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EMA/56436/2015
Committee for Medicinal Products for Human Use (CHMP)

Fabrazyme

(agalsidase beta)

Procedure No. EMEA/H/C/000370/P46 062

Genzyme Europe BV

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

Assessment report as adopted by the CHMP with all commercially confidential information deleted

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On 16 December 2014, 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.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study Evaluation of Glycosphingolipid Clearance in Patients Treated With Agalsidase Alfa who Switch to Agalsidase Beta (The INFORM Study) (AGAL19412) is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study<ies>

Not applicable. Fabrazyme is available as powder for infusion only.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

Study Evaluation of Glycosphingolipid Clearance in Patients Treated With Agalsidase Alfa who Switch to Agalsidase Beta (The INFORM Study) (AGAL19412).

1.3.2. Clinical study

Study Evaluation of Glycosphingolipid Clearance in Patients Treated With Agalsidase Alfa who Switch to Agalsidase Beta (The INFORM Study) (AGAL19412)

Description

Design: This was an open-label, multi center exploratory study in male patients with Fabry disease who were switched from agalsidase α (Replagal) 0.2 mg/kg q2w to agalsidase β (Fabrazyme) 1.0 mg/kg q2w. The study consisted of a baseline visit and 3 study-related clinical visits at Months 2, 4, and 6 for a total duration of approximately 6.5 months. At each visit after entering the study, glycosphingolipids and gastrointestinal symptoms were assessed on the day of infusion, prior to infusion. No clinical efficacy data were collected. Safety was evaluated by the incidence of adverse events (AEs) associated with protocol related procedures and other AEs not considered associated with Fabrazyme treatment. Adverse events associated with Fabrazyme treatment were also reported.

Methods

Objective(s)

This was an exploratory study that evaluated changes in glycosphingolipid levels and other Fabry disease parameters in male Fabry disease patients who were previously treated with agalsidase α (Replagal) 0.2 mg/kg every 2 weeks (q2w) and who were switched to agalsidase β (Fabrazyme) 1.0 mg/kg q2w.

Study design

This was an open-label, multi center exploratory study in male patients with Fabry disease who were switched from agalsidase α 0.2mg/kg q2w to agalsidase β 1.0 mg/kg q2w. The study consisted of a baseline visit and 3 clinical visits at Months 2, 4, and 6 for a total duration of approximately 6.5 months. At each visit after entering the study, glycosphingolipids were measured in blood and urine samples and gastrointestinal GI symptoms were assessed on the day of infusion prior to the administration of agalsidase β. No clinical efficacy data were collected. Safety was evaluated by the incidence of adverse events (AEs) associated with protocol-related procedures and other AEs not considered associated with agalsidase β treatment. Adverse events associated with agalsidase β treatment were also reported according to the reporting procedures in the product labelling.

Study population /Sample size

Male patients with a diagnosis of Fabry disease confirmed by α-galactosidase A activity and/or genotyping according to local standards and had been treated with agalsidase α at 0.2 mg/kg q2w for the 12months prior to switching to agalsidase β.

Number of patients:	Planned: Up to 30 patients
	Randomized: Not applicable
	Treated: 15
Evaluated:	Efficacy: Not applicable
	Safety: 15
	Exploratory: 15

The in- and exclusion criteria allow patients for the whole age range. The age of the patients included in this study varied from 5 to 61 yrs. The age of the paediatric patients (N=5) ranged from 5 to 18 yrs.

Treatments

NA

Duration of treatment:

6 months

Duration of observation:

6.5months

Outcomes/endpoints

Exploratory:

Mean percent change and absolute change from baseline to Months 2, 4, and 6 in plasma deacylated globotriaosylceramide (lyso-GL-3), plasma globotriaosylceramide (GL-3), and urine GL-3.

Safety:

The incidence of AEs associated with study-related procedures and other AEs that were not considered associated with Fabrazyme treatment.

Pharmacokinetics:

Not applicable

Blood samples for measurement of Fabry disease biomarkers and immunoglobulin G (IgG) titres were collected on the day of infusion prior to infusion of agalsidase β. Levels of total GL-3 in plasma and urine and lyso-GL-3 in plasma were assayed by tandem mass spectrometry. Values below quantitative limits were converted to 2.5 ng/mL for plasma lyso-GL-3, 1.0 mcg/mL for plasma GL-3, and (0.1 [mcg/mL]/creatinine [mg/mL]) × 133.13 (mg/mmol) for urine GL-3.

Statistical Methods

All enrolled patients were included in the analyses. Glycosphingolipid levels (plasma lyso-GL-3, plasma GL-3, and urine GL-3) were summarized by descriptive statistics at baseline, and at Months 2, 4, and 6 after switching to agalsidase β. The change from baseline in glycosphingolipid levels were also summarized by descriptive statistics for each visit and presented graphically. As ad hoc analyses, statistical tests on change from baseline were performed and corresponding p-values were reported. Severity scores for GI symptoms were also summarized at each visit. In addition, serum IgG antibody titres and numbers of patients with positive/negative serum IgG antibody titres were summarized by visit. Sample size was calculated using a statistically significant (p=0.001) median increase of 8.1 nM in lyso-GL-3 that had been reported among male patients previously treated with agalsidase β who switched to agalsidase α or a lower dose of agalsidase β. Based on the assumption that the reverse change would be observed among male patients who switched from agalsidase α to agalsidase β, it was estimated that there would be >90% power to detect changes in lyso-GL-3 of this order of magnitude among 20 patients.

Results

Baseline data:

All 15 patients in this study were male, primarily Caucasian (86.7%), with a confirmed diagnosis of Fabry disease of an average duration of 9.2 years.

Efficacy results

Both the mean percentage change and absolute change from baseline of plasma lyso-GL-3 levels showed statistically significant reductions at each clinical visit from Month 2 to Month 6. The mean percentage change and absolute change from baseline in plasma GL-3 showed trends in reductions at each visit during the study, but only the mean change at Month 6 was statistically significant. The percentage change and absolute change from baseline of urine GL-3 levels were not normally distributed, and thus medians were evaluated. The median percentage and absolute changes from baseline in urine GL-3 levels showed trends for reductions at every visit, but none of the changes from baseline in median urine GL-3 levels was statistically significant. Individual patient percentage changes in plasma lyso-GL-3 levels were relatively consistent across visits compared with changes in plasma GL-3 and urine GL-3. Among patients who tested positive for Fabrazyme antibodies, there was no discernible pattern observed between titres measured at any time point during the study and corresponding levels of lyso-GL-3, plasma GL-3, or urine GL-3 at these time points; however, patients

who tested negative for antibodies at baseline had among the lowest plasma levels of lyso-GL-3 and GL-3. Of the 7 patients who were sero-negative at baseline, 1 seroconverted at Month 2.

Gastrointestinal symptom patient-reported outcome (PRO) results are not reported. In order to avoid patients going through a period of time without treatment, a number of patients were switched to Fabrazyme prior to enrolment into this study. Historical blood and spot urine samples were collected from these patients to match the study time points (i.e., baseline, 2 months, and 4 months following the start of Fabrazyme as necessary, until the patient was enrolled in the study [signed the informed consent]), but PRO data could not be collected at baseline and often even at the 2- and 4-month time points, prior to consenting to participate in this study.

Safety results

The results from the safety assessments indicate that the switch from agalsidase α to agalsidase β does not result in any adverse effects. Only 1 non-serious AE of an infusion-associated reaction (IAR) was reported in 1 patient with a history of IARs during the first infusion of agalsidase β. Symptoms resolved completely after 2 days and the patient remained in the study.

1.3.3. Discussion on clinical aspects

This study demonstrates a dose effect of agalsidase α and agalsidase β on biomarker clearance when administered at their labelled doses to patients with Fabry disease. Plasma and urine glycosphingolipids were reduced after switching from 0.2 mg/kg of agalsidase α to 1.0 mg/kg of agalsidase β in patients who had previously been treated with agalsidase α for an average of 3.7 years (range: 1.6 through 14.0 years).

The results of this study suggest that plasma lyso-GL-3 may be a biomarker for short term treatment response. The most consistent responses of any of the glycosphingolipids measured after the switch to agalsidase β were seen for plasma lyso-GL-3, with statistically significant changes observed from baseline at Months 2, 4, and 6 and less variability in individual responses than in either plasma or urine GL-3. The decrease in plasma GL-3 was statistically significant at 6 months while a trend to lower median concentrations of urine GL-3 was observed at 6 months.

The safety of the switch from agalsidase α to agalsidase β is supported by this study. The one non-serious infusion associated reaction AE reported during the first infusion was mild and reversible after 2 days. Finally, the data also suggest that both products have common epitopes and comparable immunogenicity.

2. CHMP's overall conclusion and recommendation

This switch study suggests that treatment with agalsidase β will lead to lower plasma lyso-GL-3 concentrations. The clinical relevance of this observation remains to be established. As a biomarker for the follow-up of the patient plasma lyso-GL-3 might be useful.

The B/R remains positive.

No changes in the SmPC are deemed necessary.

Overall conclusion

Recommendation

No changes in the SmPC are deemed necessary.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.