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Procedure Management and Committees Support Division

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

Myozyme

alglucosidase alfa

Procedure no: EMEA/H/C/000636/P46/054

Note

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

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1. Introduction

On 29.05.2015, the MAH submitted a completed paediatric study for MYOZYME, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure PAM 054.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study AGLU07510 "A Phase 3/4, Prospective, Multinational, Open-label, Noninferiority Study of Alglucosidase Alfa Manufactured at the 160 L and 4000 L Scales in Treatment Naive Patients with Infantile-Onset Pompe Disease" is a stand-alone study.
The MAH confirmed that study PEAS (AGLU07510) is not part of an approved Paediatric Investigation Plan. The MAH has not identified any new paediatric information from this study that would need to be added to the EU Product Information.
The MAH also informed that a small clinical trial to investigate pharmacodynamics aspects (EMBASSY (AGLU07310)) in Late -Onset Pompe Disease was conducted and completed.

2.2. Information on the pharmaceutical formulation used in the study

In the United States (US), alglucosidase alfa produced at the 160 L research scale was approved for use by Pompe patients without limitation to age or age of onset. Alglucosidase alfa produced at the 4000 L scale was indicated for use in patients 8 years and older with late (noninfantile) onset Pompe disease (acid α-glucosidase [GAA] deficiency) who do not have evidence of cardiac hypertrophy.

In the European Union (EU) and other areas of the world, alglucosidase alfa produced at the 4000 L scale-up scale was approved on the basis of physico-chemical comparability to the previously approved intermediate scale product and is indicated for use by Pompe patients without limitation to age or age of onset.

This study was intended to provide clinical safety, efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) data to support comparability of alglucosidase alfa manufactured at the 160 L scale (Myozyme in the United States [US]) and 4000 L scale (Lumizyme in the US/ Myozyme throughout the rest of world), in order to support expansion of the indication of Lumizyme in the US to include infantile-onset Pompe disease patients.

With the approval on 1 August 2014 for the supplement to expand the indication for Lumizyme in the US to include all Pompe patients irrespective of age or phenotype, the Food and Drug Administration (FDA) determined that both production scales of 160 L alglucosidase alfa and 4000 L alglucosidase alfa are biochemically and clinically comparable. In light of this approval by the FDA, the justification for continuing to run this study no longer existed and, therefore, Genzyme terminated the study early.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

- A Phase 3/4, Prospective, Multinational, Open-label, Noninferiority Study of Alglucosidase Alfa Manufactured at the 160 L and 4000 L Scales in Treatment Naïve Patients with Infantile-Onset Pompe Disease (study number EFC12722 / AGLU07510).

2.3.2. Clinical study

Description

This study is a non-randomised, open-label, multicentre, multinational study of patients ≤12 months of age at study entry who had been diagnosed with infantile-onset Pompe disease.

All patients received IV infusion of 20 mg/kg of body weight qow of alglucosidase alfa produced at the 160 L scale (US patients) or at the 4000 L scale (non-US patients).

Methods

Objective(s)

The **primary objective** was to demonstrate the non-inferiority of alglucosidase alfa produced at the 4000 L scale to the 160 L scale product in terms of the change from baseline of the left ventricular mass index Z-score (LVMI-Z) after 52 weeks of treatment.

Secondary objectives were to:

- compare alglucosidase alfa produced at the 4000 L scale to the 160 L scale relating to the estimated probabilities of survival to Week 52;
- compare alglucosidase alfa produced at the 4000 L scale to the 160 L scale relating to the estimated probabilities of invasive ventilator-free survival to Week 52;
- compare the survival and invasive ventilator-free survival of the 160 L and 4000 L treatment arms to an untreated historical cohort at 12 months of age;
- assess motor development in treated patients;
- compare the safety profile of alglucosidase alfa produced at the 160 L and 4000 L scales.

The **tertiary objectives** were to:

- assess physical growth in treated patients;
- determine the PK profile of alglucosidase alfa produced at the 160 L and 4000 L scales;
- assess the effect of treatment on the change in urinary oligosaccharide (HEX4) levels.

Study design

The study was a non-randomized, open-label, multicenter, multinational study of patients less than or equal to 12 months of age at study entry who had been diagnosed with infantile-onset Pompe disease.

Patients received an intravenous (IV) infusion of recombinant human acid α glucosidase (rhGAA, alglucosidase alfa, manufactured at the 160 L or 4000 L scale dependent on region) at a dose of 20 mg/kg of body weight every 2 weeks

Study population /Sample size

Study population

In this study, patients had documented GAA enzyme deficiency with subsequent genotyping for diagnosis confirmation, were naïve to alglucosidase alfa treatment, were cross-reactive immunologic material positive, did not have decompensated heart failure or a major congenital abnormality, and were invasive ventilator-free at enrolment.

Sample size

Per the protocol, it was planned to enrol 24 patients into the study with the aim of obtaining an analysis population of 20 evaluable patients. However, only 4 patients were enrolled and treated by the time of the FDA approval on 1 August 2014.

Five patients were screened. One (1) patient, who required invasive ventilator support at screening, was a screen failure. Overall, 4 patients were enrolled and treated.

Treatments

In the study, patients received alglucosidase alfa produced at the 160 L scale (US patients) or at the 4000 L scale (non-US patients).

The total amount of alglucosidase alfa administered was adjusted to account for changes in body weight. All patients received IV infusion of 20 mg/kg of body weight qow.

Outcomes/endpoints

Efficacy:

The **primary** efficacy endpoint was change in LVMI-Z from baseline to Week 52.

Secondary endpoints were:

- estimated probability of survival to Week 52;
- estimated probability of invasive ventilator-free survival to Week 52;
- change in motor development status from baseline to Week 52 as assessed by the Gross Motor Function Measure – 88 Scale (GMFM-88) total percent scores.

Tertiary endpoints were:

- change in body length, weight, and head circumference from baseline to Week 52;
- PK parameters (maximal concentration [C_{max}], time to maximal concentration [T_{max}], area under the curve from first to last timepoints [AUC_{0-t}], clearance (CL), peripheral volume of distribution [V_z], volume of distribution at steady state [V_{ss}]), and half-life [$t_{1/2}$]) at baseline (Day 1), Week 12, and Week 52;
- change in urinary HEX4 levels from baseline to Week 52.

Safety:

Safety was evaluated in terms of continuous monitoring of AEs (all treatment-emergent AEs and events by relationship, seriousness, and severity), IARs, events occurring on the day of infusion and up to 48 hours (2 days) after infusion, and discontinuations due to AEs. Scheduled clinical and laboratory safety assessments include: clinical hematology, chemistry (including brain natriuretic peptide [BNP]), and urinalysis; anti-rhGAA immunoglobulin G (IgG) antibody and inhibitory antibody formation in patients testing positive for IgG; vital signs (blood pressure, heart rate, respiratory rate, and temperature); physical examinations; and electrocardiograms (ECGs).

Additional individual safety assessments conducted when clinically indicated and approved by the Global Safety Officer include (1) circulating immune complex detection; and (2) IgE, serum tryptase, and complement activation, following moderate, severe, or recurrent IARs suggestive of hypersensitivity reactions (IgE-mediated).

Statistical Methods

The number of patients included in this study did not provide sufficient power to conduct the statistical analysis as outlined in the protocol.

The Full Analysis Set consisted of all patients who received at least 1 infusion of alglucosidase alfa. Four (4) patients were in this data set. This study population was used for all analyses, including demographics, safety, and efficacy.

Results

- ***Recruitment / Number analysed***

The study started on 21 August 2012 (first patient enrolled) and ended on 01 December 2014 (last patient completed). In total, 4 patients with infantile-onset Pompe disease were enrolled and analysed. One (1) fifth patient, who required invasive ventilator support at screening, was a screen failure. All the 4 other patients were screened and treated with alglucosidase alfa: 1 patient received alglucosidase alfa manufactured at the 4000 L scale and 3 patients received alglucosidase alfa manufactured at the 160 L scale.

Prior to termination of the study, 2 patients in the 160 L group completed the study. The 1 patient in the 4000 L group discontinued due to termination of the study, and 1 patient in the 160 L group discontinued due to physician's decision.

- ***Baseline data***

The mean age of the patients at enrolment was 0.5 years. The mean body mass index at enrolment was 14.8 kg/m2 (range 11.2 to 16.9 kg/m2). The race/ethnicity was different among the 4 patients enrolled (black, white, multiple).

None of the patients enrolled were ventilator dependent at baseline.

All prior and concomitant medications and therapeutic procedures in this paediatric population were consistent with the patients' underlying Pompe disease and intercurrent illnesses.

- ***Efficacy results***

Efficacy was evaluated for the FAS, which included all 4 study patients

Group	**160 L group**			**4000 L group**
Patient				
Treatment duration (weeks)	52	52	31	30
Weight (kg)				
Baseline	6.5	8.9	6.2	4.1
last recorded visit	10.3	12	11.6	7.7
Height (cm)				
Baseline	64.7	72.5	63	60.5
last recorded visit	82	84.7	79.6	79.5
Head Circumference (cm)				
Baseline	41	45.3	40.6	38.4
last recorded visit	51.5	47.5	46	45

Primary efficacy variable: Change from baseline LVM-Z

Due to the presence of cardiomegaly in all 4 patients, most of the patients had a high z-score at baseline. All but 1 patient showed improvement during the course of the study.

Secondary efficacy variables:

Ventilator-free survival: Three of the four patients did not use a ventilator during their time on the study (patient began non-invasive ventilator use at Week 10, which was continuing at study discontinuation).

Motor development status and performance change: Only 1 patient declined in motor function during the trial; all other subjects improved in GMFM-88 total percent score and improved or remained the same for Dimension scores.

Agency on efficacy:

In order to support expansion of the indication of Lumizyme (alglucosidase alfa) in the US to include infantile-onset Pompe disease patients, Genzyme designed and implemented this study to assess the comparability of alglucosidase alfa produced at the 160 L and 4000 L scales in treatment naïve patients with classical infantile-onset Pompe disease

The expected duration of treatment with alglucosidase alfa (manufactured at either the 160 L or 4000 L scale) was 52 weeks (364 days) and it was planned to enrol 24 patients into the study with the aim of obtaining an analysis population of 20 evaluable patients.

However, with the approval for the supplement indication in the US on 1 August 2014, the MAH considered that the justification for continuing the study no longer existed and terminated the study early.

During this period, only 4 patients were included and only two (both treated with 160 L scales) reached the 52 weeks duration of treatment.

The very low number of patients included in this study did not provide sufficient power to conduct the statistical analysis and no conclusion can be drawn regarding the comparability of alglucosidase alfa produced at the 160 L and 4000 L scales.

- ***Safety results***

Extent of exposure

The 4 patients who received alglucosidase alfa in AGLU07510 study comprise the safety population for this report.

Group	**160 L group**			**4000 L group**
Patient				
Treatment duration (weeks)	52	52	31	30
Total number of doses received	27	31	26	16
Dose adjustment	None	10 mg/kg/week instead of 20 mg/kg/qow (between Week and Week 25) + premedication	20 mg/kg/week instead of qow (from Week 13)	None
Reason for dose adjustment	Not applicable	Recurrent IARs	SAE of respiratory failure	Not applicable

Study course	completed	completed	discontinued	discontinued

Patient was on alglucosidase alfa manufactured at the 160 L scale for 31 weeks and received a total of 26 doses. Patient was on alglucosidase alfa manufactured at the 160 L scale for 52 weeks and received a total of 31 doses. Patient was on alglucosidase alfa manufactured at the 4000 L scale for 30 weeks and received a total of 16 doses. Patient was on alglucosidase alfa manufactured at the 160 L scale for 52 weeks and received a total of 27 doses.

Two (2) patients in 160 L group had dose adjustments during the study. Due to an ongoing SAE of respiratory failure, patient received 20 mg/kg/week instead of qow starting Week 13 and until study discontinuation. As a result of recurrent IARs, patient received 10 mg/kg/week instead of 20 mg/kg/qow between Week 11 and Week 25, as well as premedication of corticosteroids and H2 receptor antagonists; study drug dose of 20 mg/kg/qow was resumed at Week 26.

Adverse events

A total of **68 treatment emergent adverse events** (AEs) were reported in 4 patients (overall safety population). All 4 patients reported at least 1 TEAE.

The majority of AEs were non-serious (55/68 AEs), mild to moderate in severity (65/68 AEs) and assessed as unrelated to the study drug (57/68 AEs). A majority of treatment-related AEs (10/11 AEs) were IARs and were reported in 2 patients.

Three AEs (3/68 AEs) were assessed as severe in 2 patients (experienced respiratory failure and experienced cardiac failure and pulmonary oedema). These 3 TEAEs were also SAEs.

The treatment-emergent adverse events, without regard to causality are summarised in Table 14.3.

TABLE 14.3
Adverse Events
Full Analysis Population

	Alglucosidase Alfa 4000L (N=1)		Alglucosidase Alpha 160L (N=3)	
System Organ Class Preferred Term	Events n	Patients n (%)	Events n	Patients n (%)
Patients with Events	5	1 (100.0)	63	3 (100.0)
Blood and lymphatic system disorders	0	0 (0.0)	1	1 (33.3)
Anaemia	0	0 (0.0)	1	1 (33.3)
Cardiac disorders	0	0 (0.0)	6	2 (66.7)
Cardiac failure	0	0 (0.0)	3	2 (66.7)
Cardiac failure congestive	0	0 (0.0)	1	1 (33.3)
Cardiomyopathy	0	0 (0.0)	1	1 (33.3)
Nodal rhythm	0	0 (0.0)	1	1 (33.3)
Ear and labyrinth disorders	0	0 (0.0)	1	1 (33.3)
Middle ear effusion	0	0 (0.0)	1	1 (33.3)
Gastrointestinal disorders	1	1 (100.0)	5	1 (33.3)
Abdominal pain	1	1 (100.0)	0	0 (0.0)
Diarrhoea	0	0 (0.0)	1	1 (33.3)
Vomiting	0	0 (0.0)	4	1 (33.3)

General disorders and administration site conditions	3	1 (100.0)	12	3 (100.0)
Device occlusion	0	0 (0.0)	1	1 (33.3)
Infusion site erythema	0	0 (0.0)	1	1 (33.3)
Pyrexia	3	1 (100.0)	10	3 (100.0)
Infections and infestations	0	0 (0.0)	12	3 (100.0)
Adenovirus infection	0	0 (0.0)	1	1 (33.3)
Bronchitis	0	0 (0.0)	1	1 (33.3)
Croup infectious	0	0 (0.0)	1	1 (33.3)
Eye infection	0	0 (0.0)	1	1 (33.3)
Fungal infection	0	0 (0.0)	1	1 (33.3)
Lobar pneumonia	0	0 (0.0)	1	1 (33.3)
Nasopharyngitis	0	0 (0.0)	1	1 (33.3)
Otitis media acute	0	0 (0.0)	1	1 (33.3)
Pneumonia	0	0 (0.0)	1	1 (33.3)
Respiratory syncytial virus infection	0	0 (0.0)	1	1 (33.3)
Upper respiratory tract infection	0	0 (0.0)	1	1 (33.3)
Urinary tract infection	0	0 (0.0)	1	1 (33.3)

TABLE 14.3
Adverse Events
Full Analysis Population

	Alglucosidase Alfa 4000L (N=1)		Alglucosidase Alpha 160L (N=3)	
System Organ Class Preferred Term	Events n	Patients n (%)	Events n	Patients n (%)
Injury, poisoning and procedural complications	0	0 (0.0)	1	1 (33.3)
Arthropod bite	0	0 (0.0)	1	1 (33.3)
Investigations	0	0 (0.0)	1	1 (33.3)
Oxygen saturation decreased	0	0 (0.0)	1	1 (33.3)
Musculoskeletal and connective tissue disorders	0	0 (0.0)	1	1 (33.3)
Muscle contracture	0	0 (0.0)	1	1 (33.3)
Nervous system disorders	0	0 (0.0)	3	3 (100.0)
Hypotonia	0	0 (0.0)	1	1 (33.3)
Nystagmus	0	0 (0.0)	1	1 (33.3)
Syncope	0	0 (0.0)	1	1 (33.3)
Respiratory, thoracic and mediastinal disorders	1	1 (100.0)	11	2 (66.7)
Aspiration	0	0 (0.0)	1	1 (33.3)
Asthma	0	0 (0.0)	1	1 (33.3)
Bronchial secretion retention	1	1 (100.0)	0	0 (0.0)
Cough	0	0 (0.0)	1	1 (33.3)
Hypoxia	0	0 (0.0)	1	1 (33.3)
Nasal congestion	0	0 (0.0)	2	1 (33.3)
Pleural effusion	0	0 (0.0)	1	1 (33.3)
Respiratory, thoracic and mediastinal disorders (contd)				
Pulmonary oedema	0	0 (0.0)	1	1 (33.3)
Respiratory disorder	0	0 (0.0)	1	1 (33.3)
Respiratory failure	0	0 (0.0)	1	1 (33.3)
Rhinorrhoea	0	0 (0.0)	1	1 (33.3)
Skin and subcutaneous tissue disorders	0	0 (0.0)	7	2 (66.7)
Dermatitis contact	0	0 (0.0)	1	1 (33.3)
Dermatitis diaper	0	0 (0.0)	1	1 (33.3)
Rash erythematous	0	0 (0.0)	1	1 (33.3)
Rash pruritic	0	0 (0.0)	1	1 (33.3)
Urticaria	0	0 (0.0)	3	2 (66.7)
Vascular disorders	0	0 (0.0)	2	1 (33.3)
Hypotension	0	0 (0.0)	2	1 (33.3)

The most frequently reported TEAE, regardless of relationship to alglucosidase alfa, was pyrexia (13 events). The next most common TEAEs, regardless of relationship to alglucosidase alfa, were vomiting

(4 events), cardiac failure (3 events), and urticaria (3 events). Patient (160 L group) experienced the most TEAEs (n=25).

There were **11 events** that were considered **related** or possibly related to alglucosidase alfa, of which the most common were pyrexia (4 events) and urticaria (3 events). The remaining 4 events that were considered related or possibly related to alglucosidase alfa were oxygen desaturation, hypotension, infusion site erythema, and nystagmus.

Death and study discontinuations for safety reasons

Two patients completed AGLU07510 study.

There were no AEs leading to discontinuation from the study.

There were 11 TEAEs that led to a change in the study drug dose. The most common events that led to an interruption in the study drug were pyrexia (3 events) and urticaria (3 events). Two additional events (adenovirus infection and pulmonary oedema) also led to a study drug interruption. There were 3 events (all experienced by Patient in 160 L group) that led to an increase in the study drug dose: respiratory failure, muscle contracture, and hypotonia.

There were no deaths during the study.

Other serious adverse events

A total of 13 treatment-emergent SAEs (13/68 AEs) were experienced by 3 patients, all in the 160 L groups (3/4 of the overall safety population) during the study.

All SAEs experienced during treatment with alglucosidase alfa are summarized by patient in the Tables below.

Patient [redacted]

Patient ID	Description	Verbatim Term (Preferred Term)	Intensity	Relationship/Outcome
[redacted]	SAE	Right upper lobe pneumonia (Lobar pneumonia)	Moderate	Not related/Recovered
	SAE	Respiratory insufficiency (Respiratory failure)	Severe	Not related/Not recovered
	SAE	Profound hypotonia (Hypotonia)	Moderate	Not related/Not recovered
	SAE	Fever (Pyrexia)	Mild	Possibly related/ Recovered
	SAE	Acute otitis media (Otitis media acute)	Mild	Not related/Recovered

Patient [redacted]

Patient ID	Description	Verbatim Term (Preferred Term)	Intensity	Relationship/Outcome
[redacted]	SAE	Syncope (Syncope)	Moderate	Not related/Recovered
	SAE	Urticaria (Urticaria)	Moderate	Related/Recovered
	SAE	Urticaria (Urticaria)	Moderate	Related/Recovered
	SAE	Adenovirus infection (Adenovirus infection)	Mild	Not related/Recovered
	SAE	Heart/Cardiac failure (Cardiac failure)	Severe	Not related/Recovered
	SAE	Pulmonary edema (Pulmonary oedema)	Severe	Not related/Recovered

Patient [redacted]

Patient ID	Description	Verbatim Term (Preferred Term)	Intensity	Relationship/Outcome
[redacted]	SAE	Upper respiratory infection (Upper respiratory tract infection)	Moderate	Not related/Recovered with sequelae
	SAE	Respiratory syncytial virus (RSV) infection (Respiratory syncytial virus infection)	Mild	Not related/Recovered

The majority of SAEs were unrelated to study drug.

Of the 13 events, 3 were considered related or possibly related to the study drug (these 3 were IARs). Patient experienced an SAE of pyrexia that was mild in severity and was considered possibly related to the study drug. The study drug was interrupted and the event resolved. Patient experienced 2 SAEs of urticaria. Both events were considered moderate in severity and related to the study drug. The study drug was interrupted due to both events, and both events resolved.

Other significant adverse events

Infusion associated reactions

An IAR was defined by Genzyme as AEs that occur during the infusion or within up to 24 hours after the start of infusion and are considered as related or possibly related to the ERT by the Investigator or the Sponsor. An event occurring ≥24 hours after the start of an infusion may be judged an IAR if a delayed reaction is considered possible by the Investigator or Sponsor.

Ten (10) IARs (at any severity grade) were reported in 2 patients (160 L group).

Patient experienced 4 events of pyrexia, all of which were mild in severity and eventually resolved. One (1) of these pyrexia events was an SAE. The other IARs this patient experienced were non-serious and included decreased oxygen saturation, hypotension, and urticaria. Patient experienced 2 events of urticaria, both of which were SAEs, moderate in severity, and eventually resolved. The other IAR experienced by this subject was infusion site erythema (non-serious), which started after infusion completion and lasted for 55 minutes. All other IARs experienced by Patient and occurred during infusion. No IARs were assessed as severe in severity, and all events eventually resolved.

Immunogenicity

Patient (4000 L group) did not test positive for IgG antibodies (seronegative) during the study. The remaining 3 patients (160 L group) did test positive for IgG antibodies (seropositive), however, there were no cases of enzyme activity inhibition, and only Patient tested positive for enzyme uptake inhibition at a single timepoint.

Patient (160 L group) seroconverted at Week 4 with an IgG titer of 1600. The maximum IgG titer for this patient during the study was 102400 from Week 26 to Week 31. Neutralizing antibody titer for this patient during the study was found to be positive once (titer of 20 at Week 26). Patient (160 L group) seroconverted at Week 4 with an IgG titer of 3200. The maximum IgG titer for this patient during the study was 25600 at Week 8. This patient did not test positive for neutralizing antibody during the study. Patient (160 L group) seroconverted at Week 4 with an IgG titer of 200. The maximum IgG titer for this patient during the study was 1600 from Week 8 to Week 18. This patient did not test positive for neutralizing antibody during the study.

For 2 patients (in 160 L group), IgE testing was performed and results for both patients were negative. Complement testing was performed for 2 patients; of these 2 patients tested, 1 tested positive for complement activation. Patients and were also tested for serum tryptase (4.7 and 3.1 μg/L, respectively); results were within the normal range (normal range: $\leq$12.5 μg/L).

Laboratory parameters

Individual patient changes in laboratory values

No worsening was observed from baseline to Week 52/early termination visit in results classified by the central lab to be at the panic level or requiring notification of the site or patient by telephone call.

Individual clinically relevant abnormalities in laboratory values

Elevated levels of creatine kinase, creatine kinase muscle-brain isoform, aspartate transaminase (AST), and alanine transaminase (ALT) have been observed in untreated infantile-onset Pompe patients (van den Hout, 2003, Pediatrics), are consistent with the underlying muscle disease, and are not related to liver pathology. Study patients typically exhibited abnormal values for selected laboratory assessments ALT, AST, creatine kinase, and lactate dehydrogenase.

No chemistry or hematology laboratory results classified by the central lab to be at the panic level or requiring notification of the site or patient by telephone call were reported as an AE (either serious or non-serious).

Vital signs and physical examination

Adverse events associated with abnormal vital signs and physical exam findings were discussed in the TEAE section.

Agency on safety:

One of the objectives of this study was to compare the safety profile of alglucosidase alfa produced at the 160 L and 4000 L scales.

The safety population of study AGLU07510 included 4 patients: 1 patient received alglucosidase alfa manufactured at the 4000 L scale and 3 patients received alglucosidase alfa manufactured at the 160 L scale. We agree that this number of patients did not provide sufficient power to conduct the statistical analysis.

Two patients (2/4) completed the study. There were no deaths during the study.

All patients experienced AEs. A total of 68 AEs were reported in both groups during the 52-week study: 5/68 of total AEs in the alglucosidase alfa 4000L treatment group, and 63/68 in the alglucosidase 160L treatment group. No relevant comparison of these proportions could be performed due to the study size. The majority of AEs were non-serious (55/68 AEs), assessed as mild to moderate in severity (65/68 AEs), and unrelated to the treatment (57/68 AEs). Three patients, all in the alglucosidase alfa 160 L group, experienced 11 AEs that were assessed by the investigator as related to alglucosidase alfa. Regardless of causality, AEs belonged to the main following SOCs: General disorders and administration site conditions (15/68 AEs), Infections and infestations (12/68 AEs), and Respiratory disorders (12/68 AEs). Ten treatment-related AEs (10/11 AEs) were characterized as IARs. The majority of IARs (all occurred in the 3 patients of 160 L group) were non-serious, mild in severity and resolved with symptomatic treatment; all patients with IARs recovered without sequelae.

No anaphylactic/allergic reactions were reported. Of 4 assessable patients, the 3 patients in the alglucosidase alfa 160 L group did test positive for IgG antibodies (seropositive), however, there were no cases of enzyme activity inhibition, and only one patient (160 L group) tested positive for enzyme uptake inhibition at a single timepoint. The peak IgG titers in these patients was equal to or below 102400 and 1 patient tested inhibitory antibody positive. IgE testing was performed in 2 patients, which was negative. Complement activation was positive in 1 of these patients and serum tryptase testing was normal in both patients.

During AGLU07510 study, treatment-related AEs (mainly IARs) were reported in 2 patients in the alglucosidase alfa 160 L group. Due to the small size of this study, no relevant comparative assessment of AEs frequency could be drawn between patients treated with alglucosidase alfa produced at the 160 L and 4000 L scales. Nevertheless, based on the data provided by the MAH, the final results of study AGLU07510 do not raise any new safety concerns as compared to previous studies and experiences in infantile-onset patients treated with alglucosidase alfa at a dose of 20 mg/kg qow.

2.3.3. Discussion on clinical aspects

Due to termination of the study and to the low number of patients included (4 patients instead of 24) this study did not provide sufficient power to conduct the statistical analysis, thus no conclusion can be drawn regarding the comparability of alglucosidase alfa produced at the 160 L and 4000 L scales.

During AGLU07510 study, treatment-related AEs (mainly IARs) were reported in 2 patients in the alglucosidase alfa 160 L group. Due to the small size of this study, no relevant comparative assessment of AEs frequency could be drawn between patients treated with alglucosidase alfa produced at the 160 L and 4000 L scales. Nevertheless, based on the data provided by the MAH, the final results of study AGLU07510 do not raise any new safety concerns as compared to previous studies and experiences in infantile-onset patients treated with alglucosidase alfa at a dose of 20 mg/kg qow.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled**

☐ **Not fulfilled**

4. Additional clarification requested

None