Amsterdam, 14 December 2023
EMA/587427/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fabrazyme

Agalsidase beta

Procedure no: EMEA/H/C/000370/P46/064

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 23	20 Nov 23	☐
☐	CHMP members comments	04 Dec 23	04 Dec 23	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 23	07 Dec 23	☐
☒	CHMP adoption of conclusions:	14 Dec 23	14 Dec 23	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On the 8th of August 2023, the MAH submitted a completed paediatric study for Fabrazyme, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). Fabrazyme is indicated in adults, children and adolescents aged 8 years and older.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study LPS16583 is a standalone study. This study is not part of an agreed Paediatric Investigational Plan (PIP).

2.2. Information on the pharmaceutical formulation used in the study

Fabrazyme consists of powder for infusion.

Each vial of Fabrazyme contains a nominal value of 35 mg or 5 mg of Agalsidase beta. After reconstitution with 7.2 ml or 1.1 mL of sterile water for injections respectively, each vial of Fabrazyme contains 5 mg/ml of Agalsidase beta.

Fabrazyme should be administered via IV infusion at a dosage level of 1 mg/kg body weight every two weeks.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study LPS16583.

Study LPS16583 was a 54-week Phase 4, open-label, single-arm study to evaluate the safety and efficacy of 1 mg/kg of Fabrazyme every two weeks in a Chinese Fabry disease patient population in the post marketing setting. This study was conducted from 15 October 2021 (first participant enrolled) through 09 March 2023 (last participant last visit) in China. This study included, among others, 4 paediatric participants <18 years of age. This study was conducted as a PMS study to fulfil the Agency requirement in China.

2.3.2. Clinical study LPS16583

Description

Study LPS16583 was a 54-week Phase 4, open-label, single-arm, PMS study to evaluate the safety and the efficacy of Fabrazyme as ERT in Chinese participants with Fabry disease (see Figure 1).

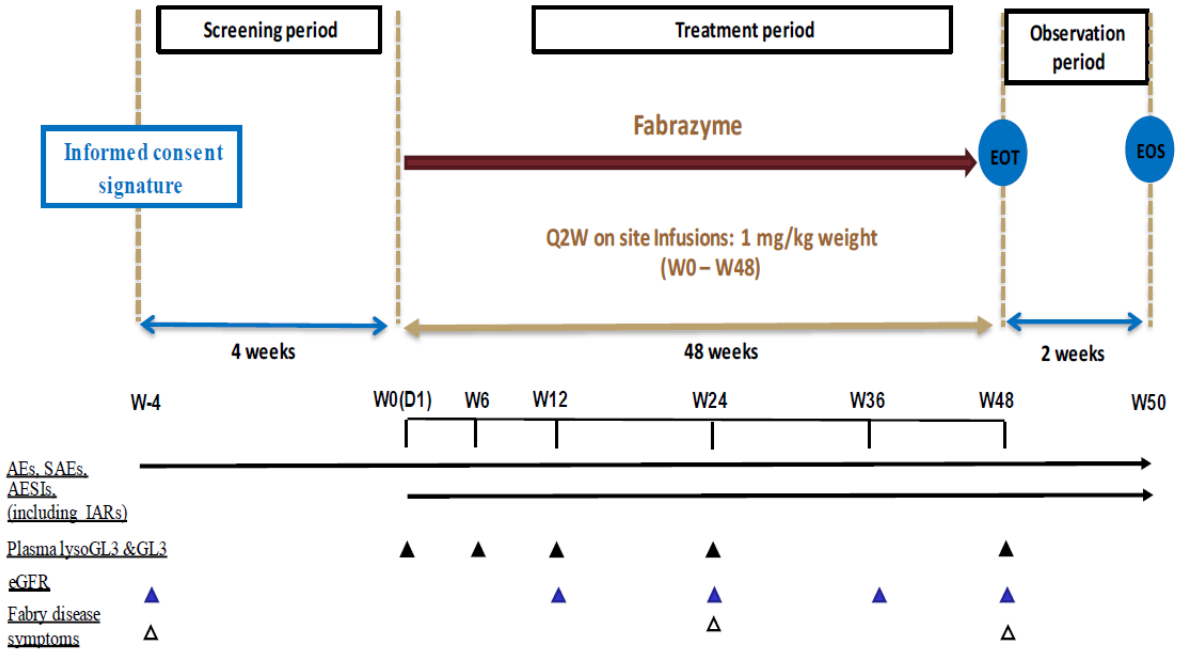

Figure 1 Graphical study design.
Abbreviations: AE = adverse event; AESI: adverse event of special interest; D = day; eGFR = estimated glomerular filtration rate; EOT = end-of-treatment; EOS = end-of-study; GL3 = globotriaosylceramide; IAR = infusion associated reaction; lyso-GL3 = globotriaosylsphingosine; Q2W = every 2 weeks; SAE = serious adverse event; W = week.

Methods

Study participants

Inclusion criteria:

This study enrolled Chinese participants, 8 years of age or older, diagnosed with Fabry disease and with documented plasma or leukocyte αGAL activity deficient below laboratory's reference range, and/or documented diagnosis by genotyping. Participants had to be naive to Agalsidase beta and Agalsidase alpha. Participants must have had one or more symptoms and signs consistent with manifestations of Fabry disease (not limited to neuropathic pain, chronic kidney disease, hypertrophic cardiomyopathy, cardiac rhythm disturbances, cerebrovascular involvement, cornea verticillata, angiokeratoma, gastrointestinal symptoms, hypo- or anhidrosis).

A female participant was eligible to participate if she was not pregnant or breastfeeding, and at least one of the following conditions applied:

- Was not a woman of childbearing potential (WOCBP)

OR

- Was a WOCBP and agreed to use an acceptable contraceptive method during the intervention period and at a minimum until 14 days after the last dose of study intervention.
- A WOCBP must have had a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within the screening period before the first dose of study intervention.

- If a urine test could not be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test was required. In such cases, the participant was excluded from participation if the serum pregnancy result was positive.

For participants aged 8 to <18 years, a parent or legal representative was required to sign the informed consent form, and the potential participant was also required to sign an informed assent form. The participant had to be able to comply with the clinical protocol, which required extensive clinical evaluations.

Exclusion criteria:

Participants who had undergone kidney transplantation or were having clinically significant organ disease (with the exception of symptoms relating to Fabry disease) which, in the opinion of the Investigator, would preclude participation in the trial. Participants who had current evidence of kidney failure or renal insufficiency, as defined by eGFR <30 mL/min/1.73 m^2.

Participants who had received substrate reduction therapy within 30 days of anticipated administration of IMPs or 5 half-lives of the previous treatment, whichever was longer. Participants who received an investigational drug, or device, other than Fabrazyme, within 30 days of anticipated IMPs administration or 5 half-lives of the previous investigational drug, whichever was longer. Or who received an investigational gene therapy.

Individuals who have life threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients included. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who were legally institutionalized. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

Participants who were employees of the clinical study site at the time of inclusion or other individuals directly involved in the conduct of the study, or immediate family members of such individuals. Any specific situation during study implementation/course that may rise ethics considerations. Participants who are sensitive to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Assessor's comment

Patients with a confirmed diagnosis of Fabry Disease are eligible, this is in agreement with the current SmPC.

Fabry disease is a rare pan-ethnic disorder and in this study only patients from Chinese descent were included, which is acceptable.

Treatments

Fabrazyme was given at 1 mg/kg body weight once every two weeks (Q2W) by IV infusion.

Assessor's comment

Dosage and method of administration is conform the SmPC for paediatric patients (8-16 years).

Objectives

Primary objective

- To evaluate the safety and tolerability of Fabrazyme (1 mg/kg, IV, Q2W) in Chinese Fabry disease participants

Secondary objectives:

- To evaluate the changes of plasma lyso-GL3 level with Fabrazyme treatment in Chinese Fabry disease participants
- To evaluate the changes of plasma GL3 level with Fabrazyme treatment in Chinese Fabry disease participants
- To evaluate the number and percentage of participants with abnormal plasma GL3 value with Fabrazyme treatment in Chinese Fabry disease participants
- To evaluate the change of symptoms of Fabry disease with Fabrazyme treatment in Chinese Fabry disease participants
- To evaluate the change in renal function with Fabrazyme treatment in Chinese Fabry disease participants

Outcomes/endpoints

Primary endpoints:

- Incidence of treatment-emergent AEs, SAEs, and AESIs, including IARs
- The change during the Treatment-emergent (TE) period of clinical laboratory (haematology and biochemistry), vital signs and ECG parameters

Secondary endpoints:

- The absolute changes and percent changes of plasma lyso-GL3 from baseline to Week 6, Week 12, Week 24 and Week 48
- The absolute changes and percent changes of plasma GL3 from baseline to Week 6, Week 12, Week 24 and Week 48
- The number and percentage of participants with abnormal plasma GL3 values per central lab reference range at Week 6, Week 12, Week 24 and Week 48
- The change of Fabry disease symptoms assessment (improved, worsen or same) from baseline to Week 24 and Week 48: angiokeratoma, sweating, chronic abdominal pain, level of activity, exercise tolerance and heat tolerance, headache, tinnitus
- The absolute change of eGFR by CKD-EPI for adult (≥18 years) and Schwartz for children (8 ≤ age <18 years) from baseline to Week 12, Week 24, Week 36 and Week 48

Assessor's comment

The objectives of Study LPS16583**Error! No document variable supplied.**were to evaluate the safety and tolerability of Fabrazyme in the Chinese Fabry disease population. Furthermore, to evaluate the changes in plasma lyso-GL3 levels, plasma GL3 levels, symptoms and renal function and to evaluate the number of patients with abnormal plasma GL3 values.

The safety and efficacy objectives and endpoints are considered relevant for Fabry disease. However, it is regretted that neuropathic pain and cardiac involvement (e.g. Left ventricular mass index) are not included in the assessment.

Sample size

Approximately 22 participants will be enrolled to study intervention to achieve an estimated total of 20 exposed participants.

Study participation for each patient will be total of 54 weeks which will include 4 weeks of screening, 48 weeks of treatment period and 2 weeks of post study treatment observation.

Randomisation and blinding (masking)

There was no randomisation and blinding procedure.

Statistical Methods

The following populations for analyses were defined (Table 1).

Table 1 Populations for analyses.

Population	**Description**
Enrolled	All participants who sign the ICF and meet inclusion and exclusion criteria
Exposed	All participants who sign the ICF and take at least 1 dose of study intervention.
Evaluable	All exposed population who do not have major protocol deviations that would have impact on efficacy evaluation.

Analysis of primary endpoints

The analysis of primary endpoint was conducted based on the exposed population.

- Incidence of AEs. The incidence rates of the following AEs during TE period were provided:
    - Any AEs
    - Serious adverse events (SAEs)
    - Adverse events of special interest (AESIs) defined as:
        - Symptomatic overdose (serious or nonserious) with IMP
        - Pregnancy of a female participant entered in the study
        - Infusion associated reactions (IARs)

  Adverse events were summarized by the preferred term (PT) and the system organ class (SOC) overall, by the severity and by the relationship to Fabrazyme. The event number for AEs were provided.

- The change during the TE period of clinical laboratory vital signs and ECG parameters. Potentially clinically significant abnormality (PCSA) analyses for clinical laboratory, vital signs, and ECG parameters during the TE period were used.

  The PCSA values were defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs. PCSA criteria will determine which participants had at least one PCSA during the TE period.

  For clinical laboratory, vital signs and ECG parameters, the number of participants with at least one PCSA during the TE period was summarized regardless of the baseline level and according to the following baseline status categories:

  - Normal/missing
  - Abnormal according to PCSA criterion or criteria

  Analyses according to PCSA was performed based on the worst value during the TE period, using all measurements.

Analysis of secondary endpoints

Secondary endpoints were based on the exposed population and analysed descriptively.

Plasma lyso-GL3 and plasma GL3 level

Reduction of lyso-GL3 and GL3 in blood was evaluated by measuring level of total plasma lyso-GL3 and plasma GL3. Blood samples were collected at the time points specified in Figure 1 and prior to treatment infusion.

Estimated glomerular filtration rate (eGFR) by serum creatinine

The eGFR was estimated from serum creatinine and height using Bedside Schwartz Formula for children (8≤ age <18 years) (Schwartz et al, *J Am Soc Nephrol* 2009). Assessments were performed at the time points specified in Figure 1.

Fabry disease symptoms

Fabry disease symptoms (angiokeratoma, sweating, chronic abdominal pain, level of activity, exercise tolerance and heat tolerance, headache, tinnitus) were assessed per the time points specified in Figure 1 and prior to treatment infusion. The change of Fabry disease symptoms assessment (improved, worsen or same) from baseline to Week 24 and Week 48 were presented.

Assessor's comment

Methods to analyse most of the endpoints are considered adequate. However, it is unclear how the Fabry disease symptoms were assessed (e.g. were questionnaires used that are validated for paediatric assessment). As clarity on this matter will not impact the outcome of this article 46 assessment (e.g. lead to changes to the SmPC), this issue is not further pursued.

Results

Participant flow

A total of 24 participants provided the informed consent and were screened. Of these, 22 participants were enrolled in the study. Two participants were not enrolled in the study due to screen failure (both met exclusion criteria).

Recruitment

This study was conducted at 6 centres that enrolled participants in China.

Baseline data

The overall mean (SD) values of age, weight, and height were 29.0 (13.5) years, 58.4 (15.1) kg, and 167.9 (11.6) cm, respectively. Majority of participants were males 18 (81.8%) compared to 4 (18.2%) female participants. All participants were Chinese, see Table 2 for demographics and patient characteristics.

In the enrolled population, 17 (77.3%) participants reported at least one medical or surgical history. The most common medical history by SOC was renal and urinary disorders (9 [40.9%] participants), and the most common medical history by PT was hypertension (5 [22.7%] participants).

There were 4 paediatric participants enrolled in this study, including 2 (9.1%) participants each from the 8 to 11 years of age group and the 12 to 17 years of age group. Among these 4 participants, there were 3 males and 1 female.

Table 2 Demographics and participant characteristics at baseline - Enrolled population

	Fabrazyme (N=22)
Age (years)	
Number	22
Mean (SD)	29.0 (13.5)
Median	29.0
Min; Max	10; 60
Age group [n (%)]	
Number	22
From 8 - 11 years	2 (9.1)
From 12 - 17 years	2 (9.1)
From 18 - 64 years	18 (81.8)
From 65 - 84 years	0
85 years and over	0
Sex [n (%)]	
Number	22
Male	18 (81.8)
Female	4 (18.2)
Race [n (%)]	
Number	22
Asian	22 (100)
Chinese	22 (100)

Baseline Weight (kg)	
Number	22
Mean (SD)	58.4 (15.1)
Median	57.3
Min; Max	26; 92
Baseline Weight by category (kg) [n (%)]	
Number	22
<25	0
25 to <50	5 (22.7)
50 to <100	17 (77.3)
≥100	0
Baseline Height (cm)	
Number	22
Mean (SD)	167.9 (11.6)
Median	170.5
Min; Max	132; 185

Number analysed

All 4 paediatric participants received the study intervention and completed the study treatment as well as the study.

Efficacy results

Assessor's comments

Only results on the paediatric patients will be assessed.

Efficacy of Fabrazyme in the paediatric participants was consistent with the overall population.

- Fabrazyme showed reduction of the plasma lyso-GL3 and plasma GL3 levels at Week 48 from baseline in all 4 paediatric participants (Table 3).
- Improvement in symptoms by Week 48 was seen in all 4 paediatric participants.
- There were no clinically meaningful changes in the eGFR parameters in all 4 paediatric participants during the study (Table 3).

Table 3. Table compiled by assessor: Change in plasma lyso-GL3, plasma GL3 and eGFR in the paediatric patients up to week 48. For simplicity, only data of week 0, 12, 24 and 48 is shown (data of week 6 for plasma levels and week 36 for eGFR were left out).
* Abnormal plasma GL3 levels, reference range 1.1-3.2 mg/L.

				PLASMA Lyso-GL3		PLASMA GL3		eGFR	
Participant	**Sex**	**Age**	**Visit**	**Value (µg/L)**	**Per-centage change from baseline (%)**	**Value (mg/L)**	**Per-centage change from baseline (%)**	**Value (mL/ min/ 1.73m²)**	**Per-centage change from baseline (%)**
	Male	15	Week 0	115		11*		210.4	
			Week 12	-	-	-	-	-	-

		Week 24	18.2	-84.17	3.25*	-70.45	188.9	-10.22
		Week 48	32.1	-72.09	3.82*	-65.27	207.9	-1.19
Male	10	Week 0	97.2		10.9*		134.4	
		Week 12	15.9	-83.64	5.18*	-52.48	162.8	21.13
		Week 24	17.3	-82.2	4.75*	-56.42	185.3	37.87
		Week 48	8.75	-91	3.45*	-68.35	145.9	8.56
Male	10	Week 0	73.1		6.7*		149.3	
		Week 12	16.6	-77.29	2.81	-58.06	145.9	-2.28
		Week 24	21.4	-70.73	4.27*	-36.27	168.3	12.73
		Week 48	11.6	-84.13	2.79	-58.36	164.1	9.91
Female	12	Week 0	3.23		2.97		172.9	
		Week 12	1.63	-49.54	2.54	-14.48	170.2	-1.56
		Week 24	2.3	-28.79	2.61	-12.12	186.6	7.92
		Week 48	1.62	-49.85	2.77	-6.73	173.4	0.29

Assessor's comments

Reductions in plasma lyso-GL3 (between -50% to -91% at week 48) and GL3 levels (between -7% to -68% at week 48) were observed in all four paediatric patients. Plasma levels of lyso-GL3 and GL3 were higher in the males than in the female patient. These reductions are in line with the results observed in the entire study population (n=22) with a mean decrease of -60% in plasma lyso-GL3 and -35% in plasma GL3 levels at 48 weeks. These plasma levels are in line with previously observed reductions in lyso-GL3. In adult patients, reductions of -39.5% in plasma lyso-GL3 levels have been observed six months after switching from Agalsidase Alfa to Agalsidase Beta treatment. With higher plasma levels of lyso-GL3 in males compared to females (Goker-Alpan, *JIMD reports* 2015). Reduction in plasma lyso-GL3 upon Agalsidase beta treatment is greater in classical male patients than in female patients (mean age = 46, Arends, *J Med Genet*. 2018).

All paediatric patients are hyperfiltrators with eGFR >130 mL/min/1.73m^2. Glomerular hyperfiltration is relatively frequent in young Fabry patients and can be regarded as an early marker of Fabry nephropathy. The eGFR did not clearly change during Agalsidase beta treatment. Which is in line with previous observations in adult patients upon Agalsidase beta treatment (SmPC). A decrease in eGFR was observed upon Agalsidase *alpha* treatment in hyperfiltrators (Mehta et al, *Lancet* 2009). However, patient numbers are too low to draw any definitive conclusions on the effect of Agalsidase beta treatment on renal function in this study.

All paediatric patients reported on activity tolerance, heat tolerance, decreased or absent sweating (some on abdominal pain, angiokeratoma and headache). The level of disease symptoms remained the same at 24 weeks and improved from baseline in all paediatric patients at 48 weeks.

As patient numbers are low and because of the single-arm trial design, no firm conclusions on efficacy can be drawn. However, these data are largely in line with the current knowledge of the clinical presentation of Fabry disease and treatment with Agalsidase beta. The male patients with the classic phenotype are often the most affected. It is agreed that no amendments to the Product Information are warranted based on these results.

Safety results

Exposure

Paediatric participants

All paediatric participants received study intervention exposure for >48 weeks. The mean (SD) duration of study intervention exposure during the study in the 4 paediatric participants was 49.93 (0.14) weeks.

Adverse events

Paediatric participants

Treatment-emergent adverse events by SOC and PT

All four paediatric participants experienced TEAEs with a total of 15 TEAEs. The most frequently reported SOC was "Infections and infestations" (8) with the most frequently reported PTPTs "Upper respiratory tract infection" (6) and "Epistaxis" (2).

Treatment-emergent adverse events by SOC and PT related to IMP

One paediatric participant experienced 2 TEAEs ("Vomiting" and "Chest discomfort") that were considered related to IMP. All other (13) TEAEs were assessed as not related to IMP.

Treatment-emergent adverse events by SOC and PT with maximal intensity

All TEAEs in these four paediatric participants were of mild or moderate intensity. The 2 TEAEs considered related to IMP were both of mild intensity.

Deaths

There were no TEAEs leading to death reported during the study.

Serious adverse events (SAEs)

There were no serious adverse events in the paediatric participants.

Discontinuations and/or dose modifications due to adverse events

There were no TEAEs leading to permanent treatment discontinuation reported during the study.

Adverse events of special interest

There were 2 AESIs in one paediatric participant, ("Vomiting" and "Chest discomfort"), both categorised as infusion-associated reactions and assessed as related to IMP. These were the only AESIs reported in paediatric participants.

Overall, the safety profile of Agalsidase beta in the paediatric participants was consistent with the overall population.

Assessor's comments

All four paediatric participants experienced TEAEs, with a total of 15 TEAEs. Only 2/15 TEAEs ("Vomiting" and "Chest discomfort"), experienced by one participant, were assessed as related to Agalsidase beta. Both (mild) TEAEs were considered infusion-associated reactions and are known to occur with Agalsidase beta treatment.

The most frequently reported PT, "Upper respiratory tract infection" (6), was reported in three paediatric participants, including three occurrences in one participant. All occurrences (in all participants) were assessed as not related to Agalsidase beta treatment and occurrences of upper respiratory tract infections could be expected with a follow-up period of approximately one year. In addition, the Agalsidase beta product information describes "Nasopharyngitis" and "Rhinitis" as known adverse reactions.

No new important safety was identified. It is agreed that, based on the presented information, no changes to the approved product information are warranted.

Evaluation of clinical laboratory tests

There were no clinically meaningful changes over time in red blood cells, platelets, and coagulation observed throughout the course of the study.

There were no clinically meaningful changes over time in white blood cells observed throughout the course of the study. Potentially clinically significant abnormally high neutrophil count was reported in 2 of 4 child participants (50%).

There were no clinically meaningful changes over time in liver function observed throughout the course of the study.

There were no clinically meaningful changes over time in metabolism observed throughout the course of the study.

There were no clinically meaningful changes over time in renal function observed throughout the course of the study.

Other safety evaluations

There were no clinically meaningful findings in the vital sign measurements and ECGs or other observations related to safety in this study.

There were no clinically meaningful changes over time in vital signs observed throughout the course of the study. The potentially clinically significant abnormalities (PCSAs) that occurred in more than 10% of participants were:

- Respiratory rate low (children): in 2 participants (50%)
- Respiratory rate high (children): in 1 participant (25%)

There were no clinically meaningful changes over time in electrocardiograms observed throughout the course of the study.

Assessor's comments

Among the four paediatric participants:

- a potentially significant abnormally high neutrophil count was reported in 2 of 4 paediatric participants

- a potentially significant abnormally low respiratory rate was reported in 2 of 4 paediatric participants

- a potentially significant abnormally high respiratory rate was reported in 1 of 4 paediatric participants.

The MAH did not provide actual values or context of these abnormal findings.

Considering:

- the (absolute) low number of reported abnormalities

- that these abnormal findings are not reflected in the reported adverse events in the paediatric participants,

it is agreed that, based on the presented information, no changes to the approved product information are warranted.

2.3.3. Discussion on clinical aspects

Study LPS16583 was a 54-week Phase 4, open-label, single-arm study to evaluate the safety and efficacy of 1 mg/kg of Fabrazyme administered every two weeks in a Chinese Fabry disease patient population. This study was conducted as a PMS study to fulfil the Agency requirement in China.

Only four paediatric patients were included. Efficacy was determined by the analysis of plasma lyso-GL3 levels, plasma GL-3 levels, change in eGFR and symptoms following Agalsidase beta treatment. Reductions in plasma lyso-GL3 (between -50% to -91% at week 48) and GL3 levels (between -7% to -68% at week 48) were observed in all four paediatric patients. Plasma levels of lyso-GL3 and GL3 were higher in the three males than in the female patient. All four patients were hyperfiltrators with eGFR > 130 mL/min/1.73m^2 and the eGFR remained rather stable during treatment. All paediatric patients reported on activity tolerance, heat tolerance, decreased or absent sweating. The level of Fabry disease symptoms improved at 48 weeks of treatment compared to baseline in all patients. Although some important symptoms of Fabry were not assessed (e.g. neuropathic pains, left ventricular mass index), the obtained results are largely in line with the current knowledge of Fabry and the treatment with Agalsidase beta.

There were no new safety signals reported in the study. All four paediatric patients experienced TEAEs, of which only 2/15 TEAEs ("Vomiting" and "Chest discomfort", experienced by one participant), were assessed as mild infusion-associated events related to the treatment. Upper respiratory tract infection, reported by three paediatric patients, was the most frequently reported PT and were all assessed as not related to the treatment.

Potentially clinically significant abnormality (PCSA) analyses for clinical laboratory, vital signs, and ECG parameters were performed. Reported PCSAs: high neutrophil count was reported in 2 of 4 paediatric participants, low respiratory rate was reported in 2 of 4 paediatric participants and high respiratory rate in 1 of 4 paediatric participants. However context and absolute values of these abnormal values were not provided by the MAH.

Considering that patient numbers are low no firm conclusions on the effects can be drawn. Therefore, issues regarding the context and values on the PCSAs and the method of symptom assessment is not further pursued as the response will not impact the outcome of this article 46 procedure (e.g. lead to changes to the SmPC). For future article 46 procedures, the MAH is requested to present a separate assessment of the paediatric data for all objectives and endpoints and discuss the clinical relevance of those data. As no abnormal results were observed in the entire study population and in the provided individual paediatric data, a separate assessment is not requested at this moment.

It is agreed with the MAH that no changes to the current SmPC of Fabrazyme are necessary.

3. Rapporteur's overall conclusion and recommendation

In conclusion, the obtained results are largely in line with the current knowledge of Fabry and treatment with Fabrazyme. No new safety signals were identified in this study.

The B/R remains positive.

No changes to the SmPC are considered necessary.

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

Not applicable