/43656/2026
Committee for Medicinal Products for Human Use (CHMP)

Variation assessment report

Invented name: Elfabrio

International non-proprietary name: Pegunigalsidase alfa

Procedure No. EMEA/H/C/005618/II/0007

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACEi	Angiotensin-Converting Enzyme Inhibitor
ADA	Anti-Drug Antibody
AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
AUC	Area Under the Curve
Cavg	Average Concentration
Chiesi	Chiesi Farmaceutici S.p.A.
CI(s)	Confidence Interval(s)
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
Cmax	Maximum Concentration
Cmin	Minimum Concentration
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
E2W	Every 2 Weeks
E4W	Every 4 Weeks
eGFR	Estimated Glomerular Filtration Rate
eGFRCKD-EPI	Estimated Glomerular Filtration Rate Calculated Based on the CKD-EPI Equation
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Questionnaire
ER	Exposure Relationship
ERT(s)	Enzyme Replacement Therapy(ies)
FCE(s)	Fabry Clinical Event(s)
FD	Fabry disease
FDA	Food and Drug Administration
Gb3	Globotriaosylceramide
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GL-3	globotriaosylceramide
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IRR(s)	Infusion-Related Reaction(s)
IRR-24H	Infusion-Related Reaction During the Infusion or Within 24 hours After Its Completion
IRR-2H	Infusion-Related Reaction During the Infusion or Within 2 hours After Its Completion
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety

IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LVMI	Left Ventricular Mass Index
Lyso-Gb3	Globotriaosylsphingosine
MAA	Marketing Authorisation Application
MAH	Marketing Auhtorisation Holder
Max	Maximum
Min	Minimum
MSSI	Mainz Severity Score Index
N/A	Not Applicable
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PopPK	Population Pharmacokinetics
PRX-102	Pegunigalsidase alfa
PT	Preferred Term
Q1, Q3	25th percentile, 75th percentile
QoL	Quality of Life
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SRT	Substrate Reduction Therapies
SS	Steady State
t1/2	Terminal Elimination Half-Life
UPCR	Urine Protein to Creatinine Ratio
US	United States of America
V	Visit
α-GAL-A	Alpha-Galactosidase-A

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Chiesi Farmaceutici S.p.A. submitted to the European Medicines Agency on 13 November 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to introduce an alternative posology regimen based on results from study PB-102-F50 (BRIGHT) and interim results from its extension study CLI-06657AA1-03 (formerly presented as PB-102-F51), as well as results of the observational patient reporting outcome study CLI-06657AA1-05. CLI-06657AA1-03 is an 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. The Package Leaflet is updated accordingly. The RMP version 1.3 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.4.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

1.1. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

Timetable	**Actual dates**
Submission date	13 November 2024
Start of procedure:	2 December 2024
CHMP Rapporteur Assessment Report	2 January 2025
PRAC Rapporteur Assessment Report	6 January 2025
PRAC members comments	8 January 2025
Updated PRAC Rapporteur Assessment Report	9 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	28 May 2025
PRAC Rapporteur Assessment Report	28 May 2025
PRAC members comments	27 May 2025
Updated PRAC Rapporteur Assessment Report	28 May 2025

Timetable	Actual dates
PRAC Outcome	5 June 2025
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	12 June 2025
Request for supplementary information (RSI)	19 June 2025
CHMP Rapporteur Assessment Report	18 September 2025
PRAC Rapporteur Assessment Report	18 September 2025
PRAC members comments	24 September 2025
Updated PRAC Rapporteur Assessment Report	22 September 2025
PRAC Outcome	2 October 2025
CHMP members comments	6 October 2025
Updated CHMP Rapporteur Assessment Report	9 October 2025
Oral Explanation	14 October 2025
Opinion	16 October 2025

1.2. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: N/A

Timetable	Actual dates
Written notice to the EMA to request a Re-examination of Elfabrio CHMP opinion on variation procedure No EMEA/H/C/005618/II/0007	28 October 2025
Rapporteur's appointment	13 November 2025
Detailed grounds for the Re-examination submitted on	1 December 2025
Start of procedure:	2 December 2025
CHMP Rapporteur Assessment Report	5 January 2026
CHMP members comments	17 January 2026
The Ad-Hoc-Expert Group (AHEG) considered the grounds for Re-examination	19 January 2026
Updated CHMP Rapporteur Assessment Report	23 January 2026
CHMP opinion:	29 January 2026

2. Scientific discussion

The marketing authorisation holder (MAH) applied for a type II variation to implement an alternative dosing regimen of 2 mg/kg body weight infused every 4 weeks (E4W) in addition to the currently approved dosing regimen of 1 mg/kg body weight infused every 2 weeks (E2W).

2.1. Introduction

Elfabrio (pegunigalsidase alfa) is approved for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of α-galactosidase) at a dosing regimen of 1 mg/kg body weight every 2 weeks.

Pegunigalsidase is a PEGylated recombinant variant form of α-galactosidase. It is used as a replacement of α-galactosidase for which the patients are deficient.

Fabry disease (also referred to as Anderson-Fabry disease) is an X-linked inborn error of metabolism characterised by subnormal or absent activity of the lysosomal hydrolase, α-galactosidase (αGAL). Deficiency of αGAL leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3) in the lysosomes of endothelial, perithelial, and smooth-muscle cells of blood vessels. GL-3 accumulation also occurs in ganglion cells of the autonomic nervous system, cardiomyocytes of the heart, epithelial cells of glomeruli and tubules in the kidney, epithelial cells of the cornea, and cell lines of many other tissues.

Because the gene encoding αGAL exists on the X-chromosome, the patient population consists mostly of hemizygous males, although some heterozygous females are also clinically affected due to lyonisation (random inactivation of one X-chromosome). Hemizygous males have extensive deposition of glycosphingolipid substrates. Most heterozygous female carriers of the gene have an intermediate level of enzymatic activity and their clinical course and prognosis is generally more benign than the hemizygous males. However, heterozygotes have been reported with disease as severe as that observed in classically affected males.

Fabry disease affects an estimated 1 in 1,000 to 9,000 people. Milder, late-onset forms of the disorder are probably more common than the classic, severe form.

The clinical manifestations of Fabry disease result primarily from the progressive deposition of GL-3 in the vascular endothelium. Excessive accumulation of GL-3 in the vascular wall results in narrowing and thrombosis of arteries and arterioles and this derangement of the vascular architecture is implicated in the development of the entire spectrum of disease manifestations. Ultimately, failure of endothelial vascular beds results in the pathophysiological events leading to peripheral neuritis, angiokeratoma corporis diffusum universale, renal failure, myocardial infarction, and cerebral infarction.

Although Fabry disease presentation is highly heterogeneous, clinical onset usually occurs during childhood or adolescence. Early manifestations include episodic crises of excruciating pain in the extremities (acroparaesthesias), the appearance of characteristic cutaneous lesions (angiokeratoma corporis diffusum universale), hypohidrosis, and the characteristic corneal and lenticular opacities.

Most importantly, Fabry disease progresses to key organ dysfunction. In the second or third decade of life, early renal accumulation of glycosphingolipids has been observed throughout the renal vessels and glomeruli, resulting in the onset of renal insufficiency and progressing to end-stage renal disease requiring dialysis and/or transplantation in the fourth and subsequent decades. These progressive alterations are most likely a result of ischaemia due to the ongoing vascular damage caused by endothelial GL-3 deposits. Hypertrophic cardiomyopathy (secondary to cardiomyocyte involvement), valvular abnormalities (secondary to valvular fibroblast and endothelial involvement) and myocardial infarction (secondary to endothelial dysfunction and small vessel occlusion) have been observed in the third and subsequent decades of life. Additionally, cerebrovascular complications may develop during the third and subsequent decades, with abnormal autonomic responses exhibited throughout the course of the disease. Progressive disease burden in symptomatic individuals results in a substantially decreased life expectancy. Fabry-related deaths are typically due to renal failure, cardiac disease or cerebrovascular disease. Thus, left untreated, symptomatic Fabry disease is usually fatal.

Currently various enzyme replacement therapies (ERTs) are available for treatment of Fabry disease.

The CHMP noted that a 4 weekly dosing regimen for authorised enzyme replacement therapy (ERT) products in Fabry disease constitutes more flexibility and potential positive impact and advantages for both patients and clinicians in terms of dosing scheme.

The currently approved posology of 1 mg/kg E2W was recommended by the CHMP as the only posology investigated in the main study PB-102-F20 and in line with the dose finding data at the time of the initial Marketing Authorisation Application (MAA). The study PB-102-F20 was 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. From a methodological/statistical point of view, the main study could not provide confirmatory evidence of efficacy of pegunigalsidase alfa and moreover the data did not allow to clearly quantify the effect of pegunigalsidase alfa. Nevertheless, the demonstration of the efficacy was based on the nature of the product (known active substance used as enzyme replacement therapy for Fabry disease), the well-understood mechanism of action, the pharmacodynamic effects observed on renal tissue that would not be expected without effective ERT and some clinical effect on the renal function.

2.2. Clinical aspects

In this type II variation, the MAH applied to implement an alternative dosing regimen of 2 mg/kg body weight infused every 4 weeks (E4W) in addition to the currently approved dosing regimen of 1 mg/kg body weight infused every 2 weeks (E2W). During the procedure it was proposed to restrict the use in ADA-negative patients.

2.2.1. Clinical pharmacology

Most of the dose justification in this application was done through population PK modelling and PK/PD modelling and simulation.

In support of the current variation, the MAH submitted data from:

A population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK-PD) analysis report "The Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of Pegunigalsidase alfa with Data from Studies PB-102-F01/F02, PB-102-F50 and PB-102-F20", report MSAR-24-0022

Population PK analysis

PopPK analysis of pegunigalsidase alfa was based on data collected from 62 Fabry disease patients: 16 of those patients (from Study PB-102-F01/F02) were treatment naïve, while the other 46 patients, from Study PB-102-F20 or PB-102-F50 (16 and 30 patients, respectively) were ERT-experienced.

The updated final model converged with all parameters estimated with good precision: fixed effects on main structural parameters have RSE≤13.3%; all other fixed effects have RSE≤35.0%; the random effects had RSE <24%. The shrinkage for ETAs were all ≤20.5%. The RUV was 36.6%.

Pegunigalsidase alfa was simulated at steady-state for two dosing scenarios (1 mg/kg E2W and 2 mg/kg E4W). The simulations were based on all the subjects in the PopPK dataset and included the covariates from the original dataset: 1000 replicate samples with replacement were drawn from 62 subjects (all patients in the PopPK dataset), including ETAs estimated in the best model and excluding the residual unexplained variability (RUV). The simulations considered the covariates as distributed in the original dataset and included: ADA titer at baseline, patient status with respect to ERT-treatment at study

enrolment (ERT-naive or ERT-experienced), and prior treatment with agalsidase beta (Yes/No) which were identified as statistically significant covariates for the best model. In summary, the simulated concentration-time profiles from first dose to steady-state were compared between 1 mg/kg E2W and 2 mg/kg E4W and resulted in a similar AUC_{4week} and C_{avg} (Table 1), assuming same infusion duration. Additionally, simulations showed C_{max} is expected to be higher by 2-fold in 2 mg/kg E4W regimen, and C_{min} 0.4-fold lower.

Table 1. Typical exposure indices from the simulations of 1 mg/kg E2W and 2 mg/kg E4W.

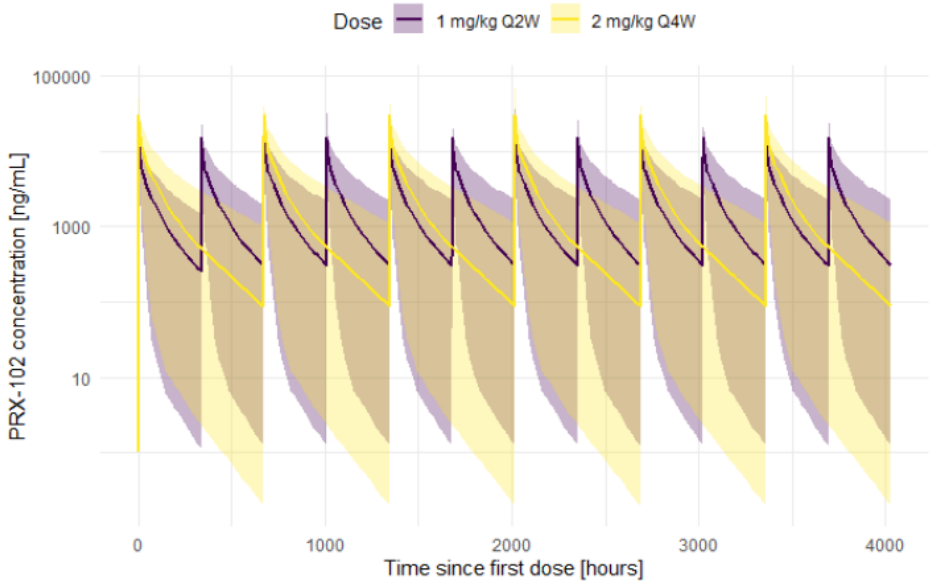
Parameter	Regimen	Mean	CV(%)	Ratio*
AUC_{4w} (ng.hr/mL)	1 mg/kg E2W	1,585,926	74.5	
	2 mg/kg E4W	1,585,926	74.5	1
C_{avg} (ng/mL)	1 mg/kg E2W	2,360	74.5	
	2 mg/kg E4W	2,360	74.5	1
$C_{max,\ 5hr\ infus.}$ (ng/mL)	1 mg/kg E2W	15,441.2	54.8	
	2 mg/kg E4W	29,898.1	53.2	1.94
$C_{max,\ 2hr\ infus.}$ (ng/mL)	1 mg/kg E2W	17,737	57.6	
	2 mg/kg E4W	34,483	56.3	1.94
C_{min} (ng/mL)	1 mg/kg E2W	639	131.8	
	2 mg/kg E4W	280	172.5	0.44

Notes: the simulations were performed using the final population PK model by drawing 1000 subjects from the population present in the population PK data; Infusion duration of 2 hours was used in the simulations (as this was median for the infusions in the data). 5 hours infusion was also simulated to represent longest infusion that occurred in the studies; all exposure indices are calculated at steady state; AUC4w is area under concentration-time curve 4 weeks post dose at steady-state; AUC_{4w} for 1 mg/kg E2W is associated with two doses of 1 mg/kg E2W; Ratio is the mean from 2 mg/kg E4W regimen over 1 mg/kg E2W regimen.

**relative to 1 mg/kg E2W regimen*

Source: sdtab501 to 504; Convert_sdtabs_to_WNL_input_30SEP2024.R; Sims_1and2mg_2hr_30MAY2024.phxproj

Figure 1. Simulation of concentration time profiles between pegunigalsidase alpha 1 mg/kg E2W and 2 mg/kg E4W.

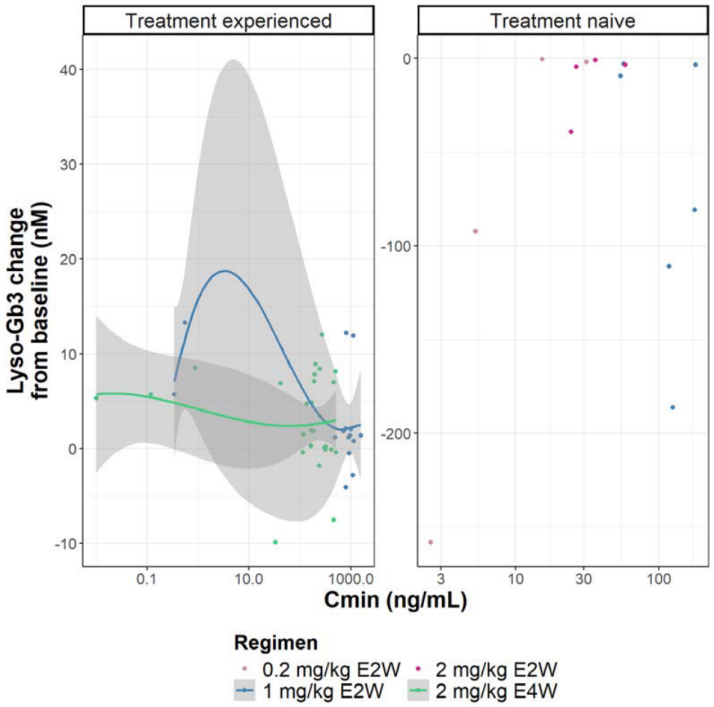


E4W = every 4 weeks; E2W = every 2 weeks
Notes: Sold line: median; shaded areas are 5th to 95th percentiles; values on y-axis are in log10 scale.
Source: MSAR 24-0022, Figure 12-14.

Population PK/PD analysis

ER analysis of plasma Lyso-Gb3 levels was based on Lyso-Gb3 data at baseline and at 12 months ± 2 weeks of treatment (11.5 to 12.5 months inclusive) collected from 57 patients (out of 61 with available PK data) with available individual measurements both at baseline and at the 12-month timepoint of treatment. Individual patient concentration-time profiles for dosing regimen assigned were simulated by PopPK model for repeated dosing to steady state to represent exposure at 12 months of dosing assuming a 2-hour infusion duration. As expected, ERT-naïve patients had higher baseline plasma Lyso-Gb3 concentrations and showed a higher decrease from baseline compared with ERT-experienced patients. ER analysis based on plasma Lyso-Gb3 change from baseline at 12 months did not show any relevant relationship with PK (i.e., C_{avg}, C_{min} and C_{max}) in the explored dose range. Considering the differences in study design, ERT-experienced patients were analysed separately from ERT-naïve patients (Figure 2.).

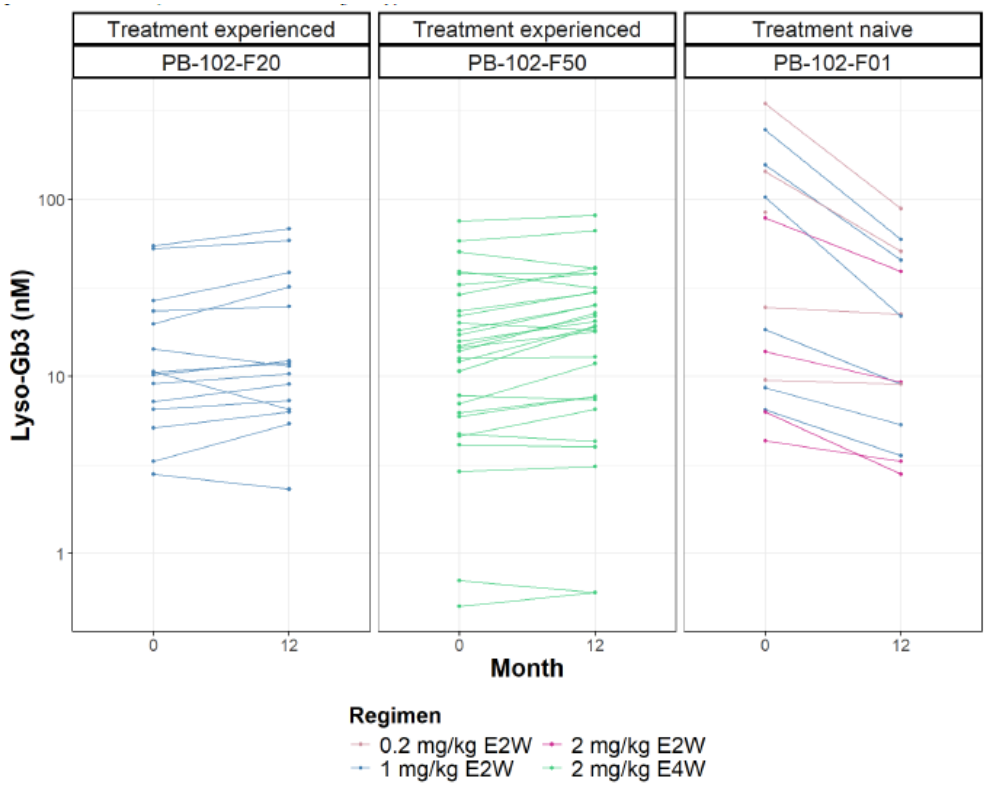
Figure 2. Scatterplot showing the relationship between plasma Lyso-Gb3 change from baseline at 12 months post dose and C min as the patients' exposure metric, stratified by patient status and regimen.



Note: C_{min} levels are plotted on the log_{10} scale. The range of values are not the same in the *two panels* for both Lyso-Gb3 and C_{min}. *Local regression (loess) is displayed as solid line with its 90% confidence interval (shaded area); the curve needs to be interpreted considering the difference in density of the data on the concentration axis; circles: observed data. Local regression was not displayed in case of naïve patients due to the low number of patients per dose level.*

Additionally, individual plasma Lyso-Gb3 concentration was explored vs time (using baseline and Month 12 data, see Figure 2). No relevant difference was detected when the relationship between exposure metrics with plasma Lyso-Gb3 change from baseline at 12 months of treatment is stratified by dosing regimen (**Figure 3**).

Figure 3. Plasma Lyso-Gb3 levels at baseline and after 12 months, by study, patient status and regimen.



Only subjects with PK data are presented in figures
Logarithmic scale used for Lyso-Gb3 axis
Source: MSAR 24-0022, Figure 12-16

Related to the safety due to the 2-fold increase in C_{max} in 2 mg/kg E4W, the MAH reasoned that an increase in IRR rates is observed in Cohort 2 (2 mg/kg every 4 weeks) compared to Cohort 1 (1 mg/kg every 2 weeks), with rates of 30% versus 23.4%, respectively. No SAEs or fatal cases have been reported in the cohort 2.

Regarding the changes in C_{min}, the MAH mostly justified this by high variability and ADA status.

2.2.2. Efficacy

It should be noted that the alternative dosing regimen of 2 mg/kg E4W had previously been claimed at the time of the initial MAA. The alternative dosing regimen was investigated in study PB-102-F50. This was an open label, switch study to assess the safety, efficacy and pharmacokinetics (PK) of pegunigalsidase alfa 2.0 mg/kg administered by IV infusion E4W for 12 months in adult patients with Fabry disease who were previously treated with ERT. Enrolled patients had to have been treated prior to the study with agalsidase beta (Fabrazyme) or agalsidase alfa (Replagal) for at least 3 years, and to have been on a stable dose (> 80% labelled dose/kg) for at least 6 months.

During the initial MAA procedure, concerns were raised about the lack of a control arm in study PB-102-F50 and doubts about the reliability of the historical data used to calculate the pre-switch eGFR slopes.

Although analysis of PK data from the 2 mg/kg pegunigalsidase alfa E4W were considered comparable to E2W at the time, such alternative regimen was not considered acceptable by the CHMP based on the

presented evidence on efficacy from the clinical studies. In addition, due to several deficiencies, the final population PK model, as presented by the applicant at time of the initial MAA, could not be used to guide dosing strategies. The applicant subsequently withdrew this alternative dosing during the initial MAA.

In support of this variation, the MAH submitted data from:

- The second interim analysis of an extension study of the PB-102-F50 study (CLI-06657AA1-03 formerly known as PB-102-F51) with a cut-off date of 31 December 2022 and a third interim of this study with a cut-off date of 25 October 2024; the first interim analysis of this study was part of the initial MAA.

- An observational study (CLI-06657AA1-05) conducted in patients enrolled in the CLI-06657AA1-03 study that aimed to describe patients' perceptions in symptoms and impacts of the E4W infusion schedule compared to their previous E2W infusion schedule.

The MAH also referred to the open-label, uncontrolled phase 3 study (PB-102-F50) which had previously been submitted at the time of the initial MAA and described above.

The MAH provided an integrated analysis of efficacy parameters (eGFR and annualised eGFR slope) from different clinical studies aiming to compare the 2 mg/kg E4W dosing regimen to the currently authorised 1 mg/kg E2W dosing regimen. This was an indirect comparison of the results of study PB-102-F50 (and the extension CLI-06657AA1-03, i.e. the data obtained with the 2mg/kg E4W regimen)) compared to the information from studies PB-102-F01/-F02/-F03, PB-102-F20, PB-102-F30 and CLI-06657AA1-04 i.e. the studies where the 1 mg/kg E2W regimen was evaluated.

In addition, the MAH further refined the integrated efficacy analyses by comparing annualised eGFR slope by dosing in matched subgroups (taking into progressive consideration the following factors sex, ADA-status, UPCR at baseline and eGFR category at baseline (≤/>60 ml/min/1.73/m^2) in ERT experienced patients. An exploratory 1-to-1 matching analysis in enzyme replacement therapy (ERT) experienced patients to mitigate the differences in baseline characteristics was also conducted.

Study PB-102-F50 and study CLI-06657AA1-03

Design, methodology and statistics

Study PB-102-F50 was an open label, switch over study aimed to assess the safety, efficacy and PK of pegunigalsidase 2.0 mg/kg administered by IV infusion E4W for 12 months in adult patients with Fabry disease previously treated with ERT (i.e. agalsidase alfa or agalsidase beta). After completion of study PB-102-F50, patients continued in study CLI-06657AA1-03.

The primary objective of these studies was to evaluate the safety of the alternative dosing regimen in patients currently treated with ERT. Explorative objectives comprised, among others: estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease – Epidemiology Collaboration equation ($eGFR_{CKD-EPI}$); eGFR slope, Plasma Lyso-Gb3 concentration, Left Ventricular Mass Index (LVMI) (g/m^2) by echocardiogram, Short Form Brief Pain Inventory (BPI), and EuroQoL 5 dimensions 5 levels questionnaire (EQ-5D-5L).

The study aimed to enrol a population earlier on in the development of Fabry disease. Therefore, the included patients were required to have an eGFR ≥ 30 ml/min/1.73m^2. Patients with a linear eGFR slope equal or worse than -2 ml/min/1.73m^2/year were excluded.

Studies PB-102-F50 and CLI-06657AA1-03 were descriptive in nature and no primary efficacy variable was defined in these studies. The studies aimed to enrol 30 patients. No formal sample size calculation was performed.

The descriptive nature of the efficacy data provided, the open label design of the 2 mg/kg/E4W study, the absence of an internal control arm and the uncertainties about the accuracy of the historical data used to calculate the pre-switch slope do not enable to conclude on the efficacy of the new proposed dosing regimen nor can be concluded that patients will remain stable during treatment with every 4 weeks regimen.

Interim analyses and data monitoring

Data presented in the clinical study report are based on the 3rd interim analysis with the cut-off date of October 2024. By this data cut-off, the last enrolled patient had reached 64 months of total treatment with pegunigalsidase alfa (12 months in study PB-102-F50 and 52 months in study CLI-06657AA1-03) (**Figure 4**).

Demography

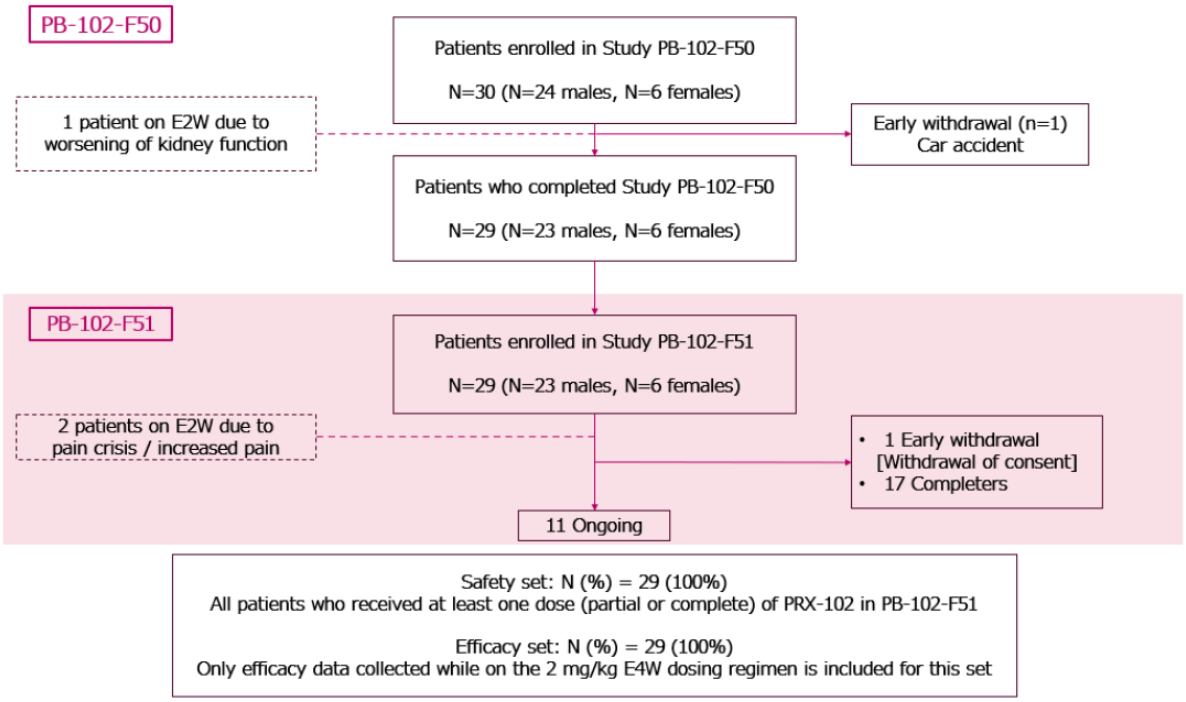
The participants in study PB-102-F50 were previously stable on agalsidase alfa or agalsidase beta but were not pegunigalsidase alfa experienced. Patients should be stable on renal function as this was an inclusion criterion.

Disposition of patients

Thirty (30) patients were enrolled, 29 patients (23 males and 6 females) completed study PB-102-F50, while one patient withdrew consent after the baseline visit. One additional patient withdrew consent during study CLI-06657AA1-03 and 28 patients were still ongoing at data lock of the 2nd interim analysis. At the data lock of the 3rd interim analysis (October 2024) 28 patients were still in study CLI-06657AA1-03. Between data lock of the 2nd and 3rd interim analyses and after FDA approval of pegunigalsidase alfa in 2023, all US patients that were still in the study discontinued study treatment (after the data lock of the 3rd interim analysis), as specified in the protocol.

One patient switched to the 1 mg/kg E2W dosing regimen due to deteriorating renal function during study PB-102-F50 but continued into study CLI-06657AA1-03. Two patients switched to the 1 mg/kg E2W dosing regimen due to increasing pain during study CLI-06657AA1-03. These patients continued to be followed-up after the switch, but were only included in analyses up until the point of switching dosing regimen.

Figure 4 Patient disposition



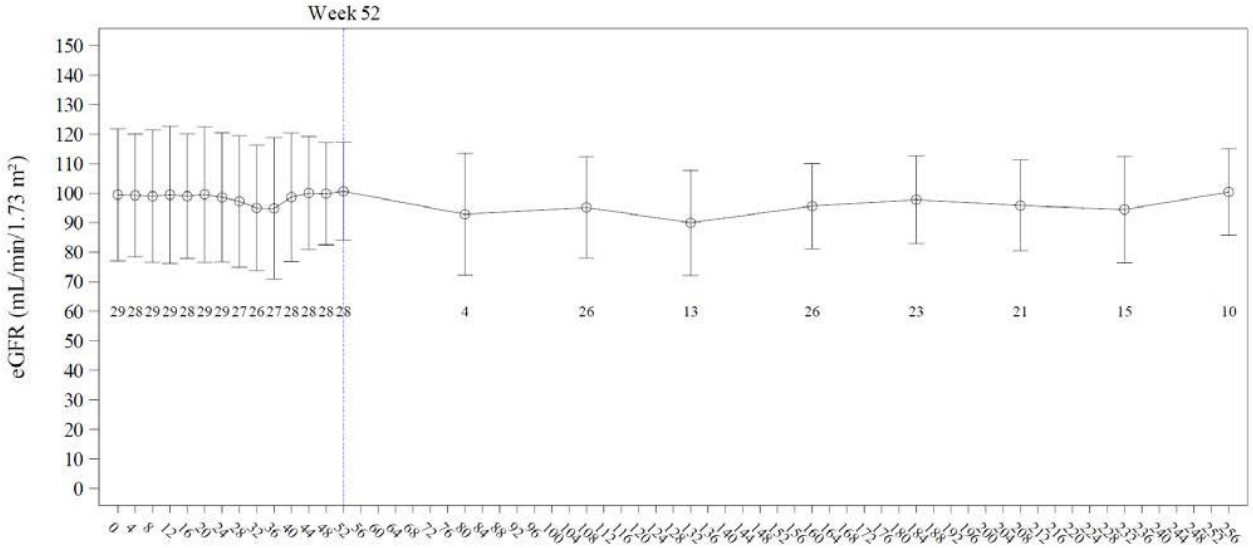
Estimated glomerular filtration rate ($eGFR_{CKD-EPI}$)

No clinically relevant change in the mean absolute eGFR values during the 5 years of observation could be observed (see Table 2 and Figure 5).

Table 2 eGFR Values and changes from baseline overall (N = 29) – Efficacy set

Week (Visit)	n	Mean (SD)
Baseline (V1)	29	99.44 (22.34)
Week 52 (V14)	28	100.65 (16.60)
Week 108 (V28)	26	95.15 (17.20)
Week 160 (V41)	26	95.62 (14.49)
Week 184 (V47)	23	97.79 (14.93)
Week 208 (V53)	21	95.83 (15.38)
Week 232 (V59)	15	94.45 (18.04)
Week 256 (V65)	10	100.40 (14.69)

Figure 5 Mean eGFR ± SD over time – Efficacy set



eGFR slope

Annualised eGFR slopes were calculated at screening (based on historical and screening eGFR values), baseline (based on historical, screening and baseline [V1] eGFR values) and during treatment (based on all post-treatment assessments up to the cut-off date). Baseline values derived from inhomogeneous data sources (historical and study data obtained during screening period and baseline visit from both central and local laboratories were used) have to be assessed with care.

The eGFR slope pre- (baseline) and post-switch (during treatment) is summarised overall in the Efficacy set in Table 3. The mean (SD) annualised eGFR slope in the Efficacy set was -1.79 (3.71) and -2.20 (2.14) ml/min/1.73m^2/year at baseline and during treatment, respectively. The analysis of individual eGFR slopes shows that 23 patients had a slope during treatment less negative than -3 ml/min/1.73m^2/year, while 6 patients more negative than -3 ml/min/1.73m^2/year.

Table 3 eGFR Slope (mL/min/1.73 m^2/year) at baseline and during treatment overall and by subgroup – Efficacy set

Population/subgroup	Baseline	During treatment*
Efficacy set		
n	29	
Mean (SD)	-1.79 (3.70)	-2.20 (2.14)
Median (Q1, Q3) [min; max]	-1.06 (-3.11, 0.12) [-13.59; 3.57]	-2.15 (-2.93, -1.10) [-8.68; 2.53]

*last measured slope in study CLI-06657AA1-03

Per protocol, patients with a negative eGFR slope of ≥ 2 ml/min/1.73m²/year at screening were excluded. However, at baseline eGFR slopes (based on historical, screening and baseline values) that were more negative than -2 ml/min/1.73m²/year were observed in some populations such as female patients, patients previously treated with agalsidase alfa, patients with non-classic Fabry disease and patients with an eGFR ≤ 60 ml/min/1.73 m².

In 6 patients the eGFR slope during the study was more negative than -3 ml/min/1.73m^2/year.

Left Ventricular Mass Index (LVMI)

Data for quantitative echocardiography evaluations, e.g., LVMI, have substantial variations. In addition, in study PB-102-F50 and study CLI-06657AA1-03 the echocardiograms were not performed in a standardized manner and/or read centrally.

At baseline, most patients had normal stress test results (19/28 patients; 67.9%). The percentage of patients with normal results increased further in the course of study PB-102-F50 (21/24 patients, 87.5% at week 52) and in study CLI-06657AA1-03 (20/22 patients, 90.9% at week 108; 18/22 patients, 81.8% at week 160; and 20/21 patients, 95.2% at week 208.

The cardiac function was generally stable over the study, with no major changes observed in qualitative echocardiography assessments. However those were not performed in a standardized manner and/or read centrally.

Plasma Lyso-Gb3

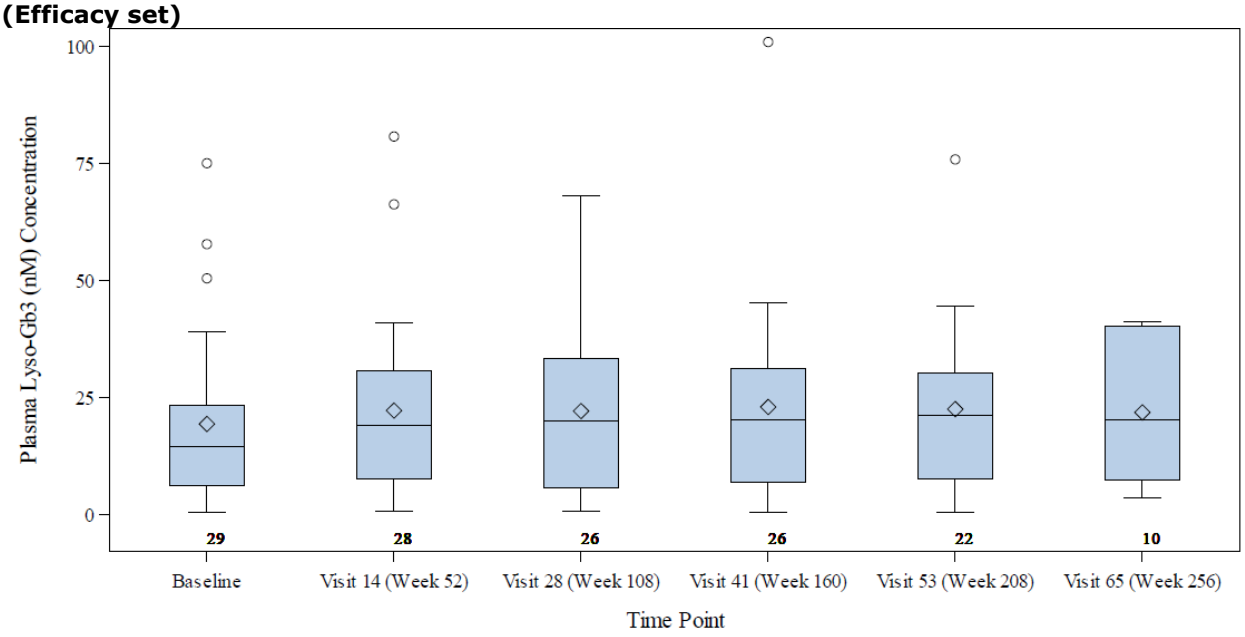
Absolute values and absolute and percentage changes from baseline in plasma Lyso-Gb3 concentrations in the Efficacy set are presented overall in Table 4.

Table 4 Summary of plasma Lyso-Gb3 concentration (nmol/l) (Efficacy set)

Observed result						Change from baseline							
n	Mean	SD	Median	Q1	Q3	Change	n	BL mean	Mean	SD	Median	Q1	Q3
Visit 1 Baseline													
29	19.4	18.05	14.5	6.2	23.3								
Visit 4 (week 12)													
29	21.3	18.60	17.7	7.0	27.1	Absolute	29	19.4	1.9	3.71	0.8	0.0	3.8
						%	29		12.7	20.25	11.4	0.0	20.7
Visit 7 (week 24)													
29	23.5	22.00	19.4	7.3	31.5	Absolute	29	19.4	4.1	6.82	2.3	0.0	6.9
						%	29		22.7	30.46	13.0	0.0	32.9
Visit 14 (week 52)													
28	22.2	19.07	19.2	7.6	30.7	Absolute	28	19.2	3.0	4.98	2.6	0.0	7.1
						%	28		22.1	27.53	21.7	-1.1	41.3
Visit 28 (week 108)													
26	22.1	18.75	20.1	5.6	33.4	Absolute	26	18.9	3.2	6.43	1.2	-0.2	7.8
							26		25.0	36.00	18.3	-4.9	40.0
Visit 41 (Week 160)													
26	23.0	20.79	20.3	7.0	31.3	Absolute	26	19.4	3.6	7.81	2.0	-0.5	9.9
						%	26		24.7	34.28	20.3	-9.5	47.3
Visit 53 (week 208)													
22	22.5	17.22	21.2	7.6	30.2	Absolute	23	20.6	2.5	8.16	2.3	-1.4	9.7
						%	23		22.8	38.58	24.1	-12.8	49.4
Visit 65 (week 256)													
10	21.8	14.80	20.4	7.5	40.2	Absolute	10	19.0	2.9	11.27	1.3	0.5	9.4
						%	10		39.4	56.71	25.6	8.7	77.7

Note 1: Legend: n=Number of patients with available data in the efficacy set, BL=Baseline, SD=Standard Deviation, Q1=25th percentile, Q3=75th percentile.
Note 2: The baseline for this study is defined as the assessment at Visit 1 [day 1] of the parent study (PB-102-F50) prior to the first infusion of PRX-102 in this regimen. If not available, the last assessment before receiving the first treatment of PRX-102 is used as baseline.

Figure 6 Boxplots of plasma Lyso-Gb3 (nM) concentration over time at each yearly visit (Efficacy set)



The numbers in the graph are the total number of patients at each yearly visit.

As can be observed from the pharmacodynamic measure (plasma Lyso-Gb3) after the switch the mean plasma Lyso-Gb3 increases by around 4 nmol/l by the week 24 visit and then does not increase further. A similar pattern is seen for the median change in Lyso-Gb3 values. However, Q3 of the change in Lyso-Gb3 values tended to increase further over time.

Therefore it can be concluded that median plasma Lyso-Gb3 concentration concentrations change from baseline at week 256 slightly increased in male participants and remained relatively stable in female participants.

Short Form Brief Pain Inventory

The majority of patients had an improvement or no change from baseline in average pain severity at all post-baseline visits (range: 69.6% to 100% of patients with data at the timepoint) according to the self-administered, patient-reported Short Form BPI questionnaire.

No major changes in the pain severity score were observed from baseline to week 256.

Mainz Severity Score Index (MSSI)

The overall mean (SD) MSSI score at baseline was 19.1 (14.46) for agalsidase alfa pretreated (N=7) and 21.0 (7.99) for agalsidase beta pretreated (N=22) patients. Overall, the observed MSSI scores during treatment tended to remain comparable to baseline irrespective of the prior treatment with agalsidase alfa or beta.

No major changes in the MSSI were observed from baseline to week 256.

Quality of Life (QoL)

The mean overall health scores tended to remain stable from baseline to week 160 and to improve slightly in the patients with data at later timepoints.

Over the treatment period, no major changes in pain perception or in the EQ-5D-5L descriptive results or overall health score were observed.

No major changes in the EQ-5D-5L were observed from baseline to week 256.

Study CLI-06657AA1-05

Study CLI-06657AA1-05 is an observational patient reporting outcome study that was performed to collect quality of life (QoL) data based on information the patients provided within a 60-minute interview when questioned about their signs and symptoms of Fabry disease.

Out of the initial 29 patients included in the study CLI-06657AA1-03, 17 patients participated in the study telephone interview. Results from this observational study show that 94 % of the patients reported improvement in at least one symptom and 75 % reported worsening in at least one symptom, especially fatigue. Fluctuating symptoms between 2 administrations have been described with a greater number of symptoms experienced during the week prior to administration. A majority of patients (63%) reported an improvement of the impact of the disease.

The results of individual interviews cannot be used independently for regulatory decision-making. Furthermore, all the evaluation criteria for individual interviews are of a purely descriptive nature, carried out on a small number of patients, and the results are of uncertain value, particularly at population level. Because of this, study CLI-06657AA1-05 is not discussed further in this assessment report.

Integrated analysis

In the absence of head-to-head comparison, the MAH provided an integrated analysis of efficacy parameters (eGFR and annualised eGFR slope) obtained from different clinical studies. The aim of this indirect comparison is to compare the 2 mg/kg E4W dosing regimen with the currently authorised 1 mg/kg E2W dosing regimen, i.e. patients from PB-102-F01/-F02/-F03, PB-102-F20, PB- 102-F30 and CLI-06657AA1-04. As a result, demographic and disease characteristics at baseline were not similar with more severe renal impairment, fewer male patients and inclusion of patients who did not previously receive ERT in the E2W cohort, which makes it near impossible to reliably compare the efficacy parameters. Also, the limitations for study PB-102-F50 and Study CLI-06657AA1-03 (raised above) remain.

Patients in the E4W cohort were younger than in the E2W cohort and the percentage of males was higher in the E4W cohort than in the E2W cohort (79.3% vs 60.2%). All patients from the E4W cohort were previously treated with ERT while 11 out of the 84 patients in the E2W cohort were naïve to treatment (although these naïve patients were not included in the integrated analyses). Mean (SD) baseline eGFR levels were higher in the E4W cohort compared to the E2W cohort (99.4 (22.34) and 78.6 (22.33) ml/min/ 1.73 m^2 respectively).

Table 5 Patient Demographics and Baseline Characteristics, ISE Efficacy Set

	Dosing regimen: pegunigalsidase alfa		
	1 mg/kg E2W (N=84)	2 mg/kg E4W (N=29)	All patients (N=113)
Age (years)			
Mean (SD)	44.4 (10.72)	40.9 (11.28)	43.5 (10.93)
Median (min; max)	45.5 (20; 60)	41.0 (19; 58)	45.0 (19; 60)
Gender, n (%)			
Male	51 (60.7%)	23 (79.3%)	74 (65.5%)
Female	33 (39.3%)	6 (20.7%)	39 (34.5%)
Age at FD diagnosis (years)			
Mean (SD)	30.3 (13.84)	26.4 (15.30)	29.3 (14.26)
Median (min; max)	30.0 (0; 52)	25.0 (2; 51)	30.0 (0; 52)
Previous ERT, n (%)			
None (naïve)	11 (13.1%)	0	11 (9.7%)
Agalsidase alfa	17 (20.2%)	7 (24.1%)	24 (21.2%)
Agalsidase beta	56 (66.7%)	22 (75.9%)	78 (69.0%)
Duration (years) of last ERT	*N = 73*	*N = 29*	*N = 102*
Mean (SD)	6.2 (3.87)	8.5 (4.85)	6.9 (4.27)
Median (min; max)	6.1 (1.1; 19.7)	6.9 (1.3; 18.4)	6.2 (1.1; 19.7)
eGFR (mL/min/1.73 m²)			
Mean (SD)	78.6 (22.33)	99.4 (22.34)	84.0 (24.03)
Median (min; max)	76.9 (30.1; 131.0)	102.1 (30.3; 135.9)	82.8 (30.1; 135.9)
Baseline eGFR (mL/min/1.73 m²), n (%)			
30 < eGFR ≤ 60	18 (21.4%)	2 (6.9%)	20 (17.7%)
60 < eGFR ≤ 90	42 (50.0%)	5 (17.2%)	47 (41.6%)
90 < eGFR ≤ 120	20 (23.8%)	17 (58.6%)	37 (32.7%)
eGFR > 120	4 (4.8%)	5 (17.2%)	9 (8.0%)
ADA status at baseline, n (%)			
Negative	62 (73.8%)	20 (69.0%)	82 (72.6%)
Positive	22 (26.2%)	9 (31.0%)	31 (27.4%)

ADA = anti-drug antibody; E2W, E4W = every 2, 4 weeks; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; FD = Fabry disease; min, max = minimum, maximum; N = number of patients in group; n = number of patients in category
Notes: Percentages are calculated on the number of subjects (N). For patients who switched to pegunigalsidase alfa in Study PB-102-F60, their age at visit 1 of -F60 is considered

Considering the indirect comparison, it is noted that the demographic and disease characteristics at baseline were not similar with a more severe renal impairment and fewer male patients in the E2W cohort which makes difficult to compare the efficacy parameters.

The results of the integrated analyses with the ANCOVA model are post-hoc, observational and exploratory and do not demonstrate that the dosing regimens are comparable. Indeed, no statistically significant difference (p=0.662) on the slope of the eGFR was observed between pegunigalsidase alfa 2 mg/kg E4W minus the reference 1 mg/kg E2W on the slope of the eGFR. However, absence of a significant difference does not equal demonstration of comparability. Absence of a significant difference may be explained by a lack of power in the statistical test to detect a clinically relevant difference, due to the small number of participants in the pegunigalsidase alfa 2 mg/kg group E4W (n=29) and the fact that the two groups were derived from different clinical trials.

An integrated analysis was not performed for other efficacy parameters, such as lyso-Gb3 levels.

Analysis of efficacy in relation to the ADA status

In study PB-102-F50 median (min;max) pre switch eGFR slope in 9 ADA-positive patients was -0.64 (-4.3;3.3) ml/min/1.73m^2/year after the switch this worsened to -8.44 (-14.1;2.7). In 20 ADA-negative patients this was -1.67 (-13.6;3.6) pre-switch and -1.22 (-8.5;8.2) after the switch. (*Note* It is observed that in the various tables the figures considering the eGFR slope for ADA-positive and negative patients differ.)

In the integrated analysis the median (min;max) eGFR slope during treatment with 1 mg/kg E2W was -2.48 (-10.41;9.92) ml/min/1.73m^2/year and -1.62 (-5.19; 1.44) in the ADA-negative patients treated with 2 mg/kg E4W. In the ADA-positive patients this was -3.47 (-19.44; 4.05) for those treated with 1 mg/kg E2W and -2.04 (-8.68; -1.24) ml/min/1.73m^2/year for the ADA-positive patients treated with 2 mg/kg E4W.

2.2.3. Safety

Three cohorts were used for the safety analysis:

Cohort 1: Patients treated with 1 mg/kg pegunigalsidase alfa dosage administered every two weeks (E2W) (n = 111 patients at baseline).

Cohort 2: Patients treated wither other ERT switched to 2 mg/kg pegunigalsidase alfa E4W (n = 30 at baseline). This cohort includes patients from study PB-102-F50 and its ongoing OLE study (CLI-06657AA1-03).

Cohort 3: Patients treated with any dose and frequency of pegunigalsidase alfa (n = 142). One additional patient received a different dose in studies PB-102-F01/-F02/-F03 and is only included in Cohort 3.

In Cohort 1, the exposure was 3519.77 patient-months, equivalent to approximately 293.3 patient-years. In Cohort 2, the exposure was 1582.42 patient-months (approximately 131.9 patient-years), which was lower than in Cohort 1.

In both cohorts, there were more male patients than female patients (70 and 24 males versus 41 and 6 females, respectively). In Cohort 1 (1 mg/kg E2W), 66% of patients were male, compared to 80% in Cohort 2, with a mean age of 43 and 41 years, predominantly White (92% and 100%). Most patients had prior ERT treatment, mainly agalsidase beta, for 6.9 years (Cohort 1) or 8.4 years (Cohort 2). ADA-positive patients tended to be more frequent in Cohort 2 compared to Cohort 1 (33% vs. 24%).

Most patients received at least one of their infusions in a home setting. In Cohort 1, 72 of 111 patients (65%) received home infusions at some point in time during treatment, compared to 22 of 30 patients (73%) in Cohort 2. Additionally, 46% of infusions in Cohort 1 and 44% of infusions in Cohort 2 were administered at home.

The frequency of related treatment-emergent adverse events (respectively 42.3% vs. 43.3%), and serious treatment-emergent adverse events was similar in Cohort 1 and 2 (respectively 32.4% vs. 33.3%). However, the frequency of related serious treatment-emergent adverse events tended to be higher in Cohort 1 (4.5% vs. 0%), as was the incidence of fatal treatment-emergent adverse events (3.6% vs. 0%). Interestingly, the frequency of severe treatment-emergent adverse events tended to be higher in Cohort 1 (35.1%) than in Cohort 2 (23.3%). Additionally, in Cohort 1, 8.1% of participants experienced treatment-emergent adverse events leading to study withdrawal, while no such events occurred in Cohort 2.

In summary, the frequency of serious treatment-emergent adverse events that were related, fatal and led to withdrawal from the study tended to be higher in Cohort 1 as compared to Cohort 2. These events were absent or tended to be observed less frequently in Cohort 2.

In Cohort 1, the system organ classes with the most common treatment-emergent adverse events were: Infections and infestations, Nervous system disorders, Musculoskeletal and connective tissue disorders. The most reported preferred terms were: Nasopharyngitis, Headache, Back pain, Diarrhoea, Fatigue, Cough (all reported in >15% of patients).

In Cohort 2, the same system organ classes were observed as in Cohort 1. The most reported preferred terms were: Coronavirus infection, Nasopharyngitis, Infusion-related reaction, Pain in extremity, Upper respiratory tract infection, Headache, Paraesthesia, Nausea, Fatigue, Cough, Hypertension, Pain, Back pain, Sinusitis (all reported in >15% of patients).

Most of the events were mild or moderate in severity and resolved with continued treatment, and the majority were not serious.

The five related serious cases reported in Cohort 1 (no related serious adverse events in Cohort 2) include bronchospasm, hypersensitivity, and chills in one patient each, as well as type I hypersensitivity in two patients.

The event rates in Cohort 1 for headaches, dizziness, arthralgia, musculoskeletal pain, diarrhoea, abdominal pain, dyspnoea, and rash tended to be higher compared to Cohort 2. However, infusion-related reactions, pain, coronavirus infection, gastroenteritis, constipation, lymphedema, and white matter lesions tended to be higher in Cohort 2 compared with Cohort 1.

The frequency of infusion related reactions and pain decreased overthe course of the treatment, however a late increase is observed.

Related treatment-emergent adverse events with higher absolute reporting rates in Cohort 2 compared to Cohort 1 included infusion-related reactions (20.0% vs. 4.5%). None of the infusion-related reaction events or pain events in Cohort 2 were severe or serious.

In Cohort 1, the highest rates of related treatment-emergent adverse events were observed in the system organ classes of Gastrointestinal Disorders, followed by General Disorders and Administration Site Conditions, and Nervous System Disorders. The preferred terms reported by the highest number of patients in Cohort 1 were Nausea (6 patients), Fatigue and infusion-related reactions (5 patients each), and Dizziness (4 patients).

In Cohort 2, the highest rates of related treatment-emergent adverse events were observed in the system organ class of Injuries, Poisoning, and Procedural Complications, followed by Gastrointestinal Disorders and General Disorders and Administration Site Conditions. The preferred term reported by the highest number of patients in Cohort 2 were infusion-related reactions (6 patients) and Pain in extremity and Headache (3 patients each).

Overall, data with the 2 mg/kg every 4 weeks dosage (Cohort 2) are reassuring. However, this cohort includes significantly fewer patients than Cohort 1 with the approved dosage (30 vs. 111 patients).

No related serious adverse events were reported under treatment with 2 mg/kg pegunigalsidase alfa E4W (Cohort 2). The 5 related serious adverse events were presented at the time of the initial marketing authorisation.

Bradycardia and left ventricular hypertrophy, were initially presented as adverse drug reactions. However, these conditions were pre-existing and are complications in Fabry disease. Subsequently, these conditions were removed from SmPC section 4.8. Upon reconsideration about the cause -effect relationship, increased hepatic enzymes were also removed as an adverse drug reaction from SmPC section 4.8.

In conclusion, in terms of safety, no major issues are observed for pegunigalsidase alfa at a dosage of 2 mg/kg E4W as compared to the previously authorized pegunigalsidase alfa 1 mg/kg E2W dosage. However, infusion-related reactions tended to occur more frequently in Cohort 2 (2 mg/kg every 4 weeks: 30%) compared to Cohort 1 (1 mg/kg every 2 weeks: 23.4%). No serious adverse events or fatal cases have been reported in Cohort 2.

Infusion related reaction

In Cohort 1, 23.4% of patients (26/111) reported infusion-related reactions. A total of 5 serious infusion-related reactions, and 4 infusion-related reactions leading to study discontinuation, were observed, all occurring during the first year of treatment.

In Cohort 2 30.0% (9/30) of patients reported infusion-related reactions. No serious infusion-related reactions or infusion-related reactions leading to study discontinuation were reported. However, a few late-onset, non-severe infusion-related reactions were observed after 4 years of treatment in ADA-negative patients. By ADA status, 50% of ADA-positive patients experienced an infusion-related reaction, compared to 21.1% of ADA-negative patients. Notably, no ADA-induced patients experienced an infusion-related reactions.

A case of throat tightness was reported as a late-onset infusion-related reaction in Cohort 2, occurring after approximately 4 years of treatment in a patient with no prior history of infusion-related reactions. This case, like other late-onset infusion-related reactions in this cohort, was non-severe, non-serious and did not require treatment discontinuation. Throat tightness was included as an adverse reaction in SmPC section 4.8.

Headache, nausea, and syncope were reported as commonly reported infusion-related adverse drug reactions in SmPC section 4.8.

Treatment-emergent adverse events leading to withdrawal from study

The dosing changes were due to clinical deterioration, but the observed effects (kidney failure and pain crises) were not directly related to the treatment. Patient already had chronic kidney disease, while the pain crises in patients and were likely related to their underlying condition.

Immunogenicity

Twenty-nine (29) patients wereenrolled. seven had prior treatment with agalsidase alfa; none tested positive for anti-agalsidase alfa IgG antibodies at screening or for anti-pegunigalsidase alfa IgG antibodies at baseline. Of the 22 previously treated with agalsidase beta, 10 tested positive for anti-agalsidase beta IgG antibodies at screening. Among these, nine also tested positive for anti-pegunigalsidase alfa IgG antibodies at baseline, indicating pre-existing cross-reactive ADA to pegunigalsidase alfa. All ADA-positive patients were male and had prior exposure to agalsidase beta.

Treatment-emergent ADA included treatment-induced ADA (patients negative at baseline who developed ADA post-treatment) and treatment-boosted ADA (patients positive at baseline who showed a ≥4-fold increase in ADA titre post-treatment).

In this study, only patients with pre-existing IgG antibodies showed positivity for anti-pegunigalsidase alfa antibodies, except one patient who developed transient, non-neutralizing de novo ADA. Only three patients exhibited boosted ADA titres after treatment. Notably, five patients (55.5% of initially positive) sero-reverted, becoming ADA-negative during the study.

No new immunogenicity findings emerged in the third interim analysis compared to the second, and no additional patients developed treatment-emergent ADA.

Overall, anti-pegunigalsidase antibodies in IgG and ADA antibodies decreased over time, with no significant difference between the 1 mg/kg and 2 mg/kg pegunigalsidase alfa dosages.

2.2.4. Overall discussion and conclusions on clinical aspects

Clinical Pharmacology

The absence of a clear dose-efficacy relationship precludes the use of data from the Population Pharmacokinetic (PopPK) study as a basis for concluding that 2mg/kg E4W is an effective posology.

The MAH developed a PopPK model suggesting that the systemic exposure for the two dosing regimens of interest was similar. However, the assessment of exposure-response relationship indicated that there is no relationship between pegunigalsidase alfa exposure with Lyso-Gb3 change from baseline at 12 months of treatment or with eGFR annualized slope. Thus, in the absence of an exposure-response relationship, the results obtained with the popPK model do not allow to conclude that the two proposed dosing regimens are of comparable efficacy.

Furthermore, in the PopPK report, the PD -response based on plasma Lyso-Gb3 and annualised eGFR slope were similar at 12 months with 1 mg/kg E2W or 2 mg/kg E4W. However, those data can only be considered exploratory since these are based on a subset of patients from clinical trials in which baseline data differed.

Efficacy

The submitted data do not allow to draw conclusion regarding the efficacy of the proposed alternative dosing regimen. This limitation arises primarily because the available data originates from open-label, uncontrolled studies, which are predominantly descriptive. As such, these studies do not provide the robust evidence required to support 2mg/kg E4W as an effective posology in the authorised population/indication.

To further support the alternative 2 mg/kg/E4W dosing compared to the 1 mg/kg/E2W the MAH further refined the integrated efficacy analyses by comparing Annualised eGFR slope by dosing in matched subgroups (taking into progressive consideration the following factors sex, ADA-status, UPCR at baseline and eGFR category at baseline (≤/>60 ml/min/1.73 m2) in ERT experienced patients. However, such subgroup analyses lead to small (or even null) number of patients per groups preventing from concluding on efficacy.

In the exploratory 1-to-1 matching analysis in enzyme replacement therapy (ERT) experienced patients to mitigate the differences in baseline characteristics, a total of 17 matched pairs could be identified suggesting comparable effects (95% CI) in the annualized eGFR slopes of both dosing regimens. However, the limited number of match pairs and the exploratory nature of the analysis does not allow to draw a conclusion or to generalize the results to the overall population included in the approved indication.

Overall, due to the lack of robust and comparative data, no conclusion can be drawn on the efficacy of the 4-weekly dosing regimen. This limitation also precludes the identification of specific subpopulations deriving clear benefit from the 4 weekly dosing regimen, with the added complication of subgroup analyses leading to small numbers of patients per group.

Safety

No major issues are observed for pegunigalsidase alfa at a dosage of 2 mg/kg E4W as compared to the previously authorized pegunigalsidase alfa 1 mg/kg E2W dosage. However, infusion-related reactions

tended to occur more frequently in Cohort 2 (2 mg/kg every 4 weeks: 30%) compared to Cohort 1 (1 mg/kg every 2 weeks: 23.4. No serious adverse events or fatal cases have been reported in Cohort 2.

During the procedure, the MAH revised their proposal for a new posology (2mg/kg E4W) at the time of the first request for supplementary information and the Oral Explanation, respectively – see below.

In responses to the first request for supplementary information (RSI), a first proposal was made to restrict the use of pegunigalsidase alfa 2 mg/kg E4W to patients previously treated with pegunigalsidase alfa 1 mg/kg E2W for at least 3 months in section 4.2 of the SmPC:

"After a minimum of 3 months of treatment with pegunigalsidase alfa 1 mg/kg every two weeks the treatment can be administered at the dose of 2 mg/kg of body weight every four weeks, based on treating physician's evaluation."

This proposal was made because only previously treated patients were included in the open label study that assessed the 2 mg/kg E4W dosing scheme (PB-102-F50). The proposed 3 months treatment with pegunigalsidase alfa at a dose of 1 mg/kg E2W was based on the time required to reach steady state. However, it should be noted that the participants in this study had previously received either agalsidase alfa or agalsidase beta and not pegunigalsidase alfa. This proposal was thus not substantiated by the available clinical data and consequently not supported by the CHMP. It was later removed from the final proposal. See further below.

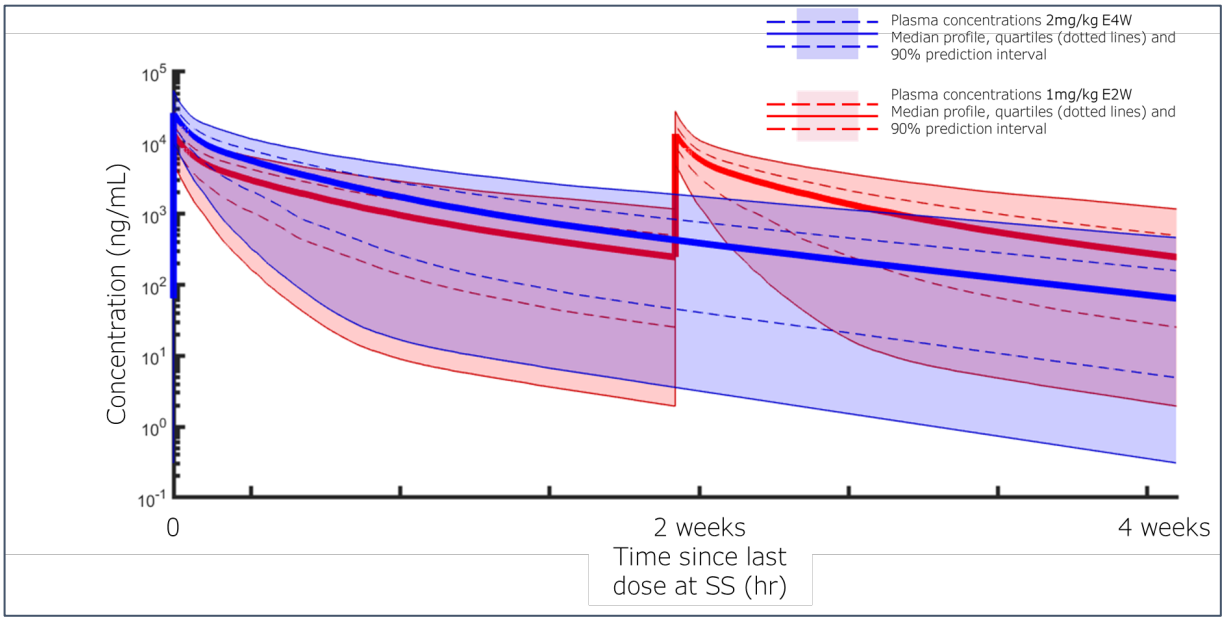
Oral explanation

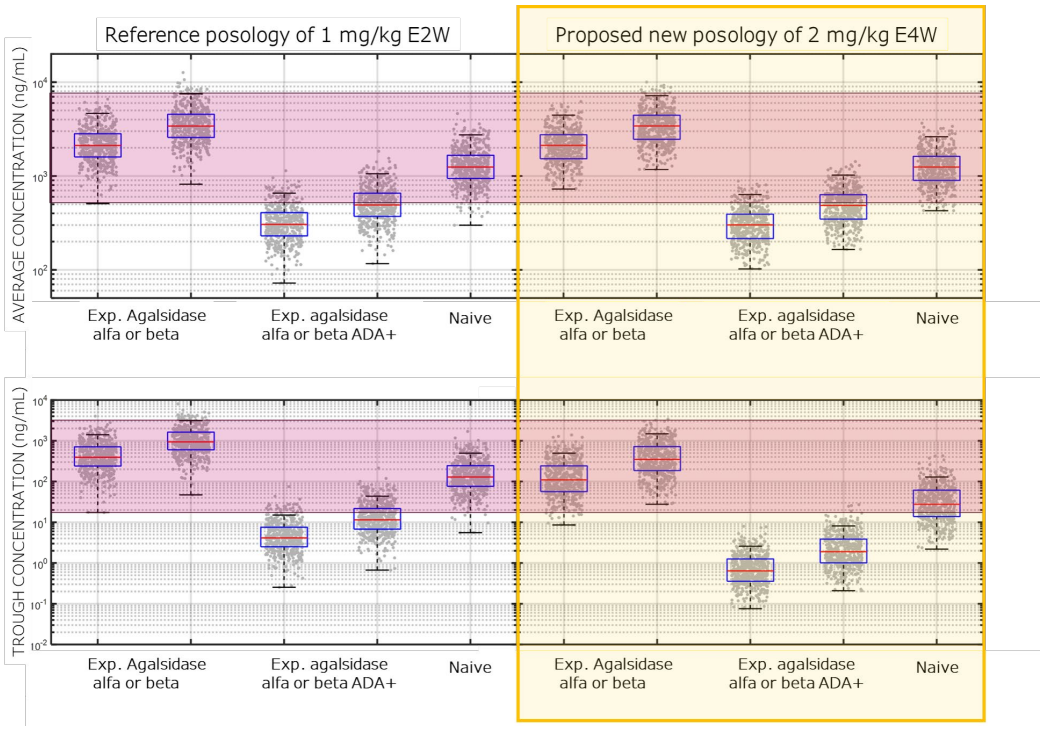
During the oral explanation, a second proposal was made to restrict the new posology (2mg/kg E4W) in patients testing negative to pegunigalsidase alfa anti-drug antibodies (ADA) in section 4.2 of the SmPC:

"The treatment can be also administered at the dose of 2 mg/kg of body weight every four weeks in patients testing negative to pegunigalsidase alfa anti-drug antibodies (ADA).

The posology of choice should be determined by the treating physician, taking into consideration the signs and symptoms of the disease, collected on the basis of a regular clinical multidisciplinary assessment. Any type of posology change between the two options deemed necessary by the physician, can be implemented starting from the next scheduled infusion."

This was based on the following simulation which showed lower exposure in ADA-positive patients previously treated with agalsidase alfa or beta for the 1 mg/kg E2W and 2 mg/kg/E4W, respectively.

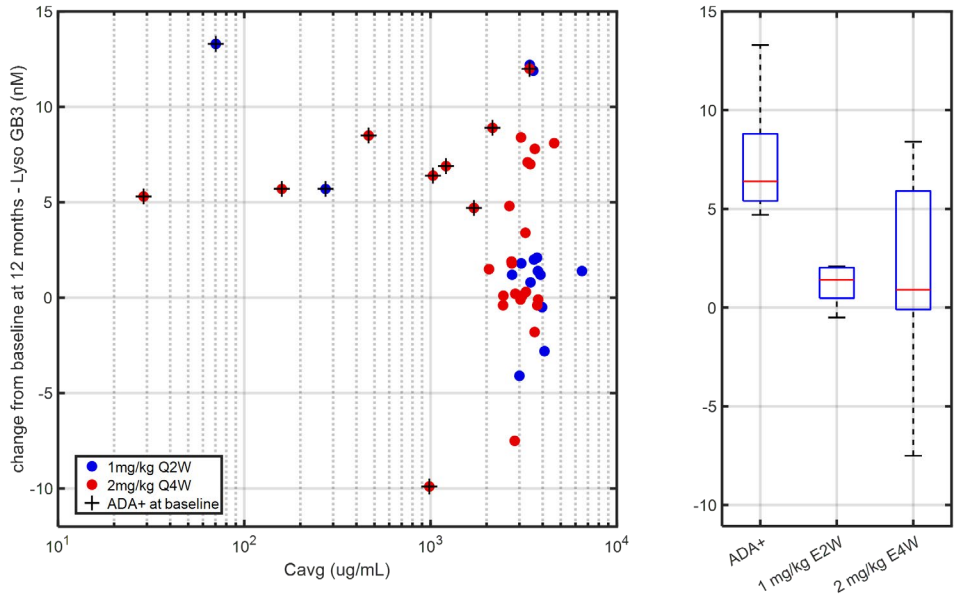




In addition, using the sub-population of patients with antibody to pegunigalsidase alfa (ADA-positive) as a reference, the applicant argued that a clear efficacy response is observed with a change from baseline at 12 months for the Lyso-Gb3 marker, which is similar for 1 mg/kg E2W and 2 mg/kg E4W:

- patients with ADA-positive at baseline are statistically different from patients with ADA-negative ($p<0.01$)

- The mean responses are not different for 1 mg/kg E2W *vs* 2 mg/kg E4W



Note : LysoGB3 change from baseline from experienced patients: data collected from studies PB-102-F50 and PB-102-F20 (PK subpopulation); Box plot display the median (red line), quartiles (box) and approx. 95th percentiles (whiskers) summarizing the clinical trial data.

Overall, the applicant claimed that such restrictive approach would limit the variability from both pharmacokinetic and clinical perspectives that could be observed in the authorised population/indication.

In addition to this proposal, the MAH proposed to add new text to clarify when a switch in posology could be considered with the introduction of an alternative posology. This proposed recommendation for the switch in posology was not substantiated by clinical data and thus not supported by the CHMP.

During the oral explanation, the MAH summarised its argumentation to support the alternative posology as follows:

Pharmacokinetics

- A revised PopPK model was developed;

- Simulations confirmed a similar exposure for the 2 mg/kg E4W and the reference 1 mg/kg E2W;

- ADAs have a major impact on PK parameters and exposure with lower C_{min} in ADA-positive patients.

Pharmacodynamic

- No exposure/response relationship was found for the range of doses tested in the clinical trials; Dose/exposure response was never an objective of the clinical trials which are characterized by limited dose and exposure range and PD markers (i.e. LysoGB3 and eGFR) with high noise to signal ratio**;**

- Treatment effect on plasma Lyso-Gb3 was comparable for 2 mg/kg E4W vs 1 mg/kg E2W using the sub-population of patients with antibody to pegunigalsidase alfa (ADA-positive) as a reference (see previous figures)

- An inferior PD response was observed in ADA-positive patients

Safety and tolerability

- A favourable safety and tolerability profile was observed for the 2 mg/kg E4W

Efficacy

- Sustained efficacy was found for the 2 mg/kg E4W with stabilization of Fabry disease across several endpoints, with a more rapid decline in kidney function in ADA-positive patients. In studies PB-102-F50 and its extension CLI-06657AA1-03 29 patients received pegunigalsidase alfa 2 mg/kg E4W for a median of 69.9 (9.3-80.1) months (≈5.8 years). Pegunigalsidase alfa 2 mg/kg E4W proved to be a safe and efficacious treatment posology, capable to stabilize Fabry disease across all the investigated efficacy and PD endpoints.

- Treatment effect on kidney function decline of the 2 mg/kg E4W proved comparable to the reference 1 mg/kg E2W

Third party intervention

The CHMP received, during the assessment of the procedure, correspondences from the Fabry International Network and a group of clinicians (hereinafter referred to as 'third parties') expressing the third parties' views about the alternative posology.

The CHMP considered those interventions in the context of its assessment and acknowledged the patients and clinical needs and the preference for a monthly regimen as opposed to a 2 weekly regimen, however the data presented by the MAH do not allow to conclude on the monthly posology in the authorised population/indication, even with a restriction in Anti-Drug-Antibody (ADA) negative patients.

Overall Conclusion

Following the Oral Explanation, the CHMP maintained their concerns raised during the procedure, on the new posology (2mg/kg E4W):

- The submitted studies do not provide the robust evidence required to support 2mg/kg E4W as an effective posology in the authorised population/indication and even with a restriction in Anti-Drug-Antibody (ADA) negative patients;

- Similar conclusions on comparison between alternative 2 mg/kg/E4W dosing and the 1 mg/kg/E2W are made on the additional integrated efficacy analysis provided to support the restriction for the proposed posology of 2 mg/kg E4W in ADA-negative patients. Only 20 patients were ADA-negative and 9 patients were ADA-positive in the study PB-102-F50, using the alternative posology of 2 mg/kg E4W.

Overall, due to the lack of robust and comparative data, no conclusion can be drawn on the efficacy of the 4-weekly dosing regimen. This limitation also precludes the identification of specific subpopulations deriving clear benefit from the 4 weekly dosing regimen, with the added complication of subgroup analyses leading to small numbers of patients per group.

In addition, the CHMP considered that uncertainties remain regarding the monthly posology in naïve patients and patients previously treated with the 1 mg/kg/E2W (every 2 weeks) dosage who switch to the 2 mg/kg/E4W since only patients previously treated with the other authorised ERT were included. the criteria guiding prescribers in selecting either the approved or the alternative posology (main scope of this variation) are not substantiated by clinical data.

2.2.5. Conclusions on clinical aspects

The submitted data do not allow to draw conclusions regarding the efficacy of the proposed alternative dosing regimen, 2mg/kg E4W (every four weeks). The absence of a clear dose-efficacy relationship precludes the use of data from the Population Pharmacokinetic (PopPK) study as a basis for concluding on 2mg/kg E4W as an effective posology;

The benefit-risk balance of Elfabrio in the currently authorised 2-weekly dosing regimen remains positive.

The CHMP recommended that any Risk Management Plan (RMP) and Product Information changes that were not related to the main scope of this procedure but were agreed during the assessment, be submitted in a separate variation procedure.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to introduce an alternative posology regimen based on results from study PB-102-F50 (BRIGHT) and interim results from its extension study CLI-06657AA1-03 (formerly presented as PB-102-F51), as well as results of the

observational patient reporting outcome study CLI-06657AA1-05. CLI-06657AA1-03 is an 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. The Package Leaflet is updated accordingly. The RMP version 1.3 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.4.

☒is not recommended for approval.

Grounds for refusal

Whereas

- The submitted data do not allow to draw conclusions regarding the efficacy of the proposed alternative dosing regimen, 2mg/kg E4W (every four weeks). This limitation arises primarily because the available data originate from open-label, uncontrolled studies, which are predominantly descriptive. As such, these studies do not provide the robust evidence required to support 2mg/kg E4W as an effective posology in the authorised population/indication and even with a restriction in Anti-Drug-Antibody (ADA) negative patients;
- The absence of a clear dose-efficacy relationship precludes the use of data from the Population Pharmacokinetic (PopPK) study as a basis for concluding on 2mg/kg E4W as an effective posology;

the CHMP has recommended the refusal of the variation to the terms of the Marketing Authorisation.

Amendments to the marketing authorisation

Not applicable

4. Re-examination of the CHMP opinion of 16 October 2025

4.1. Detailed grounds for re-examination submitted by the applicant

The MAH presented in writing arguments refuting the grounds for refusal. The MAH argumentation was as follows:

4.1.1. Ground #1

Ground #1

The submitted data do not allow to draw conclusions regarding the efficacy of the proposed alternative dosing regimen, 2 mg/kg E4W (every four weeks). This limitation arises primarily because the available data originate from open-label, uncontrolled studies, which are predominantly descriptive. As such, these studies do not provide the robust evidence required to support 2mg/kg E4W as an effective posology in the authorised population/indication and even with a restriction in Anti-Drug-Antibody (ADA) negative patients.

By way of introduction, Chiesi would like to respectfully submit that the CHMP appear to refer to the open-label studies submitted by the MAH as the sole data available. Not only is this not the case, as we will show below; but it is also evident from the plain language of the ground for refusal that there has been no holistic consideration of all data submitted (including clinical trials results) and of the length of the observation, which is quite uncommon in the rare disease field.

First, the MAH would like to briefly summarise the clinical evidence submitted to the Agency, underlining its relevance in relation to the PK/PD and PopPK model generated, all the more in the context of a rare disease indication.

The evidence supporting the efficacy of the E4W dose regimen is as follows:

- **Long-term clinical data (6 years) for the 2 mg/kg E4W regimen**, investigated in the study PB102-F50 and its extension CLI-06657AA1-03 (formerly PB-102-F51), provided confirmatory data in support of the PopPK and PKPD findings described above. These data demonstrated a sustained and efficacious effect of the treatment, contributing to disease stabilization over time in a progressive condition such as the Fabry disease.
- **Integrated analyses of efficacy parameters from multiple clinical studies were conducted to compare the 2 mg/kg E4W dosing regimen with the reference 1 mg/kg E2W regimen in terms of kidney function decline**.

Phase 3 study PB-102-F50 [Holida 2025] and its extension CLI-06657AA1-03 (previously PB-102-F51) have investigated the alternative 2 mg/kg E4W dosing regimen of pegunigalsidase alfa in Fabry patients.

Study CLI-06657AA1-03 is still ongoing; interim analyses with a cut-off date of 25 October 2024 were submitted to the Agency. Since CLI-06657AA1-03 is an extension study of PB-102-F50 with the same treatment and dosing regimen, summarised data were integrated in a longitudinal manner from PB-102-F50 baseline to the cut-off date of the interim analyses in study CLI-06657AA1-03 for those patients enrolled in the extension study.

At the cut-off date of 25 October 2024**, the median (minimum; maximum) individual exposure to this dosing regimen was 69.9 (9.3 to 80.1) months, which corresponds to 5.8 years, a period sufficiently long to assess treatment effect on kidney function decline** (Oct.2024 Interim Table 14.1.1). The minimum amount of time for conducting a reliable assessment of the eGFR slope is 2 years [Wanner 2018]. A longitudinal observation of 6 years not only confirms the efficacy of the treatment but can also sustain evidence of its effectiveness long term.

Secondly, Chiesi would like to submit the following observations:

- Although the open-label, single-arm studies PB-102-F50 and its extension CLI-06657AA1-03 provide uncontrolled efficacy data, the presented data have been generated in the context of an investigational setting, where the risk factors that can impact the interpretability of the results are controlled per protocol. The evidence generated in the context of these studies is objective and reassuring given the regularity of the timing of the assessment, that allows a precise estimation of the endpoints, the presence of a central laboratory, and the assessment of multiple secondary clinical endpoints that sustain the interpretation of the finding.
- Additionally, this data can be objectively assessed concerning the treatment effect on kidney function decline (i.e., a quantitative, laboratory measured endpoint) by means of the following indirect comparisons:
    - vs the well-established kidney therapeutic goals [Wanner 2018].
    - vs matched subgroups treated with the reference 1 mg/kg E2W in other studies.

The analysis of the above mentioned clinical data fully supports the efficacy profile of the 2 mg/kg E4W dosing regimen and its comparability to the 1 mg/kg E2W, providing confirmatory evidence of the PopPK and PKPD findings.

Analysis of kidney function decline vs kidney therapeutic goals

It is worth noting that the main goal of a lifelong treatment for a chronically progressing disease such as Fabry Disease, is the stabilisation of the renal decline (measured by the eGFR slope) towards values that are considered as much as possible close to the general population (around -1 ml/min/1.73m^2/year in the adult population) [Wanner 2018] and improved compared to what reported in the natural history study of the disease (up to eGFR slope of -10 ml/min/1.73m^2/yr in severe cases – mainly male classics) [Germain 2016].

In 2018 the European Consensus of Fabry Disease published therapeutic goals for the management of Fabry Disease, including the main pillars for real world management of these patients: with specific reference to the renal decline, patients under treatment, can be considered "stable" up to an eGFR slope of -3 ml/min/1.73m^2/yr, "progressing" if between -3 and -5 ml/min/1.73m^2/yr and "fast progressing" if the eGFR slope was lower than -5 ml/min/1.73m^2/yr [Wanner 2018].

As can be seen in Table 2 below, the continuous improvement in the values of renal function over time, testifies that not only the therapeutic target is achieved as per guidelines, but that the patients are effectively stable as demonstrated by the numerical improvement of the slope values. This can be achieved only if the measured value of the eGFR is so stable that the mathematical steepness of the slope improves over time.

Table 2: Improvement renal function over time

Summary of eGFR slope (ml/min/1.73m^2/year)	N	Exposure in months Median (min; max)	Mean (SD)	Median [min; max]
Baseline	29	-	-1.79 (3.70)	-1.06 [-13.6; 3.6]
PB-102-F50	29	≈12	-2.92 (5.64)	-1.86 [-14.1; 8.2]
CLI-06657AA1-03 1st IA Cut-off date 08.Aug.2021	29	≈40	-2.77 (2.93)	-2.47 [-8.7; 1.4]
CLI-06657AA1-03 2nd IA Cut-off date 31.Dec.2022	29	54.3 (9.3 to 60.8)	-2.20 (2.14)	-2.15 [-8.7; 2.5]
CLI-06657AA1-03 3rd SET Cut-off date 25.Oct.2024	29	69.9 (9.3; 80.1)	-1.98 (2.03)	-1.89 [-8.7; 1.4]

Kidney function parameters are also summarized for the entire CLI-06657AA1-03 population and by relevant subgroups in Table 3.

The mean and median annualized eGFR slope values for the entire population and for all subgroups, with the exception of patients positive for anti-drug antibodies (ADA) at baseline, proved to be less negative than -3.0 ml/min/1.73m^2/year, thus meaning that the targeted kidney therapeutic goal was met [Wanner 2018].

Moreover, when the analysis of the kidney function is conducted at single patient-level, only five patients out of 29 (17.2%) had an on-treatment annualized eGFR slope more negative than -3.0 ml/min/1.73m^2/year. Most of these patients had well-known risk factors associated with a worse response to ERT treatment and rapid kidney function decline, such as male sex, presence of ADA,

proteinuria and/or lack of unspecific nephroprotection with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) [Germain 2015]

Over the entire observation period, only one patient progressed to end-stage kidney disease (ESKD): this was patient, who was switched back to the 1.0 mg/kg E2W dosing regimen at Week 40 during study PB-102-F50 after the eGFR worsened from 30.29 at baseline to 23.99 ml/min/1.73m^2 at Week 40. This patient was a high-risk male Fabry patient who tested positive for neutralizing ADA and had a significant proteinuria and a low eGFR with a rapidly declining kidney function since baseline, all well-known factors associated with a poor kidney prognosis. Despite the switch to the more frequent dosing regimen, kidney function further deteriorated to ESKD at Weeks 92-94.

Most importantly, with the exception of the single patient who progressed to ESKD, the entire study population presents an eGFR above 60 ml/min/1.73m^2 and a serum creatinine below 1.3 mg/dl at last available visit of the interim analysis, a remarkable result in consideration of the prolonged treatment duration (median individual duration of 5.8 years). To further confirm our conclusion on the sustained treatment effect of pegunigalsidase alfa 2 mg/kg E4W, the mean (SD) annualized eGFR slope was -1.982 (2.03) ml/min/1.73m^2/year after 5.8 years of median individual exposure, i.e., very close to the pre-treatment baseline and stable as per literature definition [Wanner 2018].

If we take into consideration the Natural History of the disease [Branton 2002; Ortiz 2010], the published results on the eGFR slope control under treatment [Ortiz 2021], and normal loss of renal function in the general, not affected population [Wanner 2018], it appears clear that the results obtained on the renal function stabilisation, would not be possible without and effective treatment, over such a long period of time.

As can be observed, the only subgroup (even if limited in number – n=9), that display less positive clinical results is the ADA positive one, while the residual population reached an overall stability of the Lyso-Gb3 levels and also in terms of eGFR slope values.

Chiesi is confident that, if it were possible to conduct a head-to-head study, its results would not be materially different than the ones described so far.

Lack of head-to-head study

The clinical major objection raised in the procedure was the lack of head-to-head, randomised, double blind controlled evidence.

The MAH is aware that the highest level of evidence to support approval of treatment is the generation of well-controlled evidence, possibly through head-to-head, double blind, randomised clinical trials. For this discussion though there are few aspects to be taken into consideration in the evaluation of the overall package of evidence generated to support this Type II variation:

1 The indication is a rare disease, that, as per definition, does not allow the access to a large population of patients for development purposes. Nevertheless, during the overall development plan for the original approval, 142 patients have been included and composed the safety population and the attempt of running at least 1 randomised, double-blind, head-to-head trial with agalsidase beta was conducted and resulted in the PB.102-F20 trial. It is to be noted that the approval basis of pegunigalsidase alfa, is so far the only one to include comparative level of evidence among the ERTs class, not only on surrogate endpoint, but also on hard clinical ones to support approval.

2 Running a properly powered, non-inferiority trial comparing the 2 dosing regimens has proven to be unfeasible. From the statistical calculations run, to achieve a proper statistical power on a

very variable endpoint such as eGFR, the number of patients needed to be randomised is very large, making the attempt not feasible for this disease (see Table 9 for the exact estimate)

3 As mentioned, the collective evidence leading to the approval of pegunigalsidase alfa in this indication were large in number and complete.

We did run some calculations for a powered head-to-head trial with annualized eGFR slope as primary endpoint, but even with the most permissive non-inferiority margin the required sample size would make the study impracticable and stop the development of this dosing regimen.

This is not a novel approach as previously noted (Hatswell 2016), from 1999 to 2014 many medicinal products were granted an initial marketing authorisation in the EU on the basis of uncontrolled studies. Among those approved without randomised clinical trials, rare metabolic indications were often included, confirming that the challenges in implementing this type of trial design is real and recognised. Another relevant aspect highlighted by the same authors is that usually the lack of control can be mitigated through an indirect comparison with the standard of reference: this is indeed the rationale of our additional analyses aimed at comparing the efficacy of the two treatment dosing regimens, leveraging the evidence generated in the clinical investigational plan for pegunigalsidase alfa with 1 mg/kg E2W, that led to its approval in the EU and other jurisdictions. Chiesi would like to respectfully submit that if the CHMP opinion were negative due to the absence of a head-to-head study, which is objectively unfeasible for the reasons stated above, such decision would be highly disproportionate and would adversely affect the patients' interests to improve their quality of life through the new dosing regimen.

As highlighted above, the efficacy results obtained from the renal function assessment through centralised laboratory testing, over a very long period of time, show a progressive stabilisation of the renal function, indicative of a sustained efficacy over time. The MAH is convinced that running a head-to-head trial would not provide additional relevant evidence to sustain the efficacy of this dosing regimen, and would not provide different results as demonstrated in the indirect head-to-head comparison generated against pegunigalsidase alfa 1 mg/kg E2W (please refer to the sections below in the document).

Table 6: Summary of annualized eGFR slope - Overall and by subgroups – Study CLI-06657AA1-03 Efficacy Set

Visit (Week)	Overall (N=29)	Male (N=23)	Female (N=6)	ADA negative (N=20)	ADA positive (N=9)	Classic (N=15)	Non-classic (N=12)	Hyper-filtration (N=5)	No Hyperfiltr. (N=24)
Pre-treatment baseline, n	29	23	6	20	9	15	12	5	24
mean (SD)	-1.787 (3.70)	-1.142 (3.21)	-4.261 (4.71)	-2.310 (4.16)	-0.625 (2.13)	-0.565 (3.48)	-3.224 (3.89)	-1.252 (1.16)	-1.899 (4.05)
median	-1.061	-0.644	-3.120	-1.670	-0.644	0.085	-2.871	-1.061	-1.196
(min; max)	(-13.59; 3.57)	(-10.49; 3.57)	(-13.59; -0.66)	(-13.59; 3.57)	(-4.29; 3.32)	(-10.49; 3.57)	(-13.59; 2.32)	(-2.72; 0.08)	(-13.59; 3.57)
On treatment, n	29	23	6	20	9	15	12	5	24
mean (SD)	-1.982 (2.03)	-2.052 (2.20)	-1.715 (1.32)	-1.450 (1.62)	-3.165 (2.43)	-1.871 (1.60)	-2.369 (2.46)	-2.557 (1.50)	-1.863 (2.13)
median	-1.893	-1.920	-1.621	-1.621	-2.043	-2.043	-1.702	-2.295	-1.774
(min; max)	(-8.68; 1.44)	(-8.68; 1.44)	(-4.04; -0.18)	(-5.19; 1.44)	(-8.68; -1.24)	(-5.19; 1.44)	(-8.68; -0.02)	(-5.02; -1.24)	(-8.68; 1.44)

ADA: anti-drug antibody; eGFR; estimated glomerular filtration rate; Max: maximum; Min: minimum; N: number; SD: Standard deviation
eGFR slope is expressed in ml/min/1.73 m²/year
Only efficacy data collected while on the 2 mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25 Oct 2024
Two patients are missing Fabry Disease classification and are therefore not included
Source: CLI-06657AA1-03 3rd set of interim analyses - Tables 14.2.3.1-5

Table 7: Sample size estimations for a non-inferiority study on annualized eGFR slope

Treatment A SD[a]	Treatment B SD[a]	Non-Inferiority Margin[b]	80% Power			90% Power		
			N for Treatment A	N for Treatment B	Total	N for Treatment A	N for Treatment B	Total
8.9	8.9	-2.5	200	200	400	268	268	536
8.9	8.9	-2.0	311	311	622	417	417	834
8.9	8.9	-1.5	553	553	1106	741	741	1482

eGFR: estimated glomerular filtration rate; N: number of patients; SD: Standard deviation.
a SD is based on the SD of the annualized eGFR slope in pegunigalsidase alfa arm from study PB-102-F20, and it is assumed to be equal for the two treatments.
b Expressed in mL/min/1.73 m2/year

Additional post-hoc analysis: ANCOVA and 1:1 matching exercise

The MAH made another effort to support its variation request, running additional post-hoc analyses that in turn supported the efficacy of the 2 mg/kg E4W dosing regimen. This goal was achieved through the indirect comparison of the annualized eGFR slope values collected under the reference 1 mg/kg E2W, by integrating the data from different clinical studies using a model approach (ANCOVA), per matched subgroups and performing a 1:1 matching exercise with the two study population, with the objective of removing potential bias related to the different inclusion criteria of the trials.

The results of these analyses [submitted in the Response to Major Objection 4 – Efficacy, with the response document to the 1st RfSI] further confirm that the treatment effect on kidney function decline of the 2 mg/kg E4W dosing regimen is comparable to that of the reference regimen in the targeted population and by subgroups.

ANCOVA

We would like to provide additional clarifications on the ANCOVA model and a refined analysis by matched subgroups and in 1-to-1 matched pairs.

Clarifications concerning the statistical model approach

The integrated analysis with the ANCOVA model was criticized due to its post-hoc, observational and exploratory nature and the potential lack of power in the statistical test. However, this analysis is intended to supplement the totality of evidence and is not positioned as pivotal or confirmatory. Its inclusion aligns with regulatory guidance on the use of post-hoc analyses to inform benefit-risk assessments in rare disease settings where prospective subgroup analyses are often not feasible. EMA guidelines provide some comprehensive guidance for clinical developers in small populations and in particular *"In very rare diseases, the combined evaluation of single case studies may be the only way to provide evidence. In such situations, treatment conditions and data collection should be standardised and data should be of high quality and adhere to GCP standards. Such studies should be prospectively planned and described in study protocols. A systematic review of all data (including data from other sources) will add weight to the evidence. Also combined analysis of individual case reports or observational studies should be considered"* [EMA Guideline on Clinical Trials in Small Populations CHMP/EWP/83561/2005] [ICH. E9: Statistical principles for clinical trials (CPMP/ICH/363/96). 1998]

Our intent was to control the difference in baseline characteristics between the study populations in the 1 mg/kg E2W and the 2 mg/kg E4W groups, enrolled in different studies with different inclusion/exclusion criteria.

In **Figure 5** panel A the observed, unadjusted eGFR slope and its 95% confidence interval are presented. It can be observed that the patients treated with 2 mg/kg E4W have a less negative eGFR slope (-1.98 [-2.754; -1.211]) as compared to the patients treated with 1 mg/kg E2W (-2.836 [-3.830; -1.842]), whereas the 95% confidence intervals overlap.

To account for the difference in baseline characteristics, the post-hoc analysis employed an ANCOVA model adjusted for key prognostic covariates (e.g., baseline eGFR, UPCR, ADA status, age, and sex) to mitigate confounding and enhance interpretability.

The descriptive statistics focusing on ERT experienced patients and stratified by the key prognostic factors, such as sex, ADA status, urine protein-to-creatinine ratio (UPCR) and baseline eGFR,

consistently showed comparable eGFR slopes between the two regimens, supporting the robustness of the findings.

The adjusted treatment effect difference was minimal (−0.410 ml/min/1.73 m²/year), with a 95% confidence interval (CI) that included zero (-2.27, 1.45).

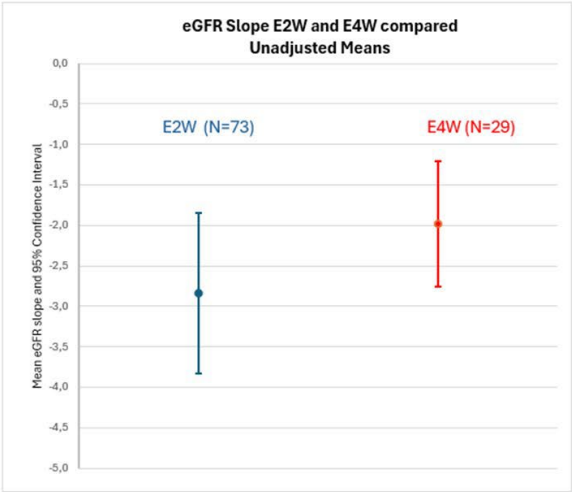
The estimated treatment effects (CI) in the annualized slope of both groups are comparable -3.5 (-4.7, -2.3) in the 1 mg/kg E2W group and -3.1 (-4.9, -1.4) in the 2 mg/kg E4W group. In addition, the confidence intervals of both groups highly overlap (**Figure 5** – panel B).

It is noteworthy that, with the adjustment for the known prognostic factors, the point estimates of annualized eGFR slope are more comparable.

The limited sample size in the 2 mg/kg E4W group (n=29) and the integration of data from separate clinical trials should not be seen as limitations. They appear reasonable and justified in light of the rare disease field and the non-availability of many new naïve patients. However, once again the findings provide valuable exploratory evidence supporting the comparability of the two regimens.

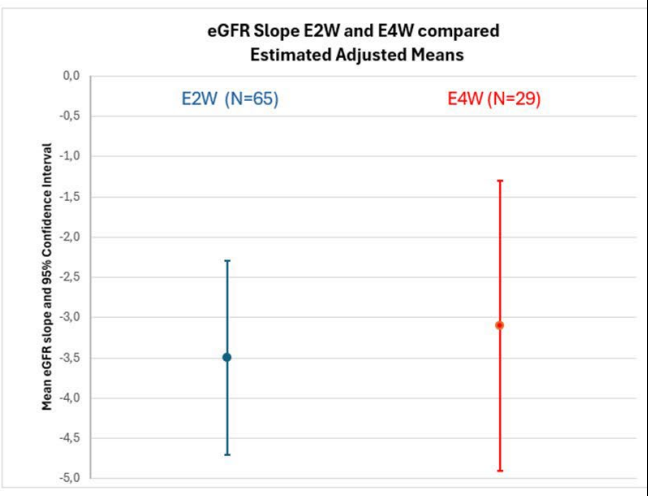
Figure 5: Comparison of the treatment effect on annualized eGFR slope ANCOVA approach – ISE efficacy set

Panel A: Unadjusted analysis in ISE ERT-experienced patients



Treatment group	N	Annualized eGFR slope Mean [95% CI]
1 mg/kg E2W treated patients	73	-2.836 [-3.830; -1.842]
2 mg/kg E4W treated patients	29	-1.982 [-2.754; -1.211]

Panel B: Analysis according to the ANCOVA Model



Treatment group	N	Annualized eGFR slope Mean [95% CI]
1 mg/kg E2W treated patients	65	-3.541 [-4.707; -2.377]
2 mg/kg E4W treated patients	29	-3.132 [-4.889; -1.375]

CI: confidence interval; eGFR: estimated glomerular filtration rate; ERT: enzyme-replacement treatment; E2W: every 2 weeks; E4W: every 4 weeks; ISE: Integrated Summary of Efficacy; SD: standard deviation.
Only efficacy data collected while on the 2 mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25 Oct 2024 Annualized eGFR slope is expressed in ml/min/1.73 m^2/year.
Source: Panel A - Table 14.2.3.1 3rd Interim Analyses with 25 Oct 2024 cut-off date, Panel B: Addendum ISE-updated analyses, Table 6 RfSI-2

The **Figure 5** represents:

- **Panel A** shows the unadjusted mean (95% CI) annualized eGFR slope values under the two dosing regimens for the whole ISE ERT-experienced population. 95% CI of the annualized eGFR slope under the 2 mg/kg E4W, even if wider because of the low number of patients (N=29), overlaps with the 95% CI of the annualized eGFR slope under the approved 1 mg/kg E2W dosing regimen, suggesting similarity in treatment effect on this efficacy endpoint.
- **Panel B** shows the estimated adjusted mean (95% CI) annualized eGFR slope values under the two dosing regimens according to the ANCOVA model. The estimated treatment effects (95% CI) in the annualized eGFR slopes of both dosing groups were comparable; the difference in treatment effect was minimal and the 95% CI included zero.

Refinement of the integrated analyses of the annualized eGFR slope by dosing group

The factors associated with a more rapid decline in kidney function and a lower ERT response in patients with Fabry disease are well characterized.

With the analysis of the Integrated Summary of Efficacy (ISE) ERT-experienced population, the distribution of the risk factors differs between the two dosing groups, as the 1 mg/kg E2W group had a more severe kidney impairment at baseline, while fewer patients in the 2 mg/kg E4W group had significant proteinuria (UPCR >0.5 g/g) and/or a low eGFR (≤60 ml/min/1.73m^2) at baseline.

Indeed, the main concern of the integrated analyses by subgroups was related to the differences in baseline demographic and disease characteristics between the dosing groups, which would make any comparison difficult.

With the aim to overcome this concern, we have further refined the integrated analyses taking into progressive consideration the following factors in the comparison by matched subgroups:

- treatment status (focus on ERT-experienced)
- sex (female/male)
- ADA-status at baseline (positive/negative)
- UPCR at baseline (≤/>0.5 g/g)
- eGFR category at baseline (≤/>60 ml/min/1.73 m2)

The results are presented separately for female and male patients (for subgroups with at least 2 patients) in Table 5 and Table 6 respectively.

Notwithstanding the limited number of patients and the lack of representation of some subgroups, the refined analyses per matched subgroups confirm the comparability in terms of mean annualized eGFR slope values with similar 95% CIs for the 2 mg/kg E4W regimen versus the reference 1 mg/kg E2W.

Emphasis in the tables below (grey highlight in the box) highlights the subgroups presenting the most known and identified risk factor for progression of the kidney disease in the context of Fabry Disease, such as presence of ADA, UCPR >0.5 g/g, eGFR <60 ml/min.

Table 8: Annualised eGFR slope by dosing regimen in ERT-experienced female Fabry patients – ISE Efficacy Set

Demographic and disease characteristics at baseline					Pegunigalsidase alfa – Annualized eGFR slope					
					1 mg/kg E2W			2 mg/kg E4W		
ERT-status	Sex	Baseline ADA	Baseline UPCR	Baseline eGFR	N (%)	Mean (SD) [95% CI]	Median (min; max)	N (%)	Mean (SD) [95% CI]	Median (min; max)
Experienced	-	-	-	-	73 (100%)	-2.836 (4.26) [-3.830, -1.842]	-2.708 (-19.44; 9.92)	29 (100%)	-1.982 (2.03) [-2.754, -1.211]	-1.893 (-8.68; 1.44)
Experienced	Female	-	-	-	29 (39.7%)	-1.796 (2.32) [-2.677, -0.916]	-2.115 (-6.17; 3.83)	6 (20.7%)	-1.715 (1.32) [-3.103, -0.327]	-1.621 (-4.04; -0.18)
Experienced	Female	Positive	-	-	0	-	-	0	-	-
Experienced	Female	Negative	-	-	29 (100%)	-1.796 (2.32) [-2.677, -0.916]	-2.115 (-6.17; 3.83)	6 (100%)	-1.715 (1.32) [-3.103, -0.327]	-1.621 (-4.04; -0.18)
Experienced	Female	Negative	>0.5	-	2 (6.9%)	-3.836 (1.03) [-13.071, 5.399]	-3.836 (-4.56; -3.11)	0	--	-
Experienced	Female	Negative	≤0.5	-	27 (93.1%)	-1.645 (2.32) [-2.563, -0.727]	-2.016 (-6.17; 3.83)	6 (100%)	-1.715 (1.32) [-3.103, -0.327]	-1.621 (-4.04; -0.18)
Experienced	Female	Negative	≤0.5	≤60	3 (10.3%)	-2.079 (3.32) [-10.333, 6.176]	-3.611 (-4.36; 1.73)	0	--	-
Experienced	Female	Negative	≤0.5	>60	24 (82.8%)	-1.591 (2.26) [-2.545, -0.637]	-1.942 (-6.17; 3.83)	6 (100%)	-1.715 (1.32) [-3.103, -0.327]	-1.621 (-4.04; -0.18)

ADA: anti-drug antibody; CI: confidence interval; eGFR; estimated glomerular filtration rate; ERT: enzyme-replacement therapy; E2W: every 2 weeks; E4W: every 4 weeks; ISE: Integrated Summary of Efficacy;max: maximum; min: minimum; n: number SD: Standard deviation; UPCR: urine protein-to-creatinine ratio
UPCR is expressed in g/g; eGFR is expressed in ml/min/1.73 m2; annualized eGFR slope is expressed in ml/min/1.73 m2/year
Only efficacy data collected while on the 2 mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25.Oct.2024
Source: Table 5.4 MATRIX OF EGFR SLOPE BY POSOLOGY, REGIMENS AND SUBGROUPS - EFFICACY SET (ERT-EXPERIENCED PATIENTS)

Table 6: Annualised eGFR slope by dosing regimen in ERT-experienced male Fabry patients – ISE Efficacy Set

Demographic and disease characteristics at baseline					Pegunigalsidase alfa – Annualized eGFR slope					
					1 mg/kg E2W			2 mg/kg E4W		
ERT-status	Sex	Baseline ADA	Baseline UPCR	Baseline eGFR	N (%)	Mean (SD) [95% CI]	Median (min; max)	N (%)	Mean (SD) [95% CI]	Median (min; max)
Experienced	-	-	-	-	73 (100%)	-2.836 (4.26) [-3.830, -1.842]	-2.708 (-19.44; 9.92)	29 (100%)	-1.982 (2.03) [-2.754, -1.211]	-1.893 (-8.68; 1.44)
Experienced	Male	-	-	-	44 (60.3%)	-3.521 (5.07) [-5.063, -1.980]	-3.406 (-19.44; 9.92)	23 (79.3%)	-2.052 (2.20) [-3.001, -1.103]	-1.920 (-8.68; 1.44)
Experienced	Male	Positive	-	-	20 (45.5%)	-4.683 (5.73) [-7.364, -2.002]	-3.752 (-19.44; 4.05)	9 (39.1%)	-3.165 (2.43) [-5.035, -1.294]	-2.043 (-8.68; -1.24)
Experienced	Male	Positive	>0.5	-	10 (22.7%)	-6.612 (7.27) [-11.814, -1.411]	-4.063 (-19.44; 4.05)	2 (8.7%)	-5.096 (5.07) -	-5.096 (-8.68; -1.51)
Experienced	Male	Positive	≤0.5	-	10 (22.7%)	-2.753 (2.85) [-4.793, -0.712]	-3.466 (-6.80; 2.64)	7 (30.4%)	-2.613 (1.42) [-3.925, -1.301]	-2.043 (-5.02; -1.24)
Experienced	Male	Positive	≤0.5	>60	10 (22.7%)	-2.753 (2.85) [-4.793, -0.712]	-3.466 (-6.80; 2.64)	7 (30.4%)	-2.613 (1.42) [-3.925, -1.301]	-2.043 (-5.02; -1.24)
Experienced	Male	Negative	-	-	24 (54.5%)	-2.554 (4.33) [-4.384, -0.723]	-2.965 (-10.41; 9.92)	14 (60.9%)	-1.337 (1.76) [-2.354, -0.320]	-1.457 (-5.19; 1.44)
Experienced	Male	Negative	>0.5	-	8 (18.2%)	-3.200 (6.28) [-8.454, 2.054]	-3.732 (-10.41; 9.92)	0	--	-
Experienced	Male	Negative	≤0.5	-	16 (36.4%)	-2.230 (3.17) [-3.919, -0.541]	-2.420 (-7.48; 6.79)	14 (60.9%)	-1.337 (1.76) [-2.354, -0.320]	-1.457 (-5.19; 1.44)
Experienced	Male	Negative	≤0.5	>60	11 (25.0%)	-1.287 (3.22) [-3.448, 0.874]	-2.028 (-5.07; 6.79)	13 (56.5%)	-1.551 (1.63) [-2.538, -0.564]	-1.920 (-5.19; 1.30)

ADA: anti-drug antibody; CI: confidence interval; eGFR; estimated glomerular filtration rate; ERT: enzyme-replacement therapy; E2W: every 2 weeks; E4W: every 4 weeks; ISE: Integrated Summary of Efficacy; max: maximum; min: minimum; n: number SD: Standard deviation; UPCR: urine protein-to-creatinine ratio
UPCR is expressed in g/g; eGFR is expressed in ml/min/1.73 m2; eGFR slope is expressed in ml/min/1.73 m2/year
Only efficacy data collected while on the 2 mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25.Oct.2024
Source: Table 5.4 MATRIX OF EGFR SLOPE BY POSOLOGY, REGIMENS AND SUBGROUPS - EFFICACY SET (ERT-EXPERIENCED PATIENTS)

In conclusion, these matched subgroup analyses, that consider several kidney prognostic factors simultaneously, show the comparability of the treatment effect for the two dosing groups, as indicated by very similar annualized eGFR slope values.

Results of the exploratory 1-to-1 matching analysis

Finally, an exploratory 1-to-1 matching analysis was conducted with the aim to compare each patient treated with pegunigalsidase alfa 2 mg/kg E4W in study CLI-06657AA1-03 to a single patient treated with 1 mg/kg E2W from the ISE ERT-experienced population matched according to baseline characteristics.

The following process was adopted to identify the matches:

- 1st step match by sex category (male/female)
- 2nd step match by baseline ADA status category (ADA-positive/ADA-negative)
- 3rd step match by baseline UPCR category (≤/>0.5 g/g)
- 4th step match by baseline eGFR category (≤/>60 ml/min/1.73 m2)
- 5th step match by age at enrolment (in a range of ±5 years)
    - Additional steps in case potential multiple matches identified, match by closest age at enrolment by baseline eGFR subcategories (<30, 30-44, 45-59, 60-89, >90 ml/min/1.73 m2)

The 1 mg/kg E2W-treated patients were used only once as a match.

In case multiple 1 mg/kg E2W-treated patients were identified as potential matches, then only the single best match (on the basis of the closest age and eventually by baseline eGFR subcategory) was used.

In case no 1 mg/kg E2W-treated patient was identified as potential match, then the 2 mg/kg E4W treated patient without match was excluded from the analysis.

With this process, in total 17 matched pairs could be identified: the listing with baseline characteristics and annualized eGFR slope of the 17 matches is provided in Appendix II (Listing 2).

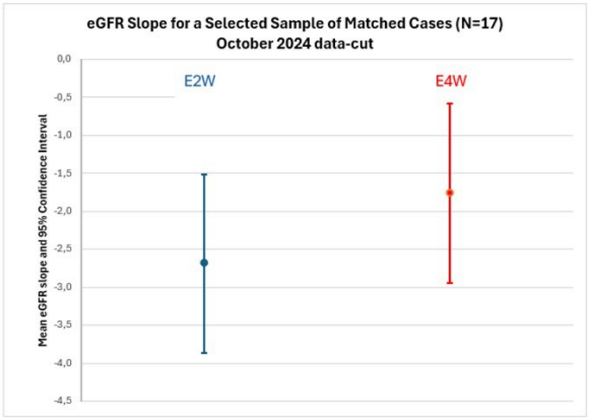
The mean (95% CI) annualized eGFR slope values were calculated for the two dosing subgroups of 17 matched pairs.

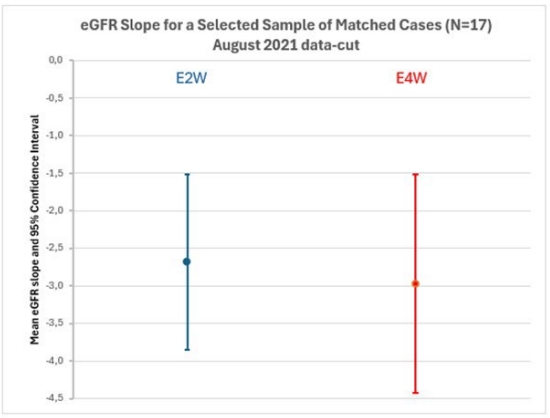
Moreover, as the data available on the 2 mg/kg E4W with the third set of interim analyses of study CLI-06657AA1-03 covered a longer treatment duration compared to the 1 mg/kg E2W treatment duration, the above analysis was repeated using the cut-off date of Aug 2021 (1st interim analysis of study CLI-06657AA1-03) in order to investigate the treatment effect of the two dosing regimens over a similar treatment duration.

The results of this exploratory analysis are provided in Figure 6 panel A and B.

Figure 6 - Comparison of the treatment effect on annualized eGFR slope with 1:1 matching – ISE efficacy set

Panel A: 1-to-1 matched analysis with Oct 2024 cut-off for 2 mg/kg E4W	Panel B: 1-to-1 matched analysis with Aug 2021 cut-off for 2 mg/kg E4W





Treatment group	N	Annualized eGFR slope Mean [95%CI]	Treatment duration Mean (SD)
1 mg/kg E2W	17	-2.683 (-3.852; -1.515)	2.66 (0.706)
2 mg/kg E4W	17	-1.763 (-2.940; -0.585)	5.29 (1.456)

Treatment group	N	Annualized eGFR slope Mean [95%CI]	Treatment duration Mean (SD)
1 mg/kg E2W	17	-2.683 (-3.852; -1.515)	2.66 (0.706)
2 mg/kg E4W	17	-2.969 (-4.426; -1.512)	2.86 (0.695)

CI: confidence interval; eGFR: estimated glomerular filtration rate; ERT: enzyme-replacement treatment; E2W: every 2 weeks; E4W: every 4 weeks; ISE: Integrated Summary of Efficacy; SD: standard deviation. Annualized eGFR slope is expressed in ml/min/1.73 m^2/year; mean treatment duration is expressed in years.
One of the 1-to-1 matched E4W subjects is patient number: this patient switched to the E2W dosing regimen after the completion of study PB-102-F50. For this patient efficacy data as well as
exposure data are only included for the period while on the 2.0 mg/kg E4W (See Errore. L'origine riferimento non è stata trovata.).
Source: Table 10 Annualized eGFR slope in ERT-experienced for the matching patients and Table 11 Duration between PRX start date and last eGFR observation for the matching patients (RfSI-2)

The Figure 6 represents

- **Panel A** shows the mean (95% CI) annualized eGFR slope values for the two 1-1 matched pair subgroups over the entire available treatment duration (cut off dates of Jul.2021 for 1 mg/kg E2W and of Oct.2024 for 2 mg/kg E4W for a mean treatment duration of 5.3 years)
- **Panel B** shows the mean (95% CI) annualized eGFR slope values for the two 1-1 matched pair subgroups at the first interim analysis of study CLI-06657AA1-03 (cut off dates of Jul.2021 for 1 mg/kg E2W and of Aug.2021 for 2 mg/kg E4W for a mean treatment duration of 2.9 years)

As it can be seen by comparing the annualized eGFR slopes under the 2 mg/kg E4W in Figure 6 Panel C (5.3 years of treatment duration) and Panel D (2.9 years of treatment duration), a smaller 95% CI and an improved point estimate on the eGFR slope were observed over the longer treatment duration. This finding not only shows the relevance of a longer observation period, but it supports the conclusion concerning the stability of the treatment effect over time.

In conclusion, this 1:1 matched analysis suggests comparable annualized eGFR slope trends between the two dosing regimens in patients with similar baseline characteristics and over similar treatment durations.

This is in line with what suggested in literature and guidelines to further support the robustness of the efficacy results, as mentioned before. In this case, the supportive data were collected over a long observation period under the E4W posology and analysed through an indirect comparison with the alternative dosing regimen of 1 mg E2W. In this specific case, it is worth noting that the indirect comparison leverages high quality data coming from other interventional studies with the comparative dosing regimen.

This evidence is in line with the conclusions of the integrated analyses on the complete population, while controlling the bias related to difference in baseline characteristics for the population, which is one of the aims of RCT for ensuring homogenous distribution of patients to the 2 treatment interventions**. The presence of 17 matched pairs** is due to the strict matching criteria and limited pool of reference patients but cannot reasonably call into question the reliability of the findings above.

Additional supportive evidence of efficacy: Plasma LysoGb3, MSSI

As Fabry disease is a systemic disease that affects different organs and systems, the evaluation of the entirety of the clinical evidence produced, including the results of the analyses on non-renal endpoints, contributes to the characterization of the efficacy profile of a therapeutic intervention in this disease. To this extent, we also briefly include and summarise below the secondary endpoints of the trial.

In studies PB-102-F50 and CLI-06657AA1-03, that have investigated pegunigalsidase alfa 2 mg/kg E4W in patients with Fabry disease, several secondary efficacy and PD endpoints have been analysed (Table 7).

Table 7: Efficacy and PD endpoints in study PB-102-F50 and its extension CLI-06657AA1-03

Efficacy pharmacodynamic endpoints	2nd interim analysis (cut-off date)	3rd interim analyses (cut-off date)
eGFR and annualized eGFR slope	Yes (31.Dec.2022)	Yes (25.Oct.2024)
Plasma Lyso-Gb3 concentration	Yes (31.Dec.2022)	Yes (14.Mar.2024)
Plasma Gb3 concentration	Yes (31.Dec.2022)	Not analysed
Urine protein-creatinine ratio	Yes (31.Dec.2022)	Yes (25.Oct.2024)
Left ventricular mass index by echocardiogram	Yes (31.Dec.2022)	Not analysed
Pain medication	Yes (31.Dec.2022)	Not analysed
Cardiac stress test	Yes (31.Dec.2022)	Not analysed
Short Form Brief Pain Invent Form	Yes (31.Dec.2022)	Not analysed
Mainz Severity Score Index	Yes (31.Dec.2022)	Yes (25.Oct.2024)
EuroQoL 5 dimensions 5 levels questionnaire	Yes (31.Dec.2022)	Not analysed
Fabry Clinical Events	Yes (31.Dec.2022)	Not analysed

eGFR: estimated glomerular filtration rate; Gb3: globotriaosylceramide; lyso-Gb3: globotriaosylsphingosine; PD: pharmacodynamic

The entire evidence is considered supportive of the efficacy of the 2 mg/kg E4W dosing regimen. In this section, we focus on the results concerning the plasma lyso-Gb3 concentration and Mainz Severity Score Index (MSSI) in consideration of their clinical relevance.

Plasma lyso-Gb3 concentrations

A reduction in plasma lyso-Gb3 levels is expected to occur within the first few months after the start of ERT treatment, with a stabilization of the levels over time. As plasma lyso-Gb3 levels increase following the discontinuation of treatment, the lack of re-accumulation after the switch to a different treatment supports the notion of stabilization of Fabry disease [Burlina 2023].

In study PB-102-F50 and its extension CLI-06657AA1-03, plasma lyso-Gb3 levels were measured periodically over the whole treatment duration. Plasma lyso-Gb3 levels and changes from baseline (PB102-F50) are presented by gender in Table 10 and by ADA status in Table 11.

At the cut-off date of 25. Oct. 2024, after a median (minimum; maximum) individual exposure to the 2 mg/kg E4W dosing regimen of 69.9 (9.3 to 80.1) months, no clinically meaningful re-accumulation of plasma lyso-Gb3 occurred in patients after the switch to pegunigalsidase alfa 2 mg/kg E4W.

In male patients, there was a slight, not clinically meaningful, increase in plasma lyso-Gb3 levels, but the median change from baseline did not exceed 5.3 nmol/l. In female patients, the median plasma LysoGb3 concentration remained stable (Table 8).

ADA-positive patients presented higher plasma lyso-Gb3 levels compared to ADA-negative at baseline and during the study with a greater change from baseline. Overall values in ADA-negative patients remained stable from baseline up to the cut-off date (Table 9).

Table 8: Plasma lyso-Gb3 levels by gender – Study CLI-06657AA1-03 Efficacy Set

	Male N=23			Female N=6		
Week (Visit)	**n**	**Median (Q1, Q3)**	**Median (Q1, Q3) Absolute Change from Baseline**	**n**	**Median (Q1, Q3)**	**Median (Q1, Q3) Absolute Change from Baseline**
Baseline (V1)	23	17.2(12.1, 32.8)	N/A	6	4.4(2.9, 5.9)	N/A
Week 52 (V14)	22	22.3(17.9, 37.9)	5.1 (0.3, 7.8)	6	4.2(3.1, 7.4)	-0.1 (-0.4, 0.2)
Week 108 (V28)	20	23.5(16.0, 37.6)	4.5 (-0.1, 9.4)	6	4.7(3.4, 6.6)	0.2 (-0.2, 0.7)
Week 160 (V41)	21	23.8(18.1, 33.2)	3.7 (0.0, 10.0)	5	4.5(3.6, 7.0)	-0.2 (-0.5, 0.6)
Week 208 (V53)	20	21.8(15,4, 30,8)	2.7 (-2.0, 7.4)	5	4.4(4.1, 6.1)	-0.3 (-1.0, 1.2)
Week 256 (V65)	18	25.8(19.2, 40.2)	4.3 (0.0, 10.0)	5	5.2(3.6, 6.4)	0.5 (-0.6, 0.7)
Week 284 (V72)	13	24.7(22.0, 36.7)	5.3 (0.0, 10.5)	3	4.9(2.5, 10.1)	0.2 (-0.4, 4.2)

N = number of patients; N = number of patients overall; N/A = not applicable; V = visit.
Note: Only efficacy data collected while on the 2mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25 Oct 2024
Source: CLI-06657AA1-03 3rd set of interim analyses - Table 14.2.4.4

Table 9: Plasma lyso-Gb3 levels by ADA status at baseline – Study CLI-06657AA1-03 Efficacy Set

	ADA negative N=20			ADA positive N=9		
Week (Visit)	**n**	**Median (Q1, Q3)**	**Median (Q1, Q3) Absolute Change from Baseline**	**n**	**Median (Q1, Q3)**	**Median (Q1, Q3) Absolute Change from Baseline**
Baseline (V1)	20	9.3(4.7, 16.0)	N/A	9	29.0(18.2, 50.5)	N/A
Week 52 (V14)	20	12.4(5.4, 20.5)	0.9(-0.1, 5.9)	8	39.4(23.9, 53.7)	6.3(5.0, 8.7)
Week 108 (V28)	20	11.5(5.3, 23.4)	0.9(-0.2, 6.4)	6	42.1(33.4, 65.2)	7.7(-8.0, 12.6)
Week 160 (V41)	19	15.1(5.5, 23.8)	0.9(-0.5, 5.4)	7	43.8(23.9, 45.3)	10.1(-5.2, 14.8)
Week 208 (V53)	18	13.1(6.1, 21.0)	1.5(-1.0, 4.5)	7	38.8(22.3, 44.6)	5.6(-11.2, 9.8)
Week 256 (V65)	17	16.9(6.4, 25.6)	1.6(0.0, 4.7)	6	40.6(40.2, 41.2)	8.6(-10.3, 11.5)
Week 284 (V72)	10	16.8(4.9, 23.5)	2.0(0.0, 5.3)	6	37.0(35.4, 40.1)	7.3(-13.8, 10.5)

n = number of patients; N = number of patients overall; N/A = not applicable; V = visit.
Note: Only efficacy data collected while on the 2mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25 Oct 2024
Source: CLI-06657AA1-03 3rd set of interim analyses - Table 14.2.4.2

Overall, no re-accumulation of the substrate occurred in patients treated with pegunigalsidase alfa 2 mg/kg E4W after a median individual exposure of 69.9 months (5.8 years). These PD results are well aligned with those previously discussed on the kidney function and are indicative of stabilization of the Fabry disease and a sustained efficacy of the treatment over time.

Similar trends in plasma lyso-Gb3 levels were observed in ERT-experienced patients treated with the reference 1 mg/kg E2W dosing regimen in other clinical studies of pegunigalsidase alfa development program.

Mainz Severity Score Index

MSSI is a scoring system developed with the aim to measure the severity of Fabry disease and to monitor the clinical course of the disease in response to ERT [Whybra 2004].

Because of the systemic nature of Fabry disease, MSSI is composed of four sections that cover the general (maximum score 18), neurological (maximum score 20), cardiovascular (maximum score 20), and renal (maximum score 18) signs and symptoms of the disease, each weighted according to its contribution to morbidity. The higher the score, the greater the impact of Fabry disease on the patient.

A total MSSI score <20 is considered as mild; a score 20≤ and ≤40 is considered moderate and >40 is considered severe [Beck 2006].

In study PB-102-F50 and its extension CLI-06657AA1-03, MSSI was periodically evaluated and scores recorded over the whole treatment duration. Data over time on total MSSI score and each section is summarised in Table 10.

At the cut-off date of 25.Oct.2024, after a median (minimum; maximum) individual exposure to the 2 mg/kg E4W dosing regimen of 69.9 (9.3 to 80.1) months, the total score and each single sub-score remained substantially stable, indicating the treatment effect of the disease stabilization in all its different domains (Table 10).

Table 10: MSSI Scores – Study CLI-06657AA1-03 Efficacy Set

Scores		Total (maximum 76)		General (maximum 18)		Neurological (maximum 20)		Cardiovascular (maximum 20)		Renal (maximum 18)	
Week (Visit)	n	Mean (SD)	Mean (SD) Change from Baseline	Mean (SD)	Mean (SD) Change from Baseline	Mean (SD)	Mean (SD) Change from Baseline	Mean (SD)	Mean (SD) Change from Baseline	Mean (SD)	Mean (SD) Change from Baseline
Baseline (V1)	29	20.5 (9.66)	N/A	5.5 (2.68)	N/A	7.0 (4.48)	N/A	6.1 (5.34)	N/A	1.9 (2.30)	N/A
Week 52 (V14)	28	19.6 (8.70)	-0.2 (3.40)	5.2 (2.74)	-0.2 (1.40)	6.9 (4.39)	0.0 (1.02)	5.4 (5.23)	-0.4 (2.27)	2.1 (2.03)	0.4 (1.67)
Week 108 (V28)	25	19.0 (9.70)	-0.7 (4.74)	4.9 (2.91)	-0.4 (1.29)	6.1 (4.24)	-0.5 (1.66)	6.3 (5.45)	0.1 (3.09)	1.8 (2.03)	0.0 (2.00)
Week 160 (V41)	25	19.9 (9.15)	-0.1 (7.39)	5.2 (2.84)	-0.2 (1.39)	5.9 (4.06)	-0.4 (3.29)	6.8 (5.46)	0.4 (3.66)	2.1 (2.04)	0.2 (1.82)
Week 208 (V53)	25	20.5 (9.83)	0.4 (4.37)	5.3 (2.84)	-0.1 (1.83)	6.7 (4.38)	0.2 (1.22)	6.4 (5.61)	0.2 (2.59)	2.1 (2.04)	0.2 (2.15)
Week 256 (V65)	24	21.3 (11.01)	1.2 (5.85)	5.2 (2.99)	-0.2 (1.28)	6.8 (5.00)	0.3 (2.30)	7.4 (5.73)	1.3 (3.52)	1.8 (2.35)	-0.2 (2.76)

MSSI = Mainz Severity Score Index; n = number of patients; N = number of patients overall; N/A = not applicable; SD = standard deviation; V = visit.
Note 1: MSSI general score range: 0-18; MSSI neurological score range: 0-20; MSSI cardiovascular score range: 0-20; MSSI Renal dysfunction score range: 0-18; Overall score is the sum over all domains. For all domains higher is worse.
Note 2: Only efficacy data collected while on the 2 mg/kg E4W dosing regimen is included for this set; cut-off date of the interim analyses: 25 Oct 2024
Source: CLI-06657AA1-03 3rd set of interim analyses - Table 14.2.10.1

As discussed in the prior sections**, the totality of the evidence generated is considered sufficient to support a positive assessment of the benefit–risk profile of the alternative 2 mg/kg E4W regimen and its comparability to the approved 1 mg/kg E2W regimen.**

Therefore, the MAH considers that a dedicated clinical study directly comparing the efficacy of the two dosing regimens would not provide additional evidence beyond what is already available.

Safety profile

The safety profile of this treatment regimen has proven to be positive, with no concerns identified during the review by the Rapporteur and Co-Rapporteur of the procedure, nor from the CHMP (see assessment report for the type II variation).

Conclusions on the first ground for refusal

For the reasons discussed in the prior sections, it is the MAH's firm view that the whole evidence submitted supports a positive assessment of the benefit–risk profile of the alternative 2 mg/kg E4W regimen and its comparability to the approved 1 mg/kg E2W regimen. Moreover, it satisfies the requirements set forth by EMA in their Guideline on the investigation of subgroups in confirmatory clinical trials; and it is aligned with recent global trends on extrapolation, modelling and simulation methodologies, including those endorsed by EMA, the Heads of Medicines Agencies of the European Union and the US FDA [6].

Moreover, the MAH would like to note that a dedicated clinical study directly comparing the efficacy of the two dosing regimens is not feasible. In any event, it would not provide additional evidence beyond what is already available.

Based on the above, the MAH would like to submit that the first ground for refusal can be effectively challenged for three reasons:

I. it states that the available data originate from open label, uncontrolled studies that are predominantly descriptive, but omits any mention to the fact that such data should be read instead in close connection with all other information submitted, namely the PopPK and PK/PD findings;

II. it does not factor in the importance of the unusually long exposure of the data subjects to the new dosing regimen, which allowed measuring the kidney function decline in a comparable manner vs. the exposure data concerning the currently authorised dosing regimen. Moreover, the median 5.8 years duration of the trial follow-up is a very long period of time for an investigational study (closer to what one can expect in RWE studies). This timeline can reassure prescribers on the sustained and prolonged efficacy of the treatment, especially in the proposed population for the label.

III. it fails to consider that a powered, active-controlled, randomized clinical trial assessing the non-inferiority of a new posology scheme versus the reference one would not be feasible, under the specific circumstances and in the context of a rare condition as the Fabry disease.

4.1.2. Ground #2

Ground #2

The absence of a clear dose-efficacy relationship precludes the use of data from the Population Pharmacokinetic (PopPK) study as a basis for concluding on 2mg/kg E4W as an effective posology.

As a preliminary comment, we would like to respectfully underline that the use of PopPK data is one of the tools accepted by the scientific and regulatory community to build evidence on the adequacy of a dosing regimen. Based on the plain language of this ground for refusal, it could be inferred that PopPK data could be used only when a clear dose-efficacy relationship has already been established: a concept which is clearly counterintuitive and would deprive any PopPK data of any utility, particularly in the context for rare diseases and complex biological drugs. From the MAH's perspective, the explanation provided by the CHMP on this point appears insufficient, ambiguous and contradictory with the recent indications on extrapolation, modelling and simulation, particularly in respect of clinical development in the rare disease field[5].

On multiple occasions EMA has highlighted the role of modeling and simulation in optimizing study design and interpretation, with explicit mention of rare diseases where patient numbers are limited as in this case. The same approach is endorsed by several literature sources [Sheiner LB 2000; Mould DR 2012; Bonate PL textbook 2011; Mishra S. 2024;]

Aligned with the above indications, the MAH will now provide as many details as possible on the PK studies and simulation adopted to support this variation application

PopPK model

During the development of the E4W schedule, the MAH elaborated the pharmacological evidence for the proposed 2 mg/kg E4W dosing regimen, comparing those against the already approved 1 mg/kg E2W.

The overall population exposed to the dose of 2 mg/kg E4W was composed by 30 patients enrolled in the PB-102-F50 trial. For the detailed considerations around the PK and PD aspects of it, please refer to the MSAR 24-0022 Population PK Report.

A Population PK (PopPK) model was developed based on data collected from an overall population of 62 Fabry disease adult patients from studies PB-102-F01/F02, PB-102-F20 and PB-102-F50, to characterise pegunigalsidase alfa PK.

The model demonstrated to be a valuable tool to leverage the available data and variabilities across the studies and optimise data interpretation allowing clinical scenarios simulations to support the decision-making process.

The PopPK model confirmed the PK results from all clinical trials, identified the different factors affecting PK and demonstrated the consistency of PK parameters across the studies, i.e. dose proportionality and linearity.

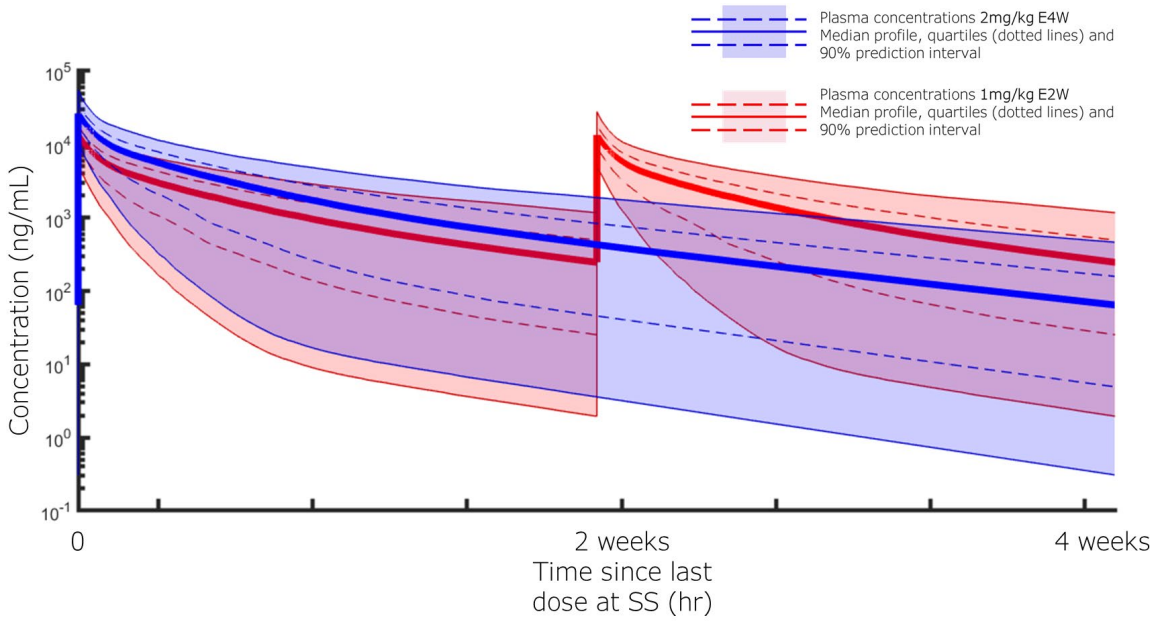
The extended half-life of pegunigalsidase alfa compared with other ERT supports the potential for sustained activity. The level of concentration of enzyme in plasma and its persistence between subsequent infusions are key determinants of delivery to target cells.

Exposure and therapeutic efficacy (Exposure response).

In the target population, the E4W dosing schedule is expected to maintain adequate exposure and consequently its therapeutic efficacy.

The Figure 7 below shows the comparability of the profiles at steady state for 2 mg/kg E4W and 1 mg/kg E2W, with PK characterized by the same average concentrations over a 4-week period (i.e. same exposure as measured by area under the curve over the 4-week dosing interval).

Figure 7. Model predicted time-plasma concentration profiles at steady state following 1 mg/kg E2W (in red) and 2 mg/kg E4W (in blue), for 1000 virtual subjects including potential covariates impacting PK; median profiles were shown with 90% prediction intervals



1 mg/kg E2W in red or 2 mg/kg E4W in blue
E2W: every 2 weeks; E4W: every 4 weeks; SS: Steady state
Source: MSAR 24-0022 Population PK Report

The simulated profiles displayed in Figure 7 assume a mean body weight of 70 kg with a normal distribution and a standard deviation of 23, as observed in the pooled dataset from the trials, for both clinical scenarios. The variability in the simulated time-plasma concentration profiles derives from the relevant covariates distribution in the population (i.e. ADA positivity at baseline, previous ERT treatment or first exposure to treatment- naive), as observed in the source data: 30% ADA positive at baseline, 10% naïve patients of which 50% (pseudo-naive – i.e. already exposed to agalsidase beta in the past but cleared from therapy for a minimum of 6 months before the baseline). The estimated variability among subjects in the PK parameters was added to this data. The continuous red and blue lines described the median simulated profiles. The shaded red and blue areas include plasma concentration profiles for 90% of the population. The dotted lines show the quartiles (i.e. 25th and 75th percentiles).

The interpretation of the data confirms the similarities in the PK parameters (e.g. the Cavg over 28 days) and show highly overlapping concentration levels at steady state, during the entire treatment period of 1 month in most of the patients. The small differences observed in the Cmax, and Cmin values, are not expected to have any impact on drug safety nor on its efficacy.

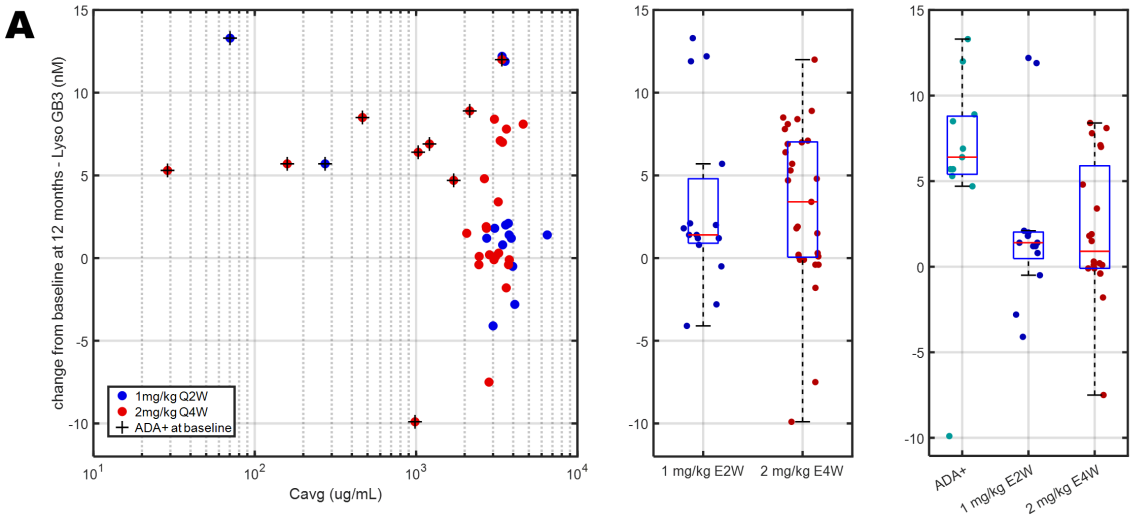
PK/PD was also explored using the globotriaosylsphingosine (Lyso-Gb3) concentrations and annualized estimated glomerular filtration rate (eGFR) slope as PD and efficacy biomarkers.

The Exposure–Response analyses demonstrates that the pharmacodynamic (PD) effects of the 2 mg/kg E4W regimen - measured by Lyso-Gb3 concentrations - and its impact on the efficacy endpoint, eGFR slope, were comparable to those observed with 1 mg/kg E2W regimen used as a reference (see **Figure 8**).

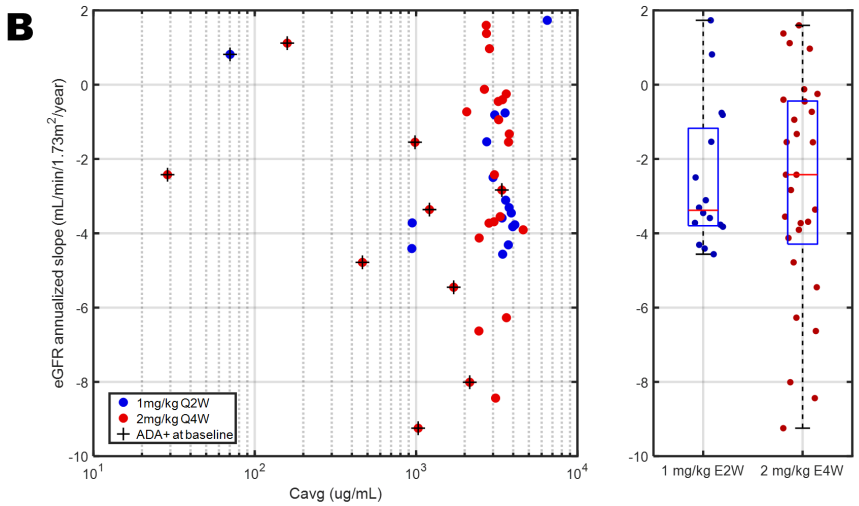
As can be observed in Panel A of **Figure 8**, the data distribution confirmed the impact of ADA on the individual PK where patients characterised by high ADA titer at baseline showed lower average concentrations of the biomarker. Additionally, the PD points distribution overall confirmed the similarity in average concentrations after the administration of 1 mg/kg E2W or 2 mg/kg E4W.

Therefore, even in presence of data variability, a clear trend of biomarker response can be observed without a clear difference between the two dosing regimens together with increased concentration of the PD biomarker in ADA positive patients. In Panel B of Figure 3 a similar finding is confirmed when evaluating the efficacy endpoint and in particular a similar response following 1 mg/kg E2W and 2 mg/kg E4W on eGFR slope, in this case with minimal impact of ADA presence.

Figure 8. Lyso-GB3 change from baseline at Month 12 and annualised eGFR slope at Month 12 following 1 mg/kg E2W or 2 mg/kg E4W treatments.



Panel A: LysoGb3 change from baseline at Month 12 *vs* average concentrations comparing 1 mg/kg E2W and 2 mg/kg E4W dosing regimens, including stratification by ADA positivity at baseline in a subpopulation of experienced patients; summary statistics by box plot are presented including patients that present ADA to pegunigalsidase alfa (graph 2 of the panel) and excluding them (graph 3 of the panel), so as to provide an additional comparison between patients that are positive *vs* patients that are negative to ADA at baseline; box and whisker plots (median; inter-quartile range; 1.5 * Inter-quartile range) are shown.



Panel B: annualised eGFR slope at Month 12 *vs* average concentrations, comparing 1 mg/kg E2W and 2 mg/kg E4W dosing regimens, including stratification by ADA positivity at baseline; summary statistics by box plot are presented including patients that have ADA to pegunigalsidase alfa (graph 2 of the panel); box and whisker plots (median; inter-quartile range; 1.5 * Inter-quartile range) are shown

Characterizing the Dose–Response Relationship in ERT

The activity of the recombinant enzyme is predominately intracellular, specifically intra-lysosomal. This feature entails that, without a direct measurement of enzyme activity at the level of the site of action (cellular space – lysosomes), large sample sizes would be required to find a clear-cut correlation among PK parameters and response parameters.

Chiesi would like to note that the other two treatments, agalsidase alfa and agalsidase beta, were approved at very different dosages back in 2001 [Replagal EPAR; Fabrazyme EPAR], evidently **without clear signals of a dose/response relationship**, with very similar results in terms of Gb3 clearance on the biopsies. This is proof of **how difficult it is for medicines with this mechanism of action, to detect a clear-cut relationship amongst dose/response parameters**. In fact the differences in PK parameters among the approved ERTs (agalsidase beta, agalsidase alfa and pegunigalsidase alfa) lack clinical relevance considering their large and established effect on substrate reduction.

Secondly, the definition of exposure response or dose - response remains challenging in the rare disease area. This may depend on many different factors, such as the small and heterogeneous population, the limitation in the biomarkers and the potential nonlinearity or saturation in the effect (i.e. enzyme replacement therapy shows threshold effects or plateau, making it difficult to define a gradient response).

However, the MAH would like to underline that the challenges in defining a mathematical relationship for exposure – response (E-R) relationship do not imply a lack of efficacy for the proposed new posology regimen for pegunigalsidase alfa, or a lack of E-R relationship in absolute terms.

Chiesi is convinced that pegunigalsidase alfa's mechanism of action is exposure-driven and for this reason a difference in the treatment effect on clinical endpoints is not expected: the total dose posology of administration. The clinical outcome is therefore linked to the presence of drug exposure following 1 mg/kg E2W or 2 mg/kg E4W, rather than to a precise dose–response curve.

Thirdly, other elements can easily impact the results when trying to identify an E-R, such as the type of efficacy endpoints and biomarkers used. They should be factored in as well when interpreting the overall findings:

- The eGFR is an objective measurement and easily quantifiable, but may show variability on single timepoints, in relation to the pathophysiology influenced by multiple, uncontrollable aspects (e.g. hydration state, concomitant drug administration, protein intake).
- The Plasma Lyso-Gb3, which has largely been used as a PD biomarker, and ultimately to monitor the therapeutic response to the treatment, is subject to multiple fluctuations as well (i.e. quantitatively large variability has been observed between subjects and within subjects, as mentioned already in the previous paragraphs).

Nevertheless, Lyso-Gb3 PK/PD data following pegunigalsidase alfa treatment (see Figure 3, panel A) are aligned with previous study results assessing the impact of ADA on Lyso-Gb3 [Bichet et al 2021].

The available data clearly show no statistically significant difference in term of biomarkers following 1 mg/kg E2W and 2 mg/kg E4W

To better interpret the results, the MAH has indeed applied two different sets of statistical tests: the *Two sample t-test* under the assumption that the data in the two groups were normally distributed, showing no statistical difference in the mean Lyso-Gb3 change from baseline at Month 12 following between 1mg/kg E2W and 2 mg/kg E4W; additionally, a *Mann-Whitney U test* was run as well, assuming a non-normally distributed data in the two groups and again no statistical difference was detected between the data distributions in the two groups.

Fourthly, providing a data stratification by ADA positivity in the subset of the experienced subjects, it appeared evident that patients with ADA to pegunigalsidase alfa had lower exposure combined with a trend in the Lyso-Gb3 change from baseline, suggesting lower efficacy (see Figure 3, Panel A).

In this case statistical tests were also run to better interpret the observed distribution, with the *Two sample t-test* and the *Mann-Whitney U test* confirming a statistically significant difference between ADA positive and negative subgroups with regards to the PD biomarker. This finding was not confirmed when repeating it with the efficacy biomarker, the eGFR slope.

This evidence is consistent with PK findings that determined the important impact of ADA on exposure and, despite some extent of variability in the biomarkers signal (mainly driven by the heterogeneity in the clinical manifestation of the disease), represent a robust proof of efficacy for the 2 mg/kg E4W dosing regimen. The ADA detrimental impact is less evident observing the results on the annualised eGFR slope (see Figure 3, panel B): even in this subgroup of patients ERT with pegunigalsidase alfa is expected to provide a positive clinical outcome.

The change from baseline Lyso-Gb3 at Month 12, together with the annualised eGFR slope at Month 12 provide robust evidence on the comparability between 1 mg/kg E2W and 2 mg/kg E4W.

Cmax and Cmin

One of the main objections during the assessment procedure, was that the lack of exposure/response relationship prevented to draw conclusions with respect to the efficacy of the proposed regimen, and that it was not clear how the change in the other parameters, such as Cmax and Cmin, could have a negative effect on the proposed posology modifications.

The MAH would like to provide its answers in respect of this objection.

First, had the efficacy of the treatment been linked to Cmax this parameter, we could have expected to see an enhanced efficacy compared to the initial approved posology: as can be seen by the results of the PopPK and PK/PD analyses presented above, this was not the case. The two posology show very comparable and overlapping point distributions on the PD and efficacy biomarkers.

The other possible clinical concern of an increased Cmax would be linked to the drug safety profile: however, safety has been assessed to be very positive also at this dose regimen and no concerns have been raised by the Rapporteur and the Co-Rapporteur on this key aspect.

Secondly, regarding the Cmin aspect of the PK curve, it should be noted that this is the only aspect in which the two dosing regimens differ, but this is fully compatible with other findings seen in the whole therapeutic class. As shown above, based on the reported half-life of agalsidase beta and agalsidase alfa, and the complete disappearance of the compounds from the circulation roughly at 72 hours after the administration, we could have expected a significantly lower efficacy compared to the pegunigalsidase alfa. This has proven to be untrue: in the PB-102-F20 trial, where the pegunigalsidase alfa was compared with agalsidase beta in a double blind, randomised controlled clinical setting, the two treatments have shown a complete overlap and similarity in terms of performance on kidney function and secondary endpoints, with a statistical non-inferiority shown at 2 years, according to the pre-defined criteria (ref. CSR PB-102-F20).

Conclusions on the second ground for refusal

Taking all the above into consideration, it seems reasonable to affirm that the treatment effect is driven by exposure, which in this case is similar for the 1mg/kg E2W and the 2mg/kg E4W, as shown by similar PK/PD between the two dosing regimens.

The MAH therefore concludes that PK and PD evidence support the new proposed posology regimen and are aligned with clinical evidence and their interpretation.

4.1.3. Additional information

Unmet need and patient reported outcome analysis

Enzyme Replacement Therapy has been a milestone in the development of treatment options for Fabry Disease patients, and a cornerstone in the clinical practice for several years now, with the ability of positively impacting the Natural History of the disease and improving life expectancy [Wanner 2018; Ortiz 2021].

On the other hand, **this is a life-long treatment with a tight schedule of administration E2W** and that requires an intravenous relatively slow infusion, impacting the everyday management and activities on patients as well as on caregivers.

It cannot be disputed that a **schedule of administration frequency E4W** is considered a major contribution to patient care as it is expected to **improve the QoL** through the reduction of the infusion burden on daily activities, and to **improve clinical outcomes by increasing treatment adherence long term.**

Numerous publications report the results of investigations regarding compliance with ERT administered E2W. The emerging consensus suggests that patient benefits within real-life contexts could be compromised due to inadequate adherence to the prescribed infusion schedule. This underscores a distinct unmet clinical need.

The majority of patients find it burdensome and difficult to travel to and from hospitals every 2 weeks. Alternative strategies such as the availability of a home care model might allow an improvement of treatment compliance and clinical outcomes, even more so in the post COVID-19

pandemic era [Concolino 2017; Nowicki 2021]. However, home care service is not always available and less frequent home care infusions would also convey a positive impact on self-perceived QoL.

This is also recognised by relevant patient organisations for Fabry disease that EMA contacted during the first phase of the pegunigalsidase alfa Marketing Authorisation Application (MAA) in the context of the EMA pilot project "CHMP early contact with patient organisations" (section 2.1.6 Patient's engagement day 120 AR overview), and from the letter sent by patients representatives of the Fabry International Network FIN (See Annex II) during this recent type II variation proposed on the label.

The Polish FD Collaborative group survey showed a significant burden for patients and their families when getting hospital infusions, especially for those with a physical disability [Kusztal 2021]. Based on a customised survey, 25% of FD patients receiving ERT spend 4 hours or more on transportation, plus an additional few hours for the hospital visit and ERT infusion. Moreover, 25% of them need frequent or full support from others, which produces an additional family burden. Germain 2019 stressed that "Solutions to alleviate the burden of bi-weekly infusions are also needed". As lifelong frequent ERT infusions have a considerable impact on patients' QoL, individual risk/benefit assessments should be made based on the disease status of the individual patient [Oder 2016; Schiffmann 2017].

On top of what is reported in literature, from our first-hand experience, through the Expanded Access Program (EAP) established in the US, or the Compassionate Use Program, currently still ongoing in EU, the duration of the treatment is even longer in presence of tolerability issues. In fact, agalsidase beta, which is a very effective treatment, has also known to be not so well tolerated in many patients: we have records of patients undergoing infusions taking up to 6 hours E2W, which is a clear hindrance to individuals routine, disruption to the working/studying rhythm and a big commitment for caregivers In addition to this, patients often report that the pre-medication regimen, when needed, in conjunction with the heavy prostration that usually follows these infusions, prolongs the recovery and requires additional time for patients to start performing at their best again [Berry 2024].

In this perspective, an alternative posology for pegunigalsidase alfa like the proposed 2 mg/kg infused every 4 weeks, which administers the same amount (mg) per month as standard E2W dosing regimen but with a reduced frequency of administration, is expected to positively impact QoL, improve compliance and ultimately treatment clinical outcomes, especially in patients where the E2W regimen represents a great burden on daily life. The 2 mg/kg E4W treatment regimen is considered to cover this clear unmet medical need.

Chiesi would like to provide a few details on its research efforts aimed at gathering evidence on the above mentioned unmet medical need for Fabry patients. In this respect, it will now describe the results of the Hope Project and the PEOPLE Study, respectively.

PEOPLE Study

More recently, a qualitative observational patient-reported outcome study was conducted by the MAH, involving patients enrolled in the ongoing PB-102-F51 trial who consented to be interviewed. The aim of this study was to better characterize the symptoms reported by enrolled patients and how the E4W posology had impacted and was perceived by the study participants (CLI-06657AA1-05- PEOPLE study).

Twenty-three of the 29 patients involved in PB-102-F51 were enrolled, and 17 of them interviewed and completed the observational study. At the time of the interview, 16 of these patients were receiving 2 mg/kg E4W. The remaining participant was transitioned to the 1mg/kg E2W posology during the trial by the treating physician.

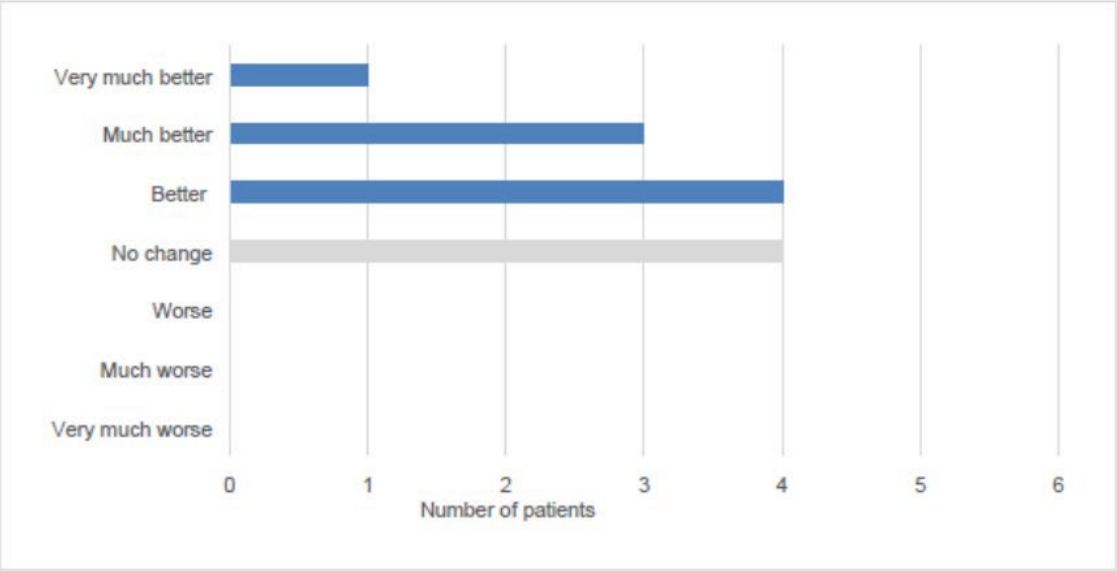
The impact of the treatment on daily living was evaluated as well. A total of 24 unique 'impacts' were reported by the 16 patients on a 4-week infusion schedule (Table 3). The most frequently reported impacts (described by ≥ 50% patients) were: impacts on physical activity and exercise reported by 13 out of 16 patients (81%), impacts on recreational activities and activities of daily living-ADLs (10/16; 63% for both), and impacts on work/school productivity (8/16;50%) as well as in social life (8/16; 50%). See table 3 below for additional details.

Table 3 impact of the treatment

No	Impacts	Total Number of Patients Reporting Impacts (N=16)	Spontaneous	Probed
1	Physical activity and exercise	13 (81%)	8 (62%)	5 (38%)
2	Recreational activities	10 (63%)	2 (20%)	8 (80%)
3	Activities of daily living	10 (63%)	4 (40%)	6 (60%)
4	Work/school productivity	8 (50%)	6 (75%)	2 (25%)
5	Sleep disturbance	7 (44%)	2 (29%)	5 (71%)
6	Social life	8 (50%)	3 (38%)	5 (62%)
7	Diet change	7 (44%)	2 (29%)	5 (71%)
8	Worry/sadness	6 (38%)	5 (83%)	1 (17%)
9	Difficulty walking	6 (38%)	3 (50%)	3 (50%)
10	HRQOL	5 (31%)	2 (40%)	3 (60%)
11	Stress	5 (31%)	4 (80%)	1 (20%)
12	Depression	4 (25%)	2 (50%)	2 (50%)
13	Difficulty traveling	4 (25%)	1 (25%)	3 (75%)
14	Anxiety	4 (25%)	4 (100%)	0 (0%)
15	Required assistance	3 (19%)	2 (67%)	1 (23%)
16	Disappointment	3 (19%)	3 (100%)	0 (0%)
17	Feeling isolated	2 (13%)	2 (100%)	0 (0%)
18	Emotional disturbance	1 (6%)	1 (100%)	0 (0%)
19	Financial issues	1 (6%)	1 (100%)	0 (0%)
20	Frustration	1 (6%)	1 (100%)	0 (0%)
21	Embarrassment	1 (6%)	1 (100%)	0 (0%)
22	Scratching	1 (6%)	1 (100%)	0 (0%)
23	Suicidal thoughts	1 (6%)	1 (100%)	0 (0%)
24	Anger	1 (6%)	1 (100%)	0 (0%)

Of the 16 patients who were on the E4W schedule, twelve were asked to provide their overall perception of changes in the signs, symptoms, and impacts they experienced during treatment with pegunigalsidase alfa. For the remaining four, the information was not collected. No patients reported a negative overall perception, four patients (4/12; 33%) reported no change and eight patients reported an improvement (8/12; 67%) in their signs and symptoms that was categorized as "better", "much better", or "very much better" (Figure 7).

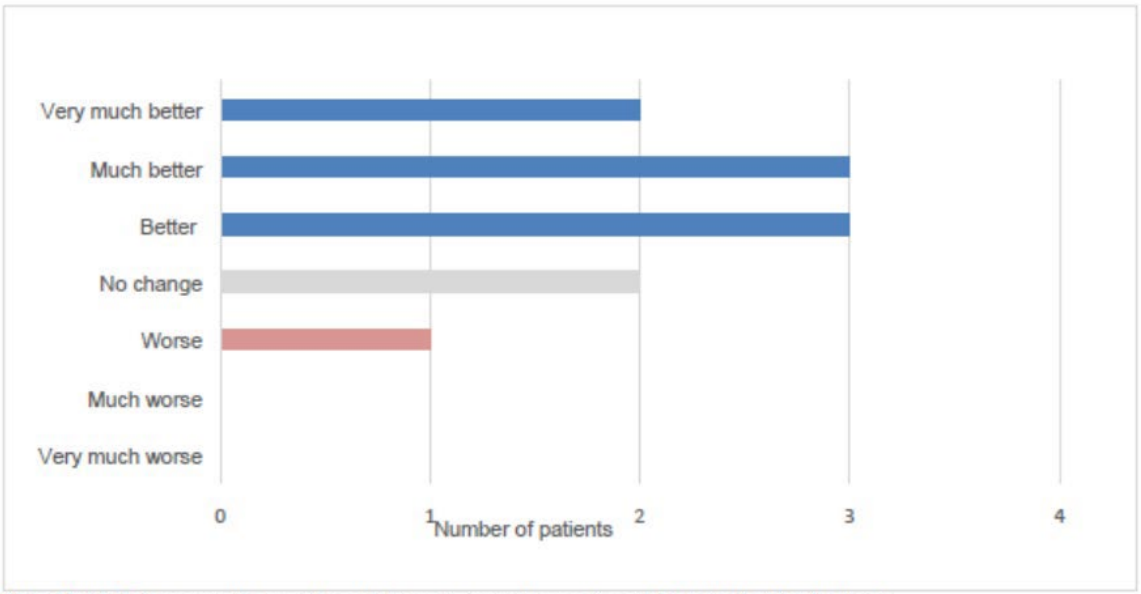
Figure 7: Overall Perception of Change in signs and Symptoms on 4-week schedule



Note. N=12. Data on overall perceptions of change in signs and symptoms were not available/not asked for 4 patients.
Blue = Improvement; Grey = No change; Red = Worsening

Moreover, of the eleven patients on the 4-week schedule who were asked the question about changes in impacts during the interview, two patients reported no change (2/11; 18%) and eight patients (8/11; 73%) stated that they experienced a positive change in their impacts (better, much better, or very much better) (Figure 8). As mentioned above, Patient 14 reported an overall worsening of impacts related to the burden of treatment and participation in a clinical trial.

Figure 8: Overall Perceptions of change in impacts on 4-week compared to 2-week schedule



Note. N=12. Data on overall perceptions of change in impacts was not available/not asked for 4 patients
Blue = Improvement; Grey = No change; Red = Worsening

During the interview, all 17 patients were asked to describe any advantages or disadvantages of the 4-week infusion schedule compared to the 2-week infusion schedule. Patients mentioned the greater convenience of the 4-week schedule that allowed them to better manage their time and activities (e.g. work) and to be more productive. The 4-week schedule was also perceived as allowing patients to lead a more normal life. In addition, due to the drug's effectiveness, patients were happy to experience improvements in their signs and symptoms of Fabry disease and this in turn, improved their quality of life. Also, the benefit of not being as medicated and sleepy due to the absence of antihistamine intake prior to the infusion was also mentioned. As presented above, the duration of the infusion was described as being disadvantageous for one patient (Patient 14) while others did not consider this a major disadvantage that outweighed all other advantages of the 4-week schedule.

HOPE Project

In addition to the Patient Reported Outcome trial PEOPLE, conducted on the population of patients exposed to the E4W schedule, the MAH has also generated data on the patient perspective on therapeutic processes and their challenges impacting the adherence over time in a small population of Fabry Disease patients in the US. The assessment was conducted as a Human Factor study with 6 patients in the US affected from Fabry Disease (HOPE Project - Report). On the specific point of "Infusion Challenges", the patients reported that the scheduling and administering of their infusion felt restrictive, and they had to work around them (see *verbatim* below):

- P1 – "*Yes, mine is once every two weeks. You've just got to be around. I've never even thought of going somewhere and trying to get it somewhere else. That would, I think, be a big challenge, on a vacation or something like that. And it's time consuming".*
- P2 – "*It used to be where I would get it [treatments] after work or I when I was working part-time I would get it on my off days. I am still working part-time, but when I started to work part-time that's when I started to get it on my off days. For school I would get it on days that I wasn't working or wasn't going to classes. I would get it then. It's always been a home nurse situation except in the very beginning when I would drive myself to the hospital and get it done there. My first infusion was 17 hours because they didn't know how to administer it. They didn't want a reaction from me. Then it was 14 hours. Then it was 10 hours, seven hours, then finally […] to a different hospital and I got it under two hours. At that point I was just getting them under two hours".*

During the interviews, the patients were offered several different solutions to potentially alleviate the burden of treatment, including the possibility of once monthly infusion, and were asked to select their preferred option. Here we report excerpts from patient interviews regarding this selection:

- P1 – "…..*Once a month would be awesome. Because it would only be once a month. You could pretty much have a life. You could put it at the beginning of the month or the end of the month and wouldn't have to worry about it for another month. When you have to do it every two weeks. And it is two hours. That's awesome too. My infusion is an hour and half. But still, it takes about 30 minutes to get me ready. And then I do a flush afterwards. I'm about three hours right now. Two hours, once a month, opposed to six hours once every two weeks. Well, three hours, once every two weeks, but six hours. I'm adding four hours a month that I can do something with*"
- P3 – "….. *In theory it sounds good. I don't necessarily know how feasible it is. But it sounds OK*".

- P4 – "…..*Where do I sign up for that? For me, I'd definitely go for that because quality of life, that's precisely why my 21-year-old isn't doing infusion. And I get it. My quality of life, if I didn't have to be infusing every two weeks. If infusion is once every four weeks and shortened time. That gives me back some of my life, say with my kids, myself. I would sign up for that in a heartbeat*.
- P6 - " …*That would be amazing*."

Positive impact of E4W on national healthcare systems

When a patient is starting a new ERT regimen it is common practice for the first few infusions to be administered in hospital as a precautionary measure. When allowed, home infusion setting is generally preferred for subsequent infusions. Administration costs for homecare infusion include the delivery of medication, cost of pre-infusion medications and disposal of waste.

E4W has the potential to reduce the annual cost of treatment administration and have a significant impact on patients' health related quality of life. Further benefits posed by reduced administrations of pegunigalsidase alfa include easing the burden on capacity of national health systems and sustainability benefits with less travelling for homecare nurses and reduced plastic waste. The less-frequent dosing schedule also has the potential to give patients an additional 13 days per year of infusion-free time, resulting in both QoL and productivity gains.

4.1.4. Overall conclusion by the MAH and proposed label

The MAH firmly believes that the evidence gathered to date, as detailed in the submitted documentation, are sufficiently robust to support the approval of the alternative posology based on:

- No safety issue identified and robust safety profile.
- PK and PD evidence support the new proposed posology regimen and are aligned with clinical evidence and their interpretation.
- Long-term clinical data available (up to 6 years of exposure to the treatment posology) for the 2 mg/kg E4W regimen, investigated in the study PB-102-F50 and its extension CLI-06657AA1-03 (formerly PB-102-F51), provided confirmatory evidence of the PopPK and PKPD findings. These data demonstrated a sustained and efficacious treatment effect, contributing to disease stabilization over time in this progressive condition.
- Integrated analyses of efficacy parameters from multiple clinical studies demonstrated a comparable treatment effect between the 2 mg/kg E4W dosing regimen and the reference 1 mg/kg E2W regimen in terms of kidney function decline.

Nevertheless, the MAH would accept restricting the use of the posology to patients ADA-negative, with the following wording to be included in **section 4.2 of the SmPC**:

> *The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once every two weeks.*
>
> *The treatment can be also administered at the dose of 2 mg/kg of body weight every four weeks in patients testing negative to pegunigalsidase alfa anti-drug antibodies (ADA).*

The posology of choice should be determined by the treating physician, taking into consideration the signs and symptoms of the disease, collected on the basis of a regular clinical multidisciplinary assessment.

Any type of posology changes between the two options deemed necessary by the physician, can be implemented starting from the next scheduled infusion

The proposal to reduce the population to the patients testing negative to pegunigalsidase alfa anti-drug antibodies (ADA) was discussed during the Oral Explanation, in line with Rapporteur's invitation to better identify the population suitable for the alternative posology E4W.

According to the MAH he restriction to ADA negative is in line with the PK/PD findings. As shown in Figure 4**, panel A** it is evident that the vast majority of patients ADA positive to the drug result in a lower exposure and a higher LysoGb3 concentration (reduced PD response), whereas the ADA negative ones show a higher exposure, even if in the presence of an heterogenous rate of PD response, which is influenced also by the baseline status of the patients, different gender representation, and previous exposure to treatments.

The product's safety profile remains confirmed. Furthermore, the proposed restriction to the more stable, ADA-negative population pursues a prudent and conservative approach. The proposed wording also includes a clear provision allowing patients to return to the every-two-week (E2W) regimen if deemed beneficial by the treating physician.

Therefore, the MAH reiterates its view that the documentation submitted supports a positive assessment of the benefit–risk profile of the alternative 2 mg/kg E4W regimen, and a confirmation of its comparability to the approved 1 mg/kg E2W posology.

Chiesi would like to respectfully submit that a new negative opinion would be unreasonable and highly disproportionate, also in light of the excellent safety profile of the product and the undisputed benefits accruing to patients switching to the new proposed dosage.

In case of residual doubts on the efficacy of the new regimen, rather than adopting a negative opinion, the CHMP could certainly avail itself of their power to recommend the performance of one or more post-authorisation studies. If needed at all, this solution would appear more proportionate, and certainly beneficial to patients in need of the additional dosing regimen, whilst respecting the precautionary principle and all other standards in terms of risk/benefit analysis.

4.2. Ad Hoc Expert Group consultation

Following a request from the MAH at the time of the re-examination, the CHMP convened a Ad Hoc Expert Group inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the MAH's response.

FINAL AD HOC EXPERT GROUP ANSWERS ON ELFABRIO (PEGUNIGALSIDASE ALFA)

1) Please comment on the grounds for negative opinion on the alternative pegunigalsidase alfa dosing regimen once every 4 weeks in view of the grounds for re-examination submitted.

The experts commented that Fabry disease is a chronic and challenging journey for all patients. The availability of various treatment options is welcome to ensure a good balance between effective

treatment and quality of life, especially when a degree of deterioration may be expected over time, with therapies intended to slow disease progression such as an enzyme replacement therapy (ERT).

From a methodological perspective, the experts agreed that the clinical evidence had strong limitations. Nevertheless, the long-term data with the observed stabilisation of the disease progression in ERT experienced patients on pegunigalsidase alfa dosing regimen once every 4 weeks was reassuring and such posology could be justified, not for all the patients but those that are stable with an ERT treatment.

From a patient perspective, the importance of improving the quality of life and clinical care was re-emphasised with less burden of treatment with the proposed new alternative posology. It was also acknowledged that data on this new posology was lacking in naïve patients with Fabry disease.

2) Taking into consideration the signs and symptoms of Fabry disease, collected on the basis of a regular clinical multidisciplinary assessment, how would you conclude in clinical practice on the suitability of the individual's current treatment?

The experts agreed that concluding on suitability of individual's current treatment (ie whether the patient is stable) is recommended to be based on a regular clinical multidisciplinary assessment and an overall clinical judgement. It would be expected that more frequent assessment than the standard annual assessment would be performed before stabilisation and also at the start of this new posology – see further details in answers to question 4). This assessment would include renal, cardiac and neurological functions as well as immunogenicity, pain control and quality of life. For the renal function in Fabry disease, lyso-Gb3 and the proteinuria were seen as more reliable measures as compared to the eGFR estimate that moves more slowly and should be relying on several timepoints. For the cardiac parameters, NT-proBNP and Troponin levels were also suggested as useful markers of disease progression.

From a patient perspective, it was mentioned that in practice most patients are only seen on an annual basis in Europe, some of them every 6 months. Although the extra follow-up is burdensome, three-monthly visits are challenging but could be reasonable especially in the context of less frequent infusions.

3) Please discuss the role of lyso-Gb3 and eGFR (value or slope) to monitor or guide treatment. Please discuss also:

a. any critical values or thresholds
b. how often lyso-Gb3 and eGFR should be measured.

For point (a), the experts agreed that sole reliance on biomarkers related to the renal function (and any critical values or thresholds on these parameters) to monitor or guide treatment does not fully reflect the clinical practice as outlined in answers to question 2. The experts also commented that Lyso GB3 variations over time should be considered rather than absolute values in patients with abnormal baseline levels; moreover this biomarker is more sensitive than eGFR estimate since it would indicate the presence or absence of an effective treatment in Fabry disease. The slope of eGFR depends on the initial stage of progression of the disease in the patient and is also prone to other comorbidities.

For point (b), see answers to question 4).

4) Please discuss any monitoring or treatment measures to mitigate potential risks associated with the proposed dosing, in particular the risk of undertreatment/disease progression.

As outlined in answers to question 2), a more frequent regular clinical multidisciplinary assessment would be expected with the introduction of a monthly administration instead of a 2-weekly administration. In particular, to mitigate the risk of undertreatment/disease progression, the experts agreed that for the first two years with the new treatment posology, a multidisciplinary assessment at month 3, month 6, month 12, month 18, month 24 could be suggested. Thereafter a yearly monitoring (or as per local protocol if more frequent) could be considered as outlined in answers to question 2. Assessment should include evaluation of all the potential organs involved and should include the relevant biomarkers (proteinuria, eGFR, NT-proBNP, troponin, lyso-Gb3).

To evaluate further the effectiveness of the new posology, data on the use in real life of the new posology could be collected through a registry post-approval.

5) Please discuss the following observations from the single arm studies PB-102-F50 and CLI-06657AA1-03 in ERT-experienced Fabry patients

a. **Median Lyso-Gb3 in males was 17 nmol/l at baseline and 22 nmol/l after 4 years of treatment. In females, median Lyso-Gb3 was 4 nmol/l both at baseline and after 4 years of treatment.**

b. **Mean (SD) eGFR slope was -1.79 (3.71) ml/min/1.73m^2/year at historical baseline and -2.20 (2.14) ml/min/1.73m^2/year during treatment.**

For point (a), the experts agreed that the observed differences in males were not clinically meaningful and noted the stabilization observed in female patients with long term treatment with the new posology. The experts further commented that whereas differences are observed in males and female in the studies, the answers to the previous questions are equally applicable to both male and female populations.

For point (b), the expert agreed that it is difficult to interpret due to the use of historical baseline. Generally, a decline of eGFR slope of more than 2-3 ml/min/1.73m^2/year is considered as indicating worsening of the renal function.

From a patient perspective, the importance of representation of females in clinical trials and not having a separation in treatment strategies between gender, noting that in the past women had not be treated due to lack of understanding of how the Fabry disease truly manifests in women.

4.3. Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the AHEG.

CHMP position on Ground #1

The MAH re-iterates the evidence supporting the efficacy of the E4W dose regimen.

<u>Open-label, uncontrolled studies</u>

The MAH argues that the evidence generated in the single-arm study PB-102-F50 and its extension CLI-06657AA1-03 is objective and reassuring given the regularity of the timing of the assessment, that

allows a precise estimation of the endpoints, the presence of a central laboratory, and the assessment of multiple exploratory clinical endpoints that sustain the interpretation of the finding.

The open label nature of study PB-102-F50 and its extension limits the value and interpretability of subjective measures. However, the CHMP acknowledged that is not expected to affect objective measures of efficacy and pharmacodynamics, such as eGFR and plasma Lyso-Gb3, especially as these were assessed at prespecified time points and determined using a central laboratory, as long as dropout rates and rates of switching to an E2W regimen are low (which was the case, see below). Hence, the fact that the study was open-label does not preclude a potential conclusion of efficacy on the basis of such objective measures.

However, the quality of the data does not reduce the uncertainties considering the baseline eGFR. The robustness of historical data to estimate the historical slope of eGFR prior to switch from agalsidase alfa/beta to a 2 mg/kg pegunigalsidase alfa E4W regimen cannot be assessed. This renders it difficult to interpret a (lack of) change in eGFR slope, as the eGFR slope at baseline may not be very reliable.

It also does not reduce the uncertainties due to the use of a single-arm design. Nevertheless, the single-arm trial (SAT) reflection paper (EMA/CHMP/458061/2024) notes:

> "*If in a SAT individual outcomes for the planned endpoint are observed that could not occur without effective treatment within the designated follow-up period for any trial participant, the SAT is able to isolate the treatment effect on that specific endpoint. Conceptually, this can allow a causal interpretation of the effect of the treatment, despite the limitations in trial design.*" It is further noted: "*This means that observations of the desired outcome for the primary endpoint should be known to occur only to a negligible extent (in number of subjects or size of the effect) in the absence of an effective treatment*."

Therefore, an uncontrolled study could be sufficient to allow a causal interpretation that there is a treatment effect, if individual outcomes are observed that could not occur (or rarely occur) without effective treatment within the follow-up period for any trial participant. In practice, individual outcomes are usually subject to measurement error and variability, such that isolation of a treatment effect can only be assessed subject to a degree of uncertainty.

Fabry disease has a highly heterogeneous clinical course. Although the clinical course is more homogeneous within subgroups of patients (e.g. classical males), substantial heterogeneity remains. In the case of renal function, the uncertainty is increased further because the eGFR slope prior to start of the study is estimated based upon lower-quality historical data. Moreover, the treatment effect on eGFR slope is not especially large, which makes it more difficult to isolate a treatment effect. Similar difficulties exist for clinical outcomes, such as echocardiography. A single-trial arm design is therefore not well-suited for such outcomes. The claim that "confirmatory" results (i.e. eGFR-slope) are presented by the MAH, is therefore not supported.

Nevertheless, the CHMP noted the absence of further discussion on the other pharmacodynamic measurement, lyso-Gb3. For the CHMP viewpoint, the lyso-Gb3 endpoint could unambiguously isolate a treatment effect in classic males, given that a very large increase in lyso-Gb3 is expected without effective ERT in these patients. This is further discussed below.

Descriptive nature of the studies

Study PB-102-F50 was set up as a descriptive study to investigate the safety and efficacy of a 2.0 mg/kg E4W dosing regimen. No primary efficacy variable was defined, and sample size was determined pragmatically.

However, the chosen endpoints are consistent with those used in the pivotal trial for the 1 mg/kg E2W dosing regimen (emphasizing eGFR and lyso-Gb3 as outcomes) and currently included in the

pegunigalsidase alfa SmPC. Consistency of results across the various time points assessed in study PB-102-F50 and its extension CLI-06657AA1-03 could address to a certain degree the methodological limitations of descriptive studies.

The sample size is considered adequate to establish absolute efficacy for the lyso-Gb3 endpoint, where a substantial increase in lyso-Gb3 is expected in the absence of effective ERT, at least in classic males. After switching to half the usual dose of agalsidase β in male patients an average increase of 8.1 nmol/l is reported after one year.[1]

The protocol specified that missing data would not be imputed. Follow-up in study PB-102-F50 and CLI-06657AA1-03 was nearly complete, with one participant withdrawing consent after the baseline visit due to a severe car accident and one additional participant withdrawing consent after week 132. The participant who withdrew consent after the baseline visit was excluded from all efficacy analyses, which can be accepted as withdrawal was likely unrelated to study treatment and disease characteristics. The participant who withdrew consent after week 132 is included in analyses up to that time point. While simple exclusion of the participant from analyses of later time points is not preferred, as missingness is probably not completely at random, the CHMP considered unlikely that efficacy of the E4W dosing regimen is overestimated due to withdrawal of this participant, as this participant (non-classic, female) consistently demonstrated very low lyso-Gb3 levels (0.40-0.70 nmol/l) and stable eGFR (baseline 61.72 ml/min/1.73m^2, week 132 63.06 ml/min/1.73m^2). Hence, the potential impact of missing data is considered minimal.

Study PB-102-F50 was initiated prior to adoption of ICH E9 R(1) and hence no estimand or intercurrent events were specified explicitly. No deaths occurred during the study or its extension, and the main intercurrent event of interest is switch to the 1 mg/kg E2W dosing regimen. This occurred in three participants: one non-classic male switched at week 40 due to deteriorating renal function, one classic male switched by week 108 due to pain crises, and one non-classic male switched by week 232 due to pain crises. These intercurrent events were handled using a "while-on-treatment" strategy, excluding data after switch to the E2W regimen. Within the context of a single-arm design, this is preferred over a treatment policy strategy, which would be anti-conservative if E2W is truly more effective than E4W.

As part of a single-arm design, it is generally recommended to prespecify a threshold that can establish the clinical benefit of the investigational treatment for the target population with sufficient certainty. While this was not done, the CHMP considered that the lyso-Gb3 endpoint could nevertheless unambiguously isolate a treatment effect in classic males, given that a very large increase in lyso-Gb3 is expected without effective ERT in these patients.

In conclusion, while pre-specification of an analysis plan and hypotheses to be tested would have been expected, it is still considered possible to conclude on efficacy given the availability of the lyso-Gb3 endpoints and the observed results (including low dropout rates and low switch rates).

<u>Efficacy of the proposed alternative dosing regimen not demonstrated</u>

Lack of robust and comparative data on the renal function (i.e. eGFR slope, i.e. a pharmacodynamic endpoint)

Based on the renal function data, no conclusion can be made as to whether the 2 mg/kg E4W regime is an effective posology.

Study PB-102-F50 and its extension study CLI-06657AA1-03 were designed to include patients with relatively mild/early-progressed Fabry disease, with an eGFR slope less negative than -2 ml/min/1.73m^2/year (under stable treatment with agalsidase beta or agalsidase alfa). The

[1] B Smid, S Rombach, J Aerts, et al. Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients. Orphanet Journal of Rare Diseases 2011, 6:69 http://www.ojrd.com/content/6/1/69

included – mainly male (81%) - patient population reported, on average, a normal baseline eGFR. The inclusion of mainly male patients reduces the known heterogeneous course of Fabry disease. Notwithstanding this homogenisation of the population it remains difficult to reliably determine, i.e. with sufficient precision, whether the E4W regimen has sufficient efficacy, as the expected course of renal function in the absence of E4W treatment is not fully clear.

The MAH has attempted to supplement the single-arm trial by using patients treated with E2W as an external control. Because there are important differences between participants with regard to eGFR slope due to the very different inclusion criteria regarding eGFR slope at screening in the E2W and E4W trials, even after matching on or controlling for sex, age, ADA status, UPCR, and baseline eGFR, no conclusions can be drawn based on the eGFR slope.

The MAH argues that a properly powered, non-inferiority trial comparing the 2 dosing regimens with regard to eGFR slope is not feasible. The CHMP agreed with the potential feasibility issue of such design, however, this argument does not reduce the onus upon the MAH to establish efficacy for their proposal.

Plasma lyso-Gb3

In general after the peripheral infusion of the enzyme it finds its way to the lysosome where it unfolds by a pH of 4. Here it catalyses the breakdown of accumulated globotriaosylceramide (Gb3) and its deacylated metabolite, lyso-Gb3, by cleaving off the terminal galactose, thus restoring normal cellular function and preventing tissue damage. Preventing the accumulation of glycosphingolipids prevents or reduces the severity of manifestations of Fabry disease. Therefore, clinical efficacy can be concluded using the stabilisation of a pharmacodynamic endpoint (either eGFR or lysoGb3). Typically this is done by PK assessment, however due to the complexity of the data a classical PK/PD assessment is not possible.

In males with classic Fabry the treatment effect on lyso-Gb3 is very large. Untreated classic males have been reported to have lyso-Gb3 values >100 nmol/l (e.g. median 286 nmol/l, range 51-489, Rombach et al., 2010). Since ERT is expected to result in lyso-Gb3 levels that are not observed among untreated classic males, it is considered possible to isolate a treatment effect on lyso-Gb3 in classic males using a single-arm trial. Lyso-GB3 levels are not expected to remain stable when a patient is untreated, or treated with an ineffective ERT. Therefore a stabilisation of lyso-Gb3 in treatment experienced patients is considered sufficient to conclude on effectiveness. The AHEG agreed with these conclusions.

Moreover, it is possible to isolate a treatment effect based upon the change in lyso-Gb3, at least in classic males. In this case the expected course of illness is well-characterised, and the treatment effect is exceptionally large in treatment-naïve patients (EMA/CHMP/430688/2024). Despite this, a small (underpowered) randomized trial with an E2W control arm would still have been preferable, although uncertainties would remain even if a small control arm had been included as it would only have been possible to rule out very large differences between E4W and E2W, which are unlikely *a priori* given the similarities in PK.

Based on the accumulated knowledge in the last 25 years it is expected that male patients after stopping treatment show a loss of response. This is to be expected within 6 months[2]. Published literature mentions an increase in plasma lyso-Gb3 from a median of 22.5 nmol/l to 32.4 nmol/l after one year in males who had their agalsidase beta dose reduced or were switched to agalsidase alfa (Smid et al., 2011). Even in classic male patients on stable ERT some increase in lyso-Gb3 (on average

[2] E Riccio, C Garofalo, I Capuano, et al. New insights in efficacy of different ERT dosages in Fabry disease: Switch and switch-back studies data following agalsidase beta shortage. Update of systematic review. Genetics in medicine Volume 1, Issue 11008052023

about 1 nmol/l/year) is not unusual[3]. An increase was also seen in the pivotal trial for the 1 mg/kg E2W regimen (+3.3 nmol/l over 2 years).

The submitted results suggest stabilisation in lyso-Gb3 levels in participants stable on ERT over time, (median [Q1, Q3] plasma lyso-Gb3 at baseline in males was 17.2 [12.1, 32.8] nmol/l, at 24 months lyso-Gb3 was 23.5 [16.0, 37.6] nmol/l and at 48 months 21.8 [15.4, 30.8] nmol/l).

For the sub-group of classical male patients (N=15) stable on ERT median (Q1, Q3) lyso-Gb3 at baseline was 22.0 nmol/l (12.6, 39.0), at 24 months 28.7 nmol/l (20.6, 42.5), and at 48 months 23.1 nmol/l (18.0, 38.8). Lyso-Gb3 levels were stable among females. The mean change in lyso-Gb3 levels after 24 and 48 months of follow-up were +3.2 nmol/l and +1.6 nmol/l in the full group of participants and +3.6 nmol/l and +0.0 nmol/l among males with classic Fabry, specifically.

An integrated analysis of lyso-Gb3 levels using historical data from the E2W trials to construct an external control arm was not submitted during the assessment of this alternative regimen. Nevertheless, based on the results from study PB-102-F50 and its extension study CLI-06657AA1-03 and the AHEG outcome, the CHMP concluded that lyso-Gb3 is stable over the 4 years of observation. This conclusion is especially strengthened by the effects reported for classical male patients in whom a steep increase in lyso-Gb3 is expected in a non-effective treatment, and in whom the reported data may be considered highly unlikely if 2 mg/kg E4W was not an effective posology.

Safety

Based on the data it is concluded that overall, safety data with the 2 mg/kg every 4 weeks dose are reassuring. Further it is concluded that the MAH has provided data regarding the dose change. In terms of safety, no major issues were observed compared to the previously authorised dose.

It would be expected that lack of efficacy could translate to a notable increase of adverse events over the 6 years of follow-up. Even in a less effective dose this should be observed (especially in classical male patients). Therefore, the lack of an increase in adverse events supports the use of 2mg/kg E4W regimen.

CHMP position on Ground #2

The CHMP agreed that the relationship between dose and efficacy is partially governed by the pharmacokinetic and pharmacodynamic properties of pegunigalsidase alfa. The MAH argues that similar exposure would result in similar efficacy., the assessment of this question can be translated to identifying the rate-limiting step in the dose-pk-pd-efficacy relationship.

A population pharmacokinetic modelling approach was used by the MAH to quantify the population pharmacokinetics in 62 Fabry patients based on study data of **F01/02, F20 and F50**. Simulations indicated that no effect on $AUC_{0\text{-}4week}$ was present during a dosing interval, in line with the linear assumptions of the population PK model, but that, in line with pharmacokinetic theory, C_{max} was higher (2 fold, C = Dose/V) and C_{min} was lower (0.4 fold) with the Q4W dose.

The mode of action of enzyme replacement therapies, like pegunigalsidase, is to supplement biological active α-GAL-A enzyme to Fabry patients as this enzyme is deficient or absent in these patients (EMEA/H/C/005618/0000). The deficiency/absence results in massive storage of Gb3 and related glycolipids (e.g. Lyso-Gb3) in cells of the vascular system, cardiomyocytes, neuronal cells and kidney cells as well as elevated levels in the circulation. Lyso-Gb3 is therefore assumed to be a downstream biomarker for Gb3 accumulation within cells.

[3] H Sakuraba, T Togawa, T Tsukimura and H Kato. Plasma lyso-Gb3: a biomarker for monitoring Fabry patients during enzyme replacement therapy. Clinical and Experimental Nephrology. Volume 22, pages 843–849, (2018).

Enzyme replacement therapies, like pegunigalsidase alfa, and, similarly, agalsidase beta and agalsidase alfa, have been shown to temporarily suppress lyso-Gb3 accumulation (effect in treatment naïve patients of E2W). The lyso-Gb3 levels after pegunigalsidase alfa administration can be expected to reflect a balance between a reduced production of lyso-Gb3 (i.e. enhanced removal of Gb3 by supplementing biological active α-GAL-A enzyme) and endogenous elimination of lyso-Gb3. When the therapeutic effect of pegunigalsidase alfa gradually diminishes (e.g. because of lower concentrations of pegunigalsidase alfa at the site of action), lyso-Gb3 levels can be expected to gradually re-accumulate until a next dose is administered.

Based on the current data no clear relationship between pegunigalsidase alfa exposure and Lyso-Gb3 change from baseline at 12 months of treatment can be quantified. The 2-fold higher C_{max} and 0.4-fold lower C_{min} with the 2 mg/kg E4W could impact efficacy and safety. The increase in C_{max} is not expected to be clinically relevant based on the safety profiles seen for the 2 mg/kg E4W dosing regimen. The lyso-Gb3 concentrations were stable after switching from agalsidase alfa and beta to pegunigalsidase alfa 2 mg/kg E4W, which suggest a lack of effect of the lower C_{min} on the Lyso-Gb3 concentrations. This is further supported by the lack of an effect of the PK profile (i.e., the short half-lives of agalsidase alfa and beta versus longer half-live of pegunigalsidase alfa) on the Lyso-Gb3 concentrations. In line with the AHEG outcome, even in the absence of a clear/direct demonstration of comparable exposure-response between doses, the long-term data with the observed stabilisation of the disease progression in ERT experienced patients support pegunigalsidase alfa dosing regimen once every 4 weeks, not for all the patients but those that are stable with an ERT treatment.

With regard to the additional information provided during the re-examination procedure (see 4.3.1), the CHMP noted that these were not specifically addressing the grounds for refusal and thus would not be commented further. Nevertheless the CHMP reiterated their acknowledgement that a 4 weekly dosing regimen for authorised enzyme replacement therapy (ERT) products in Fabry disease offers greater flexibility in dosing for patients and clinicians.

5. Risk Management Plan

The CHMP endorsed the Risk Management Plan version 1.5 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	• Hypersensitivity Reactions (infusion related)
Important potential risks	• Medication errors in the home infusion setting
Missing information	• None

Pharmacovigilance plan

None

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Important Identified Risk		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Hypersensitivity Reactions (infusion related)	Routine risk minimisation measures: • SmPC section 4.4. • PL section 2 Additional risk minimisation measures: • HCP brochure • Patient/caregiver/HCP guide	Routine pharmacovigilance • Regular review of safety reports • Signal detection activities • Inclusion of discussion in the EU Periodic Safety Update Report (PSUR) Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Important Potential Risk		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Medication errors in the home infusion setting	Routine risk minimisation measures: • SmPC section 4.2 • SmPC section 6 Additional risk minimisation measures: • HCP brochure • Patient/caregiver/HCP guide	Routine pharmacovigilance • Regular review of reports • Signal detection activities • Inclusion of discussion in the EU Periodic Safety Update Report (PSUR) Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

6. Update of the Product information

As a consequence of this new posology, sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. Particularly, a new warning with regard to treatment monitoring for patients switched to pegunigalsidase alfa 2 mg/kg body weight once every 4 weeks has been added to the product information. The Package Leaflet has been updated accordingly.

7. Benefit-risk balance following re-examination

Therapeutic Context

Disease or condition

Fabry disease (also referred to as Anderson-Fabry disease) is an X-linked inborn error of metabolism characterised by subnormal or absent activity of the lysosomal hydrolase, α-galactosidase (αGAL). Deficiency of αGAL leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3) in the lysosomes of endothelial, peri-epithelial, and smooth-muscle cells of blood vessels.

The clinical manifestations of classic Fabry disease result primarily from the progressive deposition of GL-3 in the vascular endothelium. Ultimately, failure of endothelial vascular beds results in the pathophysiological events leading to peripheral neuritis, angiokeratoma corporis diffusum universale, renal failure, myocardial infarction and cerebral infarction. Clinical features of Fabry disease in women encompass a wide spectrum of symptoms, including angiokeratomas, early strokes, myocardial hypertrophy, arrhythmias, gastrointestinal disorders, and renal involvement.

Although Fabry disease presentation is highly heterogeneous, clinical onset usually occurs during childhood or adolescence. Early manifestations include episodic crises of excruciating pain in the extremities (acroparaesthesias), the appearance of characteristic cutaneous lesions (angiokeratoma corporis diffusum universale), hypohidrosis, and the characteristic corneal and lenticular opacities.

Fabry disease progresses to key organ dysfunction. Typically, in the classic form during the second or third decade of life renal insufficiency develops, progressing to end-stage renal disease requiring dialysis and/or transplantation in the fourth and subsequent decades. Hypertrophic cardiomyopathy (secondary to cardiomyocyte involvement), valvular abnormalities (secondary to valvular fibroblast and endothelial involvement) and myocardial infarction (secondary to endothelial dysfunction and small vessel occlusion) have been observed in the third and subsequent decades of life. Additionally, cerebrovascular complications may develop during the third and subsequent decades, with abnormal autonomic responses exhibited throughout the course of the disease. Progressive disease burden in symptomatic individuals results in a substantially decreased life expectancy. Fabry-related deaths are typically due to renal failure, cardiac disease or cerebrovascular disease. Left untreated, symptomatic Fabry disease is usually fatal.

Available therapies and unmet medical need

Enzyme replacement therapy (ERT) is a primary treatment option for Fabry disease. ERT involves regular infusions of synthetic α-galactosidase (αGAL) to replace the deficient enzyme and help reduce Gb3 accumulation. An intravenous (IV) infusion of agalsidase alfa or beta enzyme (agalsidase alfa or agalsidase beta) has to be administrated every two weeks. Patients may receive an antihistamine and other medications before therapy to prevent an allergic reaction.

Oral chaperone therapy: Chaperones are small molecules that repair faulty αGAL). The mended enzymes can then break down the fatty substance. With this therapy, a pill (migalastat [Galafold]) has to be administrated every other day to stabilize the patient. Not everyone with Fabry disease can be treated with this medication. It depends on the specific genetic mutation in the GLA gene if someone is eligible for this treatment.

Main clinical studies

In support of this variation, the MAH submitted data from:

- Study PB-102-F50 and the extension of study CLI-06657AA1-03 (formerly known as PB-102-F51)
- An observational study (CLI-06657AA1-05)
- Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis including data from studies PB-102-F01/F02, PB-102-F50 and PB-102-F20 (M&S report 24-0022)
- An indirect comparison of patients from PB-102-F50 and the extension of study CLI-06657AA1-03 with patients from PB-102-F01/-F02/-F03, PB-102-F20, PB- 102-F30 and CLI-06657AA1-04

Study PB-102-F50 and Study CLI-06657AA1-03

Study PB-102-F50 was an open label, switch over study aimed to assess the safety, efficacy and PK of pegunigalsidase 2.0 mg/kg administered by IV infusion E4W for 12 months in adult patients with Fabry disease previously treated with ERT (i.e. agalsidase alfa or agalsidase beta).

Study CLI-06657AA1-03 is an ongoing long-term extension of Study PB-102-F50 that aim to assess long-term (median follow-up 58 additional months) safety and efficacy of pegunigalsidase alfa 2 mg/kg E4W.

Thirty (30) patients were enrolled, 29 patients (23 males and 6 females) completed study PB-102-F50. At the data lock of the last interim analysis (study CLI-06657AA1-03; October 2024) 11 patients were still in the study (a considerable part of the patients stopped around the time of the data lock due to registration in the US but are still included in the final analysis).

Population PK and PK/PD analysis

The PopPK model was updated to develop a simulation tool to extrapolate and compare the clinical scenarios of interest and in particular evaluate the PK following 1 mg/kg E2W versus 2 mg/kg E4W dosing regimens. The previously established population PK model was updated with data from treatment-experienced patients that switched to the 2 mg/kg E4W dosing regimen in Study PB-102-F20, which included patients with declining renal function, and study PB-102-F50. Additionally, PK/PD analyses were performed and the dataset was updated with Lyso-Gb3 and eGFR data at 12 months measured in Study PB102-F20 and PB102-F50.

Integrated analyses

The integrated analyses aimed to compare the 29 patients on an E4W regimen in study PB-102-F50 and its extension to treatment-experienced patients on an E2W regimen (n=73) in other studies with regard to eGFR slope. The MAH submitted ANCOVA models controlling for baseline sex, age, ADA status, UPCR, and eGFR as well as an analysis of matched subgroups and 1-to-1 matching analyses matching patients on the same variables.

Favourable effects

Simulations performed using the population PK model indicated that AUC_{4week} and C_{avg} were similar between 1 mg/kg E2W and 2 mg/kg E4W. The C_{max} is simulated to be 2-fold higher for the 2 mg/kg E4W regimen, and C_{min} 0.4-fold lower.

Treatment experienced patients maintained overall stable Lyso-Gb3 concentrations after switch from a comparator to E4W independent of the C_{min}

The mean (SD) annualised eGFR slope in the Efficacy Set was -1.79 (3.71) and -2.20 (2.14) ml/min/1.73m^2/year at baseline and during treatment, respectively.

Mean plasma Lyso-Gb3 at baseline was 19.4 (SD 18.05) nmol/l and 22.1 (SD 18.75) nmol/l at week 108. In classical male patients median (Q1, Q3) baseline lyso-Gb3 was 22.0 (12.6, 39.0) nmol/l, at 24 months 28.7 (20.6, 42.5), and at 48 months 23.1 (18.0, 38.8). The mean change in lyso-Gb3 levels after 24 and 48 months of follow-up were +3.2 and +1.6 in the full group of participants and +3.6 and +0.0 among males with classic Fabry, specifically.

Uncertainties and limitations about favourable effects

PK analysis

Based on the current data no clear relationship between pegunigalsidase alfa exposure and Lyso-Gb3 change from baseline at 12 months of treatment can be quantified. The 2-fold higher C_{max} and 0.4-fold lower C_{min} with the 2 mg/kg E4W regimen could impact efficacy and safety. The increase in C_{max} is not expected to be clinically relevant based on the safety profiles seen for the 2 mg/kg E4W dosing regimen. The lyso-Gb3 concentrations were stable after switching from agalsidase alfa and beta to pegunigalsidase alfa 2 mg/kg E4W, which suggest a lack of effect of the lower C_{min} on the Lyso-Gb3 concentrations. This is further supported by the lack of an effect of the PK profile (i.e., the short half-lives of agalsidase alfa and beta versus longer half-live of pegunigalsidase alfa) on the Lyso-Gb3 concentrations.

Study PB-102-F50 and Study CLI-06657AA1-03

Fabry disease affects multiple organ systems including the kidneys and the cardiovascular system. The course of Fabry disease is very heterogeneous, and a treatment effect on eGFR cannot be isolated in a single-arm trial. Understanding the variability of the condition which may affect multiple organ systems, the treatment response, and the ability to monitor disease progression, is key to the assessment of this variation.

The available data originates from an uncontrolled study with descriptive efficacy analyses. In this case this can be accepted considering that the outcomes (especially lysoGb3) are objectively measured at multiple timepoints and can be compared against clinically established thresholds.

The population consists mainly of male Fabry patients, who are stable on ERT. This selection of the Fabry population supports sensitivity of the trial for differences in efficacy as in (classical) male patients the changes between an effective, less effective and non-effective treatment are the largest. Therefore this limitation does not hamper assessment.

The mean lyso-Gb3 and the eGFR at the end of the follow-up indicate that some of the patients show a clinically relevant deterioration. Careful treatment monitoring of these and other clinical parameters (e.g. left ventricular mass, evaluation of proteinuria) is required to mitigate this risk.

Integrated analyses

The integrated analyses were post-hoc and exploratory. Sample sizes in subgroup analyses and the matching analyses are limited, as can be expected for this condition. This uncertainty is accepted.

Due to differences in inclusion criteria with regard to baseline eGFR slope, it is likely that important differences between the E2W and E4W populations remain even after controlling or matching for baseline sex, age, ADA status, UPCR, and eGFR. This limits the importance that can be given to the analyses related to the renal function.

Subgroups

Data on selected Fabry disease subgroups are extremely limited, notably patients with anti-drug antibodies and female patients. Careful treatment monitoring should mitigate this uncertainty.

No data have been submitted for treatment-naïve patients starting on an E4W regimen.

Unfavourable effects

The most reported preferred terms of treatment-emergent adverse events were: coronavirus infection, nasopharyngitis, infusion-related reaction, pain in extremity, upper respiratory tract infection, headache, paraesthesia, nausea, fatigue, cough, hypertension, pain, back pain, sinusitis (all reported in >15% of patients).

Infusion related reactions (IRRs) were reported by 30.0% (9/30) of patients. No serious IRRs or IRRs leading to study discontinuation were reported. However, a few late-onset, non-severe IRRs were observed after 4 years of treatment in ADA-negative patients. By ADA status, 50% of ADA-positive patients experienced an infusion-related reaction (IRR), compared to 21.1% of ADA-negative patients. Notably, no ADA-induced patients experienced an IRR.

Uncertainties and limitations about unfavourable effects

The available data originate from an uncontrolled study. Considering the observed long-term data on lyso-Gb3, and on safety, the new posology (pegunigalsidase alfa 2 mg/kg E4W) is considered safe in stable patients on ERT treatment, provided that adequate treatment monitoring is in place. Guidance on treatment monitoring has been included in the product information.

Effects Table

Effects Table for proposed dosing regimen, based on study PB-102-F50 and study CLI-06657AA1-03 (data cut-off: October 2024).

Effect Short Description Unit	Treatment baseline	Control during treatment	Uncertainties/ Strength of evidence
Favourable Effects			
Mean (SD) eGFR slope [ml/min/1.73m^2/year]	-1.79 (3.71)	-2.20 (2.14)	Unc: PD parameter No internal control arm, course of Fabry disease very heterogeneous, doubts about reliability of historical eGFR data, descriptive data SoE very weak
Mean (SD) lyso-Gb3, from baseline to week 108 [nmol/l]	19.4 (18.05)	22.1 (18.75)	Unc: PD parameter No internal control arm, descriptive data
Unfavourable Effects			
IRR	Unknown	30.0% (9/30)	Unc. No baseline data SoE weak

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Based on the popPK analysis it can be concluded that the exposure, in terms of $AUC4_{week}$ and C_{avg}, to the drug is comparable in both regimens. As expected based on pharmacokinetic principles, the C_{max} is simulated to be 2-fold higher for the 2 mg/kg E4W as compared to the 1 mg/kg E2W regimen, and C_{min} 0.4-fold lower as compared to the 1 mg/kg E2W regimen. The effects of these observations on the lyso-Gb3 concentrations appears negligible, i.e. the lyso-Gb3 data demonstrate stabilisation in ERT-treated patients switching to the new posology.

No clinically relevant deterioration based on eGFR and lyso-Gb3 was observed. However, the provided renal data and analyses do not robustly demonstrate that the 2 mg/kg/E4W dosing regimen is an effective posology.

Based on the stabilisation of the lyso-Gb3 efficacy is to be expected for most Fabry patients. Especially the observed stabilisation in the classical male patients supports this conclusion. In line with the AHEG outcome, even in the absence of a clear/direct demonstration of comparable exposure-response between doses, the long-term data with the observed stabilisation of the disease progression in ERT experienced patients support pegunigalsidase alfa dosing regimen once every 4 weeks, not for all the patients but those that are stable with an ERT treatment.

No major safety issues are observed compared to the previously authorised dose.

To mitigate the risk of under treatment a warning in 4.4 is included in the SmPC indicating that patients should be monitored after switching to a E4W regimen. Based on renal function, echocardiology and biochemistry the efficacy of the E4W regimen should be assessed in Fabry disease patients. Patients showing loss of control of disease progression should return to their initial or other enzyme-replacement treatment.

Given the positive benefit-risk of 1 mg/kg pegunigalsidase alfa E2W and the well-established mode of action, it is considered possible to infer efficacy of pegunigalsidase alfa 2 mg/kg E4W based upon lyso-Gb3 levels. Hence, the benefit-risk balance is considered positive in patients on stable ERT.

Balance of benefits and risks

Despite the methodological limitations and the absence of a quantifiable dose efficacy-relationship from the submitted data, the lyso-GB3 is a reliable marker of the absence or presence of an effective ERT treatment. The data on lyso-GB3 showed stabilisation in patients switching to the new posology and the safety profile of Elfabrio is similar between the new and approved posology. Such effect could not be achieved without the presence of effective treatment. A slight increase in infusion Related Reactions was observed but without any (Serious Adverse Events) SAEs or fatal cases in the E4W cohort.

Hence, the benefit-risk balance is considered positive in patients on stable ERT.

Additional considerations on the benefit-risk balance

The CHMP noted that a 4 weekly dosing regimen for authorised enzyme replacement therapy (ERT) products in Fabry disease offers greater flexibility in dosing for patients and clinicians.

8. Conclusions following re-examination

Based on the submitted data it is concluded that the 2mg/kg E4W regimen is effective and that it can be considered an alternative for Fabry patients stable on ERT, provided adequate treatment monitoring is in place.

9. Recommendation following re-examination

Final outcome

Based on the arguments of the MAH and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion considers the following variation acceptable and therefore recommends by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to introduce an alternative posology regimen based on results from study PB-102-F50 (BRIGHT) and interim results from its extension study CLI-06657AA1-03 (formerly presented as PB-102-F51), as well as results of the observational patient reporting outcome study CLI-06657AA1-05. CLI-06657AA1-03 is an 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. The Package Leaflet is updated accordingly. The RMP version 1.5 has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

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