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

Cerezyme

Imiglucerase

Procedure no: EMEA/H/C/000157/P46/047

Note

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

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1. Introduction

On 12 April 2024 the MAH submitted a completed paediatric study for Cerezyme, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures, requested by the Chinese authorities.

A short critical expert overview has also been provided.

Cerezyme (imiglucerase) was initially approved in the EU for adults and paediatrics with confirmed diagnosis of Gaucher disease type 1 who exhibit clinically significant visceral manifestations of the disease. Since 2003, the EU license has been extended to include treatment for non-neuronopathic symptoms of Gaucher disease type 3.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that LPS16031 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

There is no specific paediatric formulation of imiglucerase. The used formulation is a powder or solution for injection, which was administered by IV infusion over 1-2 hours every two weeks.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study LPS16031; a Phase 4, open label study to assess the efficacy and safety of imiglucerase treatment in Chinese participants with Gaucher disease type 3.

2.3.2. Clinical study LPS16031

Description

This study was conducted as a post marketing surveillance (PMS) study to fulfil the Agency requirement in China and included 8 paediatric participants <18 years of age.

Methods

Study participants

Enrolled in this study were patients diagnosed with GD type 3 with neurological manifestations and naïve to ERT. Patients should be above 2 years of age and have a spleen and/or liver volume larger than upper limit of normal (ULN) at Screening.

Treatments

Cerezyme (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dose would be 60 U/kg once every 2 weeks. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration. Dosage adjustments should be made on an

individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the participant's clinical manifestations.

Objective(s)

The primary objectives were:

- To evaluate the efficacy on hematologic manifestations
- To evaluate the safety profile of imiglucerase in maximum dose in the label (60U/kg, IV biweekly).

The secondary objectives were:

- To evaluate the efficacy on visceral manifestations
- To evaluate the efficacy on bone disease
- To evaluate the effect on quality of life

Outcomes/endpoints

Primary efficacy endpoint: the mean changes in hemoglobin and platelet count between baseline and the end of 12 months.

The primary safety endpoint was assessed by Adverse events (AEs), changes from baseline through study completion in laboratory tests (clinical chemistry, hematology, and urinalysis), vital signs, physical examination, 12-lead electrocardiogram (ECG).

Secondary endpoints:

- Mean changes from baseline to 12 months in spleen and liver volume.
- Changes in frequency, duration and severity of bone pain and number of bone crises over the period of one year.
- the mean changes between baseline and the end of 3 months, 6 months, 9 months and 12 months in the Measurement Model for the Pediatric Quality of Life Inventory (PedsQL).

The efficacy criteria for success included improved and stable hematologic parameters (primary efficacy endpoint), organ volumes and bone disease that are defined below. The spleen volume assessments did not apply to patients who have had a total splenectomy.

Hematological Parameters

Hemoglobin level $\geq$ 110 g/L for women and children or $\geq$120 g/L for male in 1 year,

AND

Increase platelet counts sufficiently to prevent surgical, obstetrical, and spontaneous bleeding:

- Nonsplenectomized patients with thrombocytopenia $> 50\times10^9$/L should increase 1.5- to 2-fold from baseline
- Nonsplenectomized patients with thrombocytopenia $< 50\times10^9$/L should increase 1.5-fold from baseline
- Splenectomized patients with thrombocytopenia should normalize in 1 year

Organ Volume

If applicable, spleen volume (in MN) should decrease by 30%-50% from Screening

AND

If applicable, liver volume (in MN) should decrease by 20%-30% from Screening

Bone Disease

Reduction or remission in bone pain.

AND

Remission of bone crises

Sample size

Sample size and power: approximately 12 patients would be assigned to study intervention in order to yield at least 10 evaluable patients at the end of 52 weeks. Patient drop-out rate would be monitored for the purpose of adjusting the sample size. Considering the small sample size, the 95% confidence interval was calculated using a t-distribution, assuming the standard deviation of ~0.559. With 10 assessable patients at the end of the study, the precision of the mean of the change of haemoglobin from baseline to 12 months will be 0.5 g/dL, or 31%.

Randomisation and blinding (masking)

Statistical Methods

Analyses populations were defined as follows:

- Evaluable population: All subjects without key protocol deviations
- Safety population: All subjects who received at least 1 dose of study intervention

Handling of missing data:

For the subjects who early terminate the treatment and whose efficacy is not observed at the end of 12 months of treatment, the analysis variables will be carried forward by last observation carried forward (LOCF) method.

Analysis of efficacy:

The paired t-test will be used to compare the changes in hemoglobin and platelet count measurements at baseline and at the end of 12 months of treatment.

The hemoglobin and platelet count at baseline and scheduled post-baseline visits will be analyzed using a mixed-effect model for repeated measures (MMRM), and the modified mean and its 95% confidence interval for each visit will be calculated. Baseline values will be included as covariates in the model.

Splenectomized and non-splenectomized patients will be distinguished. The number, mean, standard deviation, median, maximum and minimum of hemoglobin and platelet counts at baseline and each scheduled post-baseline visit as well as changes from baseline will be summarized.

To assess the robustness of the analysis results, the following sensitivity analyses will be performed on changes from baseline in hemoglobin and platelet counts:

1) Sensitivity analysis 1 (including efficacy assessment results of another hospital): the efficacy assessment results of another hospital will be included in the efficacy data analysis, and the data analysis will be performed using MMRM model.

2) Sensitivity analysis 2 (results of subjects who completed the study): only subjects who completed 12 months of treatment and had no missing primary efficacy endpoint will be included in the sensitivity analysis 2 for efficacy analysis, and data analysis will be performed using the MMRM model.

3) Sensitivity analysis 3 (multiple imputation for missing data): missing data will be imputed using multiple imputation method, and the imputed data will be analysed using the MMRM model.

4) Sensitivity analysis 4 (excluding out-of-window efficacy assessment results at month 12): after excluding out-of-window efficacy assessment results at month 12, the number, mean, standard deviation, median, maximum and minimum of hemoglobin and platelet counts at baseline and at the end of 12 months of treatment and their changes from baseline will be summarized. The out-of-window efficacy assessment at Month 12 is defined as hematologic efficacy assessment at Month 12 which is performed beyond the window of 12*30 $\pm$ 7 days from the date of the first dose.

Spleen and liver volumes will be measured at screening, months 6 and 12, at dose change, at the time of significant clinical complications, and at early termination, if applicable. MRI will be used for volume measurements. At the study visit, if the patient's spleen volume (in MN) increases > 25% from the screening value, or the patient's liver volume (in MN) increases > 20% from the screening value, the corresponding volume measurement must be repeated within approximately 4 weeks. Values obtained from repeated measurements will be used for study analysis.

The efficacy analysis method of visceral manifestations is the same as that of hematology manifestations.

Results

Participant flow

A total of 13 patients were screened and 12 eligible patients were enrolled to receive the treatment. A total of 12 (100%) patients completed the treatment and completed the study.

Study conduct

A total of 2 (16.7%) patients had major protocol deviations. One patient failed to complete Visit 14 and Visit 15 due to COVID-19, and therefore results of efficacy and safety at the end of the study were not collected. This event was classified as a major protocol deviation of laboratory assessments/procedures because primary efficacy results were missing. In another patient, SAE was not reported within 24 hours as protocol required, causing a major protocol deviation of study procedures, as delayed reporting may pose a safety risk to the patient.

A total of 9 (75.0%) patients had minor protocol deviations due to COVID-19. The most frequent minor protocol deviation category due to COVID-19 was subject compliance/dose. Nine (75.0%) patients missed one or more doses or did not receive treatment within the window period. As these protocol deviations did not affect collection of primary efficacy data or cause missing of primary efficacy data, they were considered as minor deviations.

Prior and concomitant therapy

All 12 patients reported at least once prior medication usage. The most common previous medications were antiepileptics and cough and cold preparations (8 patients each, 66.7%), followed by drugs to treat anaemia (6 patients, 50.0%), vitamins (5 patients, 41.7%) and drugs for treatment of bone diseases (4 patients, 33.3%).

A total of 11 (91.7%) patients received concomitant medications during the study. The most common medication were antiepileptics and cough and cold preparations (reported by 8 patients each, 66.7%), followed by analgesics (5 patients, 41.7%), psycholeptics, vitamins (reported by 4 patients each, 33.3%) and systemic antibacterials (3 patients, 25.0%).

A total of 7 (58.3%) patients received prior non-pharmacological treatment. Among them, 3 (25%) patients had undergone total splenectomy, and 1 (8.3%) had undergone partial splenectomy. The other 3 patients had undergone appendicectomy, patent ductus arteriosus repair and bone operation.

Baseline data

A total of 9 (75.0%) patients were male, and 3 (25.0%) patients were female. Only one patient (8.3%) belonged to an ethnicity other than Han, while the rest of the patients were Han. There were 8 paediatric patients and 4 adult patients enrolled at screening. The median age of all patients was 16.0 (range: 3-58) years and the median BMI was 18.550 (range: 14.06-23.42) kg/m2. Two patients were 17 at the time of screening, and one became adult before starting the treatment, and the other during the course of 1-year treatment.

A total of 4 (33.3%) patients had a family history of Gaucher disease and all patients had neurological manifestations, including a history of one or more epileptic seizures (focal-onset seizures or generalized-onset seizures) and had changes in EEG (epileptic discharge or nonspecific abnormality).

Table 1: Baseline characteristics (all patients).

Parameters	Total, N=12 N(%)
Time from date of first symptom to this study (months)	
Mean (SD)	144.11 (137.07)
Median	119.05
Min, Max	4.4 - 536.2
Time from date of first diagnosis to this study (months)	
Mean (SD)	62.95 (40.72)
Median	71.65
Min, Max	3.4 - 126.5
Glucosylsphingosine (Lyso-GL-1) (ng/mL)	
Mean (SD)	340.046 (124.56)
Median	420.0

Min, Max	113.1 - 420.0
Hemoglobin (g/L)	
Mean (standard deviation)	123.7 (18.13)
Median	118.0
Min, Max	102 - 155
Platelet count (10 ^ 9/L)	
Mean (standard deviation)	193.7 (157.45)
Median	149.0
Min, Max	33, 515
Liver volume (MN)	
Mean (standard deviation)	1.805 (0.77)
Median	1.43
Min, Max	0.92 - 2.99
Spleen volume (MN)	N=8
Mean (standard deviation)	11.31 (5.86)
Median	13.51
Min, Max	4.15 - 18.91

Number analysed

All the 12 treated patients were included in the evaluable population and in safety population.

Efficacy results

Primary efficacy endpoints

The mean (SD) hemoglobin of 12 patients was 123.7 (18.13) g/L at baseline. The primary efficacy results of 11 patients were collected. At the end of treatment, the mean (SD) hemoglobin was 137.2 (17.47) g/L and the mean (SD) of change from baseline was 12.8 (11.33) g/L (P = 0.0038) (Table 2, Figure 1).

The last observation carried forward (LOCF) method was performed in all 12 patients who completed the study. Based on LOCF method, the mean (SD) hemoglobin was 136.8 (16.70) g/L, and the mean (SD) of change from baseline was 13.2 (10.87) g/L (P=0.0015).

After receiving 1-year treatment, all 12 patients with or without splenectomy reached the therapeutic goal for haemoglobin, with haemoglobin of ≥ 110 g/L in female and paediatric patients and ≥ 120 g/L in male patients.

The mean (SD) platelet count of 12 patients was 193.7 (157.45) $\times 10^9$/L at baseline. At the end of treatment, the mean (SD) platelet count was 277.4 (191.24) $\times 10^9$/L and the mean (SD) of change from baseline was 112.9 (98.09) $\times 10^9$/L (P = 0.0034) (

Table 2, Figure 2). Based on LOCF method, the mean (SD) platelet count was 304.9 (205.81) $\times 10^9$/L, and the mean (SD) of change from baseline was 111.3 (93.70) $\times 10^9$/L (P = 0.0017).

Ten out of 12 patients reached the therapeutic goal of platelet count normalization. Among them, platelet count in 6 out of 8 non-splenectomised patients and in 2 out of 4 splenectomised patients increased 1.5- to 2- fold from baseline. The platelet count remained normal in the other 2 splenectomised patients.

Results of changes in hemoglobin and platelet count at each time point in patients with splenectomy and without splenectomy showed a similar trend. For patients with splenectomy, at the end of treatment, the mean (SD) haemoglobin was 130.0 (13.75) g/L and the mean (SD) of change from baseline was 7.0 (3.00) g/L. The mean (SD) platelet count was 552.7 (97.14) $\times 10^9$/L and the mean (SD) of change from baseline was 227.7 (133.25) $\times 10^9$/L. For patients without splenectomy, at the end of treatment, the mean (SD) hemoglobin was 139.9 (18.75) g/L and the mean (SD) of change from baseline was 15.0 (12.68) g/L. The mean (SD) platelet count was 174.1 (69.90) $\times 10^9$/L and the mean (SD) of change from baseline was 69.9 (30.20) $\times 10^9$/L.

In all sensitivity analyses, compared with baseline, increased trend in hemoglobin and platelet count could be observed, which was consistent with primary efficacy analysis.

Table 2: Primary Efficacy Endpoint: Efficacy on Hematologic Manifestations (Efficacy in Hemoglobin and Platelet Count at the End of 12 Months) - Evaluable Population

Parameter	Visit	Measured Value N=12	Change from Baseline N=12
Hemoglobin (g/L)	Baseline		
	Number of subjects	12	
	Mean (standard deviation)	123.7 (18.13)	
	Median	118.0	
	Minimum-maximum	102 - 155	
	End of 12-month treatment		
	Number of subjects	11	11
	Mean (standard deviation)	137.2 (17.47)	12.8 (11.33)
	Median	137.0	10.0
	Minimum-maximum	118 - 165	2 - 35
	Change from baseline (paired t-test)		
	t-value	3.752	
	P-value	0.0038	
	End of 12-month treatment (LOCF)[1]		
	Number of subjects	12	12
	Mean (standard deviation)	136.8 (16.70)	13.2 (10.87)
	Median	135.0	10.0
	Minimum-maximum	118 - 165	2 - 35
	Change from baseline (paired t-test)		
	t-value	4.196	
	P-value	0.0015	
Platelet count (10^9/L)	Baseline		
	Number of subjects	12	
	Mean (standard deviation)	193.7 (157.45)	
	Median	149.0	
	Minimum-maximum	33 - 515	
	End of 12-month treatment		
	Number of subjects	11	11
	Mean (standard deviation)	277.4 (191.24)	112.9 (98.09)
	Median	209.0	77.0
	Minimum-maximum	108 - 663	30 - 330
	Change from baseline (paired t-test)		
	t-value	3.818	
	P-value	0.0034	
	End of 12-month treatment (LOCF)[1]		
	Number of subjects	12	12
	Mean (standard deviation)	304.9 (205.81)	111.3 (93.70)
	Median	225.0	77.0
	Minimum-maximum	108 - 663	30 - 330
	Change from baseline (paired t-test)		
	t-value	4.113	
	P-value	0.0017	

Figure 1: Line Chart of Mean Changes in Hemoglobin by Visit for All Subjects - Evaluable Population

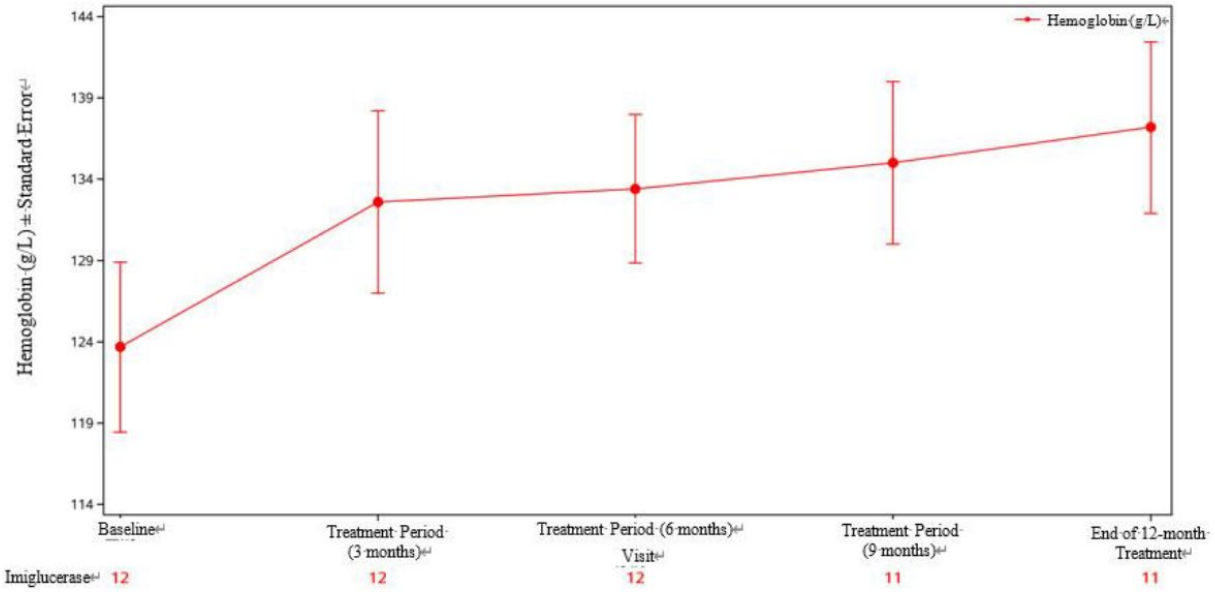
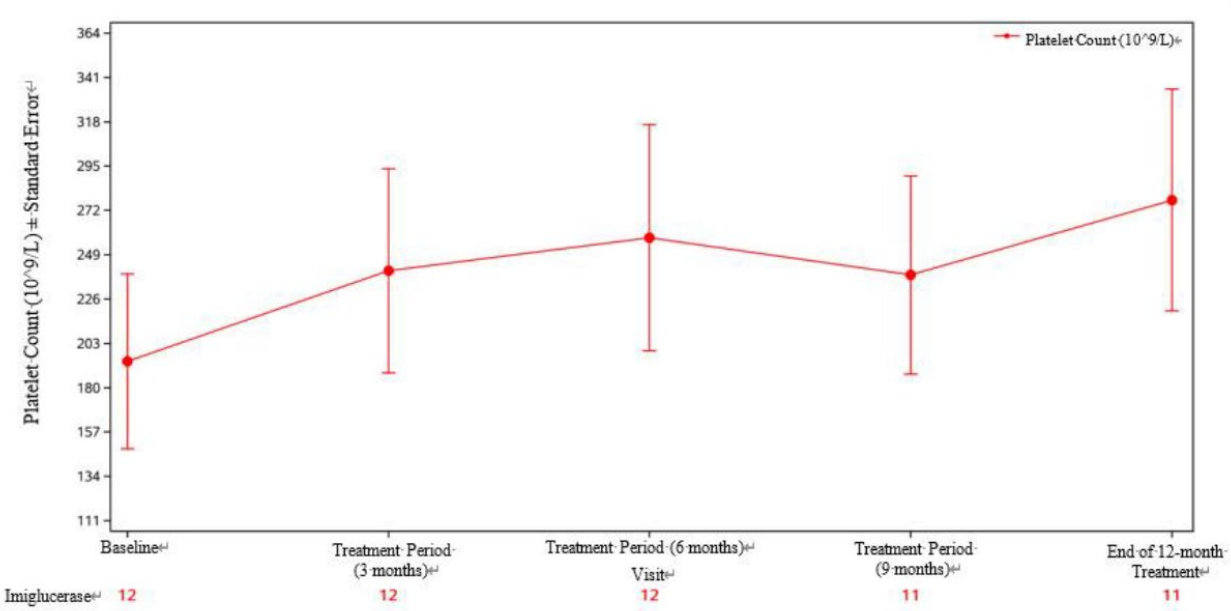


Figure 2: Line Chart of Mean Changes in Platelet Count by Visit for All Subjects - Evaluable Population



Secondary efficacy

At baseline, median (SD) spleen volume in 8 patients was 11.309 (5.862) MN. Seven patients had completed the study with end-of-treatment spleen volume results collected. Spleen volume decreased over one year of treatment with a mean reduction (SD) from baseline of 7.334 (4.393) MN (Figure 3). The LOCF method was performed in those 8 patients who completed the study. Based on LOCF method, the volume reduction (SD) from baseline was 6.418 (4.824) MN.

Baseline median (SD) liver volume in 12 patients was 1.805 (0.771) MN. Ten patients had completed the study with end-of-treatment liver volume results collected. At the end of treatment, a mean reduction (SD) from baseline was seen in liver volume of 0.558 (0.445) MN (Figure 4).

The LOCF method was performed in those 12 patients who completed the study. Based on LOCF method, the volume reduction (SD) from baseline was 0.482 (0.443) MN. The results indicated a decrease in spleen and liver volume after 12-month treatment.

Of the 8 non-splenectomy patients, 6 patients were observed to have a more than 40% reduction in spleen volume from baseline at the end of 12-month treatment, including 2 patients with a reduction of 70.8% and 80.9%, respectively. Four out of 8 non-splenectomised patients and 3 out of 4 splenectomised patients experienced more than 20% reduction in liver volume.

Figure 3: Line Chart of Changes in Spleen Volume by Visit for Individual Subjects - Evaluable Population

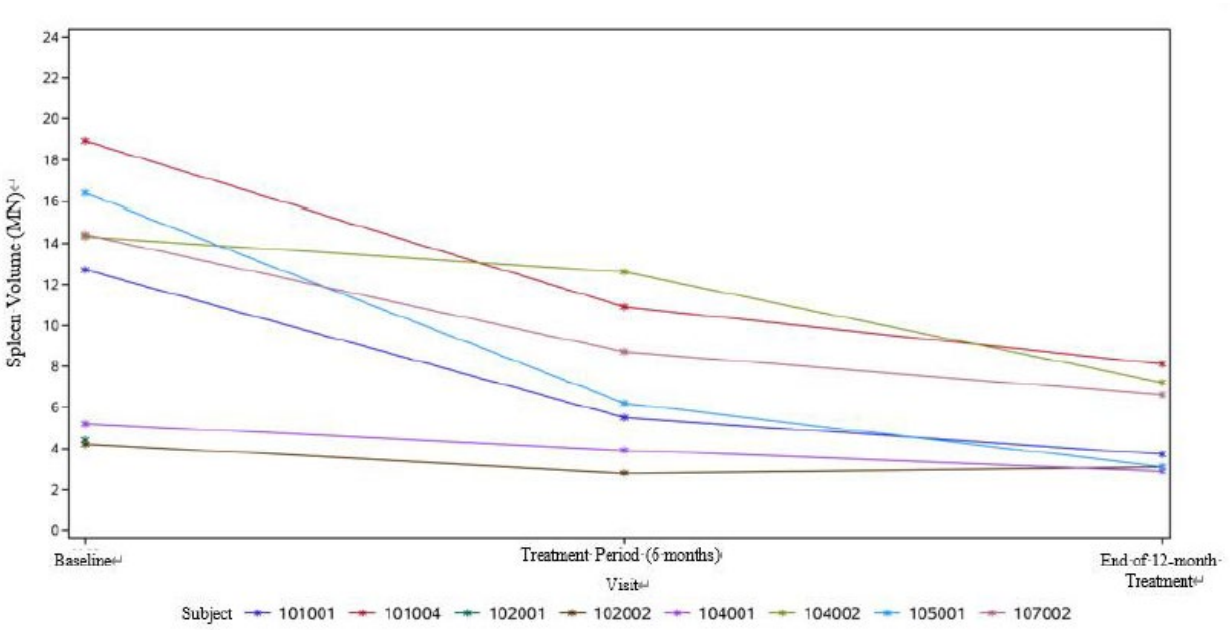
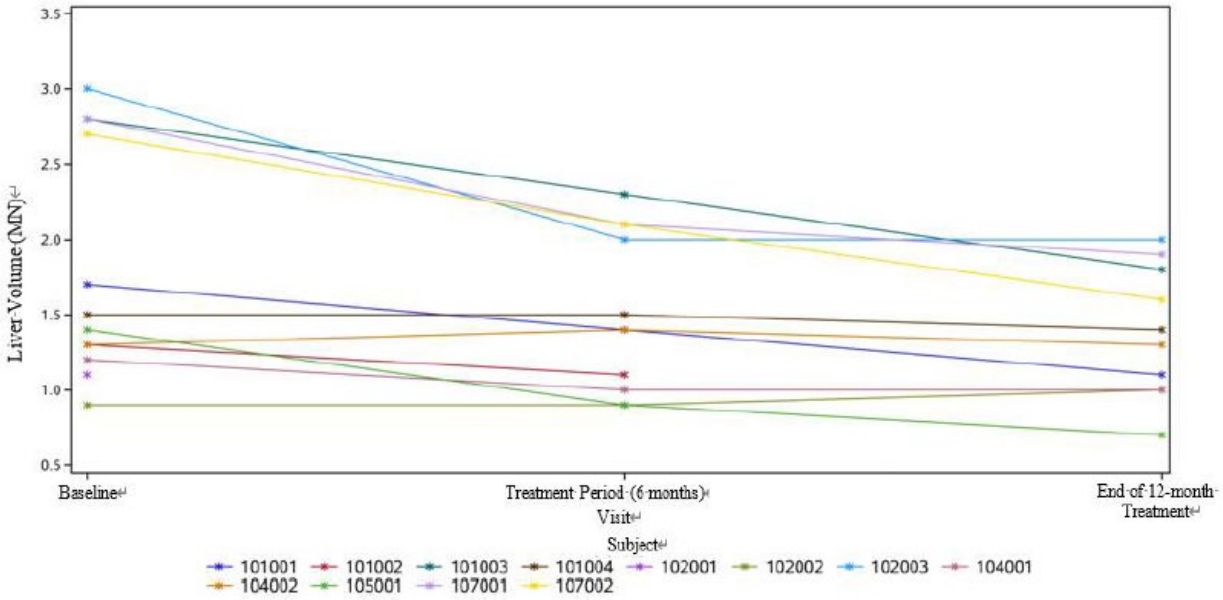


Figure 4: Line Chart of Changes in Liver Volume by Visit for Individual Subjects - Evaluable Population



Bone disease assessments and skeletal involvement

Mean values of total bone mineral density, T score and Z score increased at the end of 12-month treatment from baseline, while those of right femur decreased. The mean values of bone marrow burden score for femur and lumbar spine decreased at the end of 12-month treatment from baseline.

Mean frequency of bone pain increased over the treatment period whereas mean duration of bone pain and severity of bone pain decreased. Median values of frequency and duration of bone pain were not changed and remained 0 across the 12-month treatment. Median value of severity of bone pain decreased at the end of 12-month treatment from baseline. Bone crisis was not reported in any of the patients and during the study, no new bone crisis was reported.

Table 3: Secondary Efficacy Endpoint: Efficacy on Bone Disease (Efficacy in Frequency, Duration and Severity of Bone Pain and Number of Bone Crisis at the End of 12 Months) - Evaluable Population

Parameter	Visit	Measured Value N=12	Change from Baseline N=12
Frequency of bone pain (times/month)	Baseline		
	Number of subjects	9	
	Mean (standard deviation)	5.64 (9.994)	
	Median	0.00	
	Minimum-maximum	0.0 - 30.0	
	Pain on exertion or exertion	1 (8.3)	
	Intermittent or irregular pain	2 (16.7)	
	End of 12-month treatment		
	Number of subjects	10	8
	Mean (standard deviation)	16.95 (43.208)	14.84 (47.750)
	Median	0.00	0.00
	Minimum-maximum	0.0 - 137.0	-9.7 - 132.7
	Pain on exertion or exertion	1 (8.3)	
	Intermittent or irregular pain	1 (8.3)	
Duration of bone pain (minutes)	Baseline		
	Number of subjects	8	
	Mean (standard deviation)	48.9 (115.51)	
	Median	0.0	
	Minimum-maximum	0 - 330	
	Pain on exertion or exertion	1 (8.3)	
	Intermittent or irregular pain	2 (16.7)	
	Persistent pain	1 (8.3)	
	End of 12-month treatment		
	Number of subjects	9	7
	Mean (standard deviation)	1.2 (3.31)	-54.3 (119.28)
	Median	0.0	0.0
	Minimum-maximum	0 - 10	-320 - 0
	Pain on exertion or exertion	1 (8.3)	
	Intermittent or irregular pain	1 (8.3)	
	Persistent pain	1 (8.3)	
Severity of bone pain	Baseline		
	Number of subjects	12	
	Mean (standard deviation)	2.04 (2.340)	
	Median	1.50	
	Minimum-maximum	0.0 - 6.5	
	End of 12-month treatment		
	Number of subjects	12	12
	Mean (standard deviation)	0.92 (1.505)	-1.13 (1.625)
	Median	0.00	-1.00
	Minimum-maximum	0.0 - 5.0	-5.0 - 1.0

Quality of life

Baseline PedsQL results were collected in 7 pediatric patients who completed the study with results available. Mean (SD) mental health score was 58.33 (26.533) at baseline and decreased to 51.63 (33.283) at the end of 12-month treatment period. The score decreased over the 12 months of treatment. Similarly, baseline mean (SD) physical health score decreased from 55.37 (23.306) at baseline to 49.11 (30.609) at the end of 12-month treatment.

Safety results

Exposure

All 12 patients enrolled in the study received Cerezyme. The median number of treatment cycles was 25.0 and the median treatment duration was 11.90 months. Ten patients completed 25 treatment cycles, while the other two patients (subject number 101002 and 101004) completed 22 and 24 treatment cycles, respectively. The mean (SD) actual cumulative dose was 63650.9 (26473.29) U and the mean (SD) actual dose was 55.66 (4.987) U/kg.

Mean drug compliance was 92.7%. Eleven patients were in good compliance (80-110%). One (8.3%) patient having completed the treatment missed 6 doses during the 12-month treatment period, five of which due to COVID-19 and one was due to AE of respiratory tract infection, and therefore compliance was below 80%.

Adverse events

Overall, 12 (100%) patients experienced 89 TEAEs. The most frequently reported TEAEs by SOC were infections and infestations and musculoskeletal and connective tissue disorders (8 patients each, 66.7%), followed by nervous system disorders (6 patients, 50.0%).

The most frequently reported TEAEs by preferred term were upper respiratory tract infection and epilepsy (4 patients each, 33.3%), followed by arthralgia (3 patients, 25.0%), COVID-19, respiratory tract infection, bone pain, pain in extremity, face injury, abdominal pain, diarrhoea, hypokalaemia, refraction disorder, rash and pyrexia (each TEAE reported by 2 patients, 16.7%) (Table 4).

Table 4: Summary of Treatment-Emergent Adverse Events by SOC and Preferred Term - Safety Population

	Total N=12	
System Organ Class Preferred Term	Number of Subjects n (%)	Number of Events
Treatment-emergent adverse events	12 (100)	89
Infections and infestations	8 (66.7)	22
Upper respiratory tract infection	4 (33.3)	15
COVID-19	2 (16.7)	2
Respiratory tract infection	2 (16.7)	2
Nasopharyngitis	1 (8.3)	1
Conjunctivitis	1 (8.3)	1
Herpes virus infection	1 (8.3)	1
Musculoskeletal and connective tissue disorders	8 (66.7)	15
Arthralgia	3 (25.0)	4
Bone pain	2 (16.7)	5
Pain in extremity	2 (16.7)	2
Bone lesion	1 (8.3)	1
Bone infarction	1 (8.3)	1
Joint effusion	1 (8.3)	1
Arthritis	1 (8.3)	1
Nervous system disorders	6 (50.0)	11
Epilepsy	4 (33.3)	5
Headache	1 (8.3)	2
Ataxia	1 (8.3)	1
Lethargy	1 (8.3)	1
Generalised tonic-clonic seizure	1 (8.3)	1
Dizziness	1 (8.3)	1
Gastrointestinal disorders	3 (25.0)	8
Abdominal pain	2 (16.7)	2
Diarrhoea	2 (16.7)	2
Vomiting	1 (8.3)	2
Nausea	1 (8.3)	1
Abdominal pain upper	1 (8.3)	1
Investigations	3 (25.0)	7
Alanine aminotransferase increased	1 (8.3)	1
Electroencephalogram abnormal	1 (8.3)	1
Vitamin B12 decreased	1 (8.3)	1
Electrocardiogram T wave peaked	1 (8.3)	1
Blood homocysteine increased	1 (8.3)	1
Blood folate decreased	1 (8.3)	1
Neutrophil count decreased	1 (8.3)	1
Injury, poisoning and procedural complications	3 (25.0)	5
Face injury	2 (16.7)	2
Lip injury	1 (8.3)	1
Skin abrasion	1 (8.3)	1
Humerus fracture	1 (8.3)	1
Metabolism and nutrition disorders	3 (25.0)	4
Hypokalaemia	2 (16.7)	2
Hypocalcaemia	1 (8.3)	1
Hyperphosphataemia	1 (8.3)	1

Respiratory, thoracic and mediastinal disorders	3 (25.0)	4
Rhinitis allergic	1 (8.3)	1
Cough	1 (8.3)	1
Productive cough	1 (8.3)	1
Sneezing	1 (8.3)	1
General disorders and administration site conditions	3 (25.0)	4
Pyrexia	2 (16.7)	3
Fatigue	1 (8.3)	1
Eye disorders	3 (25.0)	4
Refraction disorder	2 (16.7)	2
Ocular hypertension	1 (8.3)	1
Amblyopia	1 (8.3)	1
Skin and subcutaneous tissue disorders	3 (25.0)	3
Rash	2 (16.7)	2
Dermatitis allergic	1 (8.3)	1
Cardiac disorders	2 (16.7)	2
Arrhythmia supraventricular	1 (8.3)	1
Tachycardia	1 (8.3)	1

Overall, 3 (25.0%) patients experienced 7 drug-related TEAEs (Table 5). By preferred term, 1 patient reported abdominal pain, diarrhoea, electrocardiogram T wave peaked and arrhythmia supraventricular, 1 patient reported alanine aminotransferase increased (from baseline 10.4 U/L to 50.4 U/L with the ULN at 50 U/L), and 1 patient reported ataxia and ocular hypertension. Incidence of each drug-related TEAE was 8.3%. All these events were mild in severity. Except for ataxia, other drug-related TEAEs were recovered.

Table 5: Summary of Treatment-emergent IMP-related Adverse Events by SOC and Preferred Term – Safety Population

	Total N=12	
System Organ Class Preferred Term	Number of Subjects n (%)	Number of Events
Treatment-emergent IMP-related adverse events	3 (25.0)	7
Investigations	2 (16.7)	2
Alanine aminotransferase increased	1 (8.3)	1
Electrocardiogram T wave peaked	1 (8.3)	1
Gastrointestinal disorders	1 (8.3)	2
Abdominal pain	1 (8.3)	1
Diarrhoea	1 (8.3)	1
Nervous system disorders	1 (8.3)	1
Ataxia	1 (8.3)	1
Cardiac disorders	1 (8.3)	1
Arrhythmia supraventricular	1 (8.3)	1
Eye disorders	1 (8.3)	1
Ocular hypertension	1 (8.3)	1

Deaths

There was no death in the study.

Serious adverse events (SAEs)

Of all 12 patients, 1 (8.3%) patient experienced 1 SAE of humerus fracture. The event was not related to study intervention and the outcome was recovered.

Discontinuations due to adverse events

There was no TEAE leading to discontinuation of study intervention.

Adverse events of special interest

AESIs of this study are defined as follows:

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP.
- Alanine transaminase (ALT) or aspartate aminotransferase (AST) > 3ULN and Total Bilirubin > 2 ULN.

There was no AESI in the study.

Clinical chemistry

Clinical chemistry of 5 patients were normal or not clinically significant at baseline but turned clinically significant during the study. The details are as follows:

- Potassium level of 2 (16.7%) patients was assessed as clinically significant at the 6th month of the treatment (decreased from baseline 3.8 mmol/L to 3.3 mmol/L in 1 patient and decreased from baseline 4.02 mmol/L to 3.24 mmol/L in 1 patient) which were considered TEAEs of hypokalaemia. The abnormalities returned to normal at the 8th month of the treatment (at 3.6 mmol/L) and by the end of treatment (at 3.68 mmol/L) respectively. Outcomes of both TEAEs were recovered.
- Alanine aminotransferase level in 1 (8.3%) patient was assessed as clinically significant at the 3rd month of the treatment (increased from baseline 10.4 U/L to 50.4 U/L). This was associated with an IMP-related TEAE of alanine aminotransferase increased. The abnormality returned to normal at the following visit (at 19.2 U/L) and the outcome of the TEAE was recovered. For this patient, alkaline phosphatase level increased from baseline 40.5 U/L to 67.3 U/L at the end of treatment. Aspartate aminotransferase level decreased from baseline 20.35 U/L to 17.575 U/L. Direct bilirubin level decreased from baseline 9.8 µmol/L to 7.7 µmol/L. Total bilirubin level decreased from baseline 26.1 µmol/L to 16.8 µmol/L. All of the above changes were considered as clinically significant and none were reported as TEAEs.
- Calcium level of 1 (8.3%) patient was assessed as clinically significant at the 1st month of the treatment (decreased from 2.11 mmol/L at baseline to 2.07 mmol/L) which was considered TEAE of hypocalcaemia. The calcium levels returned to normal (at 2.13 mmol/L) at the following visit and remained normal until the end of treatment. The outcome of the TEAE was recovered.
- Homocysteine level of 1 (8.3%) patient was assessed as clinically significant at the 3rd month of the treatment (increased from baseline 36.08 µmol/L to 80.50 µmol/L) which was considered as TEAE of blood homocysteine increased. The abnormality did not return to normal by the end of treatment and the outcome of the TEAE was improved to 19.68 µmol/L (normal range: 3.7-13.9 µmol/L), from a baseline value of 36.08.

- Vitamin B12 level of 1 (8.3%) patient was assessed as clinically significant by the end of treatment (decreased from baseline 211 pg/mL to 85 pg/mL) which was associated with either Gaucher disease or other conditions, but not considered as a TEAE.

No clinically significant changes were found in iron, total iron binding capacity and ferritin of all the patients during the study.

Overall, incidence of changes in clinical chemistry was relatively low, and most of the changes were recovered.

No clinically significant changes were found in urinalysis of all the patients during the study

Electrocardiograms

There was no apparent increased cardiac safety risk with treatment as determined by changes in overall 12--lead ECG status. One patient (8.3%) had normal ECG status at baseline but turned to clinically significant at the 6th month of the treatment which was related to TEAE of electrocardiogram T wave peaked and arrhythmia supraventricular. The abnormality returned to normal by the end of the treatment, and the outcome of both TEAEs was recovered.

2.3.3. Discussion on clinical aspects

In the EU, the extension of the indication to treat the non-neurological symptoms of Gaucher type 3 patients was approved in 2003 based on a literature review and data obtained from the ICGG Gaucher patient registry. The data at hand showed a comparable response to ERT between non-neuronopathic and neuronopathic Gaucher patients with regard to the systemic manifestations of Gaucher disease.

Data from Gaucher type 3 patients is not specifically described in the approved SmPC. It is mentioned that it is unknown if treatment also has an effect on neurological manifestations of the disease.

LPS16031 is a phase 4 open label study in GD3 patients. This post-marketing study was requested by the Chinese national competent authority. As the study enrolled also paediatric patients, study results are submitted to EMA as an art 46 procedure.

The study enrolled GD3 patients with neurological manifestations of the disease, hepatomegaly and/or splenomegaly (> ULN), aged >2 yoa, who were naïve to ERT. There was no inclusion criterium with respect to the baseline Hb and platelet counts, as is usually seen in studies for GD. This target population is acceptable as it represents GD3 patients. However, in clinical practice in Europe, it is unlikely that patients diagnosed with GD will remain untreated for a prolonged period of time. As ERT is known not to cross the blood-brain-barrier, the efficacy objective is to study efficacy on haematological and visceral symptoms. Hence, the presence of visceral symptoms as an inclusion criterium is logical.

Primary objective was safety and efficacy on haematologic manifestations of the disease, measured as change from baseline to week 52 in haemoglobin and platelet count. Secondary endpoint was efficacy on visceral manifestations of the disease, measured as change from baseline to week 52 in liver and spleen volume. In addition, secondary endpoints were the change in bone crises and HR-QoL. The endpoints are considered clinically relevant and appropriate to measure the efficacy of ERT.

The MAH defined success criteria for the study, including improved and stable hematologic parameters and decreases in liver and spleen volume. No formal responder analyses were defined in the SAP, but numbers of patients meeting the success criteria were reported in the CSR.

The sample size is limited, as the company aimed to include at least 10 evaluable patients. No target with regard to the inclusion of paediatric patients was set. In addition, no separate analysis of efficacy

is foreseen in the SAP between paediatric patients and adults. As a result, in the CSR, data is not presented separately for these two subgroups.

Primary and secondary analyses are not clearly specified in the SAP, as both paired t-tests and MMRM seems to be used to analyse the changes in the efficacy parameters over time. However, this issue is not further pursued. Given the limited sample size, statistical analysis is considered of limited value. In the assessment, therefore, mainly descriptive data is presented.

Data is presented for the splenectomised and non-splenectomised patients separately, which makes sense as this influences several key characteristics of the disease. In clinical practice in Europe, since the availability of ERT, splenectomy is not the mainstay of treatment.

In total 13 patients were screened and 12 patients were enrolled in the study. Twelve patients received treatment and completed the 52 week study period. There was a relatively low number of female patients included (25%) given that both males and females are at equal risk of Gaucher disease. The interval between first symptoms/diagnoses and onset of treatment in the study is relatively large (median of 6 years delay between diagnosis and inclusion in the study). This might be reflective of the difference in clinical practice standards between China and the EU. The majority of patients had moderate splenomegaly and hepatomegaly but it ranged from mild to severe. Four patients underwent a (partial) splenectomy prior to screening.

Median age was 16, but the age of included patients ranged from 3-58. There were 8 paediatric patients enrolled at screening, but 2 patients who were 17 at the time of screening turned 18 just before the start of treatment and during the treatment.

Haemoglobin and platelet counts increased over time. After 1 year of treatment, all patients reached the therapeutic goals for hemoglobin and 10/12 patients reached the therapeutic goal of platelet count normalisation. For the paediatric patients, a mean (SD) change from baseline to week 52 was observed of 12.6 (10.0) g/L for haemoglobin and of 134.1 (109.19) 10^9 g/L for the platelet counts. Seven/8 paediatric patients reached the predefined success criteria for the haematological parameters. These results are in line with what can be expected based on knowledge of effectiveness of imiglucerase treatment. The effects are clinically relevant.

The company describes a LOCF approach for all included patients which is not understood. According to the SAP, only for those patients for whom the 12 months data is missing, LOCF is conducted. As efficacy data is only missing for 1 patient at 12 months, this issue is not further pursued.

Both liver and spleen volume (in non-splenectomised patients) decreased within one year of treatment. For the paediatric patients, a mean (SD) decrease from baseline to week 52 in liver volume (-6.228 (6.595)) and or spleen volume (-0.551 (0.466)) were observed. Five/8 paediatric patients reached the predefined success criteria for organ volume. The observed effects are in line with what can be expected and are clinically meaningful.

With regard to bone pain, the frequency of bone pain episodes increased from a mean of 2.97 per month to 19.93 times per month. However, the duration of bone pain decreased significantly from an average of 55.9 minutes to 1.6 minutes. The severity of bone pain also decreased. This is a bit puzzling and difficult to interpret. The decrease in duration and severity of bone pain seems like a meaningful improvement for the patients.

HR-QoL decreased during the study, as measured by the PedsQL in the paediatric patients. The company indicates that this was likely due to the COVID pandemic, during which this study was conducted. This explanation can be accepted. Drawing conclusions from the very small sample size and the relatively short observation period of one year would in any case be challenging.

The safety of imiglucerase is mainly characterized by hypersensitivity reactions, labelled as common in the SmPC. Interestingly, no hypersensitivity reactions were observed in the current study. The size of the study population is probably too limited to pick up these ADR's. Patient narratives are not provided so causality of the reported TEAE's cannot be established.

The abnormalities with regard to clinical chemistry can most likely be attributed to the disease.

There were no treatment related SAE's and no deaths or treatment discontinuations due to AE's. Overall, the provided safety data do not raise concerns.

3. Rapporteur's overall conclusion and recommendation

In conclusion, the provided data support the efficacy of imiglucerase in treating the hematological an visceral manifestations of type 3 Gaucher disease. It is questioned how representative the provided data are for patients treated in the EU (different SOC). In addition, it was already known that comparable efficacy on hematological and visceral symptoms as in GD1 patients could be expected for GD3 patients. Hence, it is not considered of additional value to include the presented data in the SmPC.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Since this is an art 46 procedure, the data from paediatric patients are particularly of interest. However, the underlying data for this subpopulation cannot be found in the dossier. The company is requested to either indicate the place of the underlying data or to provide it (data on haemoglobin, platelet count, spleen and liver volume and bone pain frequency/duration/severity for all patients aged <18 yoa at screening). As part of the response, the company is requested to provide the numbers of paediatric patients reaching the predefined success criteria for the study.

MAH responses to Request for supplementary information

The Company is providing the following adapted tables for pediatric data on hemoglobin, platelet count, spleen and liver volume, and bone pain frequency / duration / severity for all patients aged < 18 years of age at screening in Table 6, Table 7 and Table 8, respectively.

Primary Efficacy Endpoint: Hemoglobin and Platelet Count

Primary efficacy analysis showed that there was a gradual increase from baseline in hemoglobin and platelet count during 12-month imiglucerase treatment. Summaries of hemoglobin and platelet count values at the end of 12 months and at each time point are shown in Table 6.

Table 6: Primary Efficacy Endpoint: Efficacy on Hematologic Manifestations (Efficacy in Hemoglobin and Platelet Count at the End of 12 Months) - Evaluable Pediatric Population

Parameter	Visit	Measured Value N=8	Change from Baseline N=8
Hemoglobin (g/L)	Baseline		
	Number of subjects	8	
	Mean (standard deviation)	116.8 (9.84)	
	Median	116.0	
	Minimum-maximum	106 - 137	
	End of 12-month treatment		
	Number of subjects	7	7
	Mean (standard deviation)	128.9 (14.21)	12.0 (10.63)
	Median	123.0	10.0
	Minimum-maximum	118 - 151	2 - 35
	Change from baseline (paired t-test)		
	t-value	2.987	
	P-value	0.0244	
	End of 12-month treatment (LOCF) [1]		
	Number of subjects	8	8
	Mean (standard deviation)	129.4 (13.23)	12.6 (10.00)
	Median	125.0	10.0
	Minimum-maximum	118 - 151	2 - 35
	Change from baseline (paired t-test)		
	t-value	3.571	
	P-value	0.0091	
Platelet count (10^9/L)	Baseline		
	Number of subjects	8	
	Mean (standard deviation)	204.4 (162.14)	
	Median	149.0	
	Minimum-maximum	69 - 515	
	End of 12-month treatment		
	Number of subjects	7	7
	Mean (standard deviation)	300.0 (210.92)	140.0 (116.56)
	Median	209.0	109.0
	Minimum-maximum	113 - 663	30 - 330
	Change from baseline (paired t-test)		
	t-value	3.178	
	P-value	0.0191	
	End of 12-month treatment (LOCF) [1]		
	Number of subjects	8	8
	Mean (standard deviation)	338.5 (223.58)	134.1 (109.19)
	Median	255.5	101.0
	Minimum-maximum	113 - 663	30 - 330
	Change from baseline (paired t-test)		
	t-value	3.474	
	P-value	0.0103	

Note: LOCF = Last Observation Carried Forward.

[1] For the subjects who early terminated the treatment and whose efficacy was not observed at the end of 12 months, the results of hemoglobin and platelet count for the subjects would be carried forward by LOCF method. At the time of the interim analysis, the efficacy endpoint for the subjects who had not completed the study would not be carried forward.

Source: Table 14.2.1.1

Secondary Efficacy Endpoint: Spleen and Liver Volume

The results indicated a decrease in spleen and liver volume after 12-month treatment. Summaries of efficacy in spleen and liver volume at the end of 12 months and at each time point are shown in Table 7.

Table 7 Secondary Efficacy Endpoint: Efficacy on Viscera Manifestations (Efficacy in Spleen Volume and Liver Volume at the End of 12 Months) - Evaluable Pediatric Population

Parameter	Visit	Measured Value N=8	Change from Baseline N=8
Spleen volume (MN)	Baseline		
	Number of subjects	5	
	Mean (standard deviation)	10.414 (5.744)	
	Median	12.700	
	Minimum-maximum	4.15 - 16.42	
	End of 12-month treatment		
	Number of subjects	4	4
	Mean (standard deviation)	4.125 (1.655)	-7.785 (5.058)
	Median	3.425	-8.395
	Minimum-maximum	3.08 - 6.57	-13.28 - -1.07
	Change from baseline (paired t-test)		
	t-value	-3.079	
	P-value	0.0542	
	End of 12-month treatment (LOCF) [1]		
	Number of subjects	5	5
	Mean (standard deviation)	4.186 (1.439)	-6.228 (5.595)
	Median	3.710	-7.800
	Minimum-maximum	3.08 - 6.57	-13.28 - 0.00
	Change from baseline (paired t-test)		
	t-value	-2.489	
	P-value	0.0676	
Liver volume (MN)	Baseline		
	Number of subjects	8	
	Mean (standard deviation)	1.834 (0.795)	
	Median	1.535	
	Minimum-maximum	0.92 - 2.82	
	End of 12-month treatment		
	Number of subjects	6	6
	Mean (standard deviation)	1.340 (0.483)	-0.702 (0.437)
	Median	1.330	-0.780
	Minimum-maximum	0.68 - 1.91	-1.07 - 0.11
	Change from baseline (paired t-test)		
	t-value	-3.930	
	P-value	0.0111	
	End of 12-month treatment (LOCF) [1]		
	Number of subjects	8	8
	Mean (standard deviation)	1.283 (0.422)	-0.551 (0.466)
	Median	1.110	-0.660
	Minimum-maximum	0.68 - 1.91	-1.07 - 0.11
	Change from baseline (paired t-test)		
	t-value	-3.347	
	P-value	0.0123	

Note: LOCF = Last Observation Carried Forward.

[1] For the subjects who early terminated the treatment and whose efficacy was not observed at the end of 12 months, the results of spleen and liver volume for the subjects would be carried forward by LOCF method. At the time of the interim analysis, the efficacy endpoint for the subjects who had not completed the study would not be carried forward.

Source: Table 14.2.2.1

Secondary Efficacy Endpoint: Bone Disease Assessments & Skeletal Involvement

Improvement was observed in bone disease assessments and skeletal involvement. A summary of frequency, duration and severity of bone pain is shown in Table 8. Of note, as Gaucher disease is a progressive, exacerbation of bone disease might still occur even when on enzyme replacement therapy. In fact, risk factors for bone disease were previously identified including genotype, late diagnosis (> 2 years after symptom initiation), or delay in onset of treatment (>2 years from diagnosis). In addition, previous reports indicated that the treatment of bone disease requires a longer period of continuous therapy. Considering that patients only had 1-year treatment in this study, a longer period of treatment in the future could be better able to ameliorate the continued progression of bone disease.

Table 8 Secondary Efficacy Endpoint: Efficacy on Bone Disease (Efficacy in Frequency, Duration and Severity of Bone Pain and Number of Bone Crisis at the End of 12 Months) - Evaluable Pediatric Population

Parameter	Visit	Measured Value N=8	Change from Baseline N=8
Frequency of bone pain (times/month)	Baseline		
	Number of subjects	7	
	Mean (standard deviation)	2.97 (4.546)	
	Median	0.00	
	Minimum-maximum	0.0 - 12.2	
	Intermittent or irregular pain	1 (12.5)	
	End of 12-month treatment		
	Number of subjects	7	6
	Mean (standard deviation)	19.93 (51.632)	19.78 (55.450)
	Median	0.00	0.00
	Minimum-maximum	0.0 - 137.0	-9.7 - 132.7
	Intermittent or irregular pain	1 (12.5)	
Duration of bone pain (minutes)	Baseline		
	Number of subjects	7	
	Mean (standard deviation)	55.9 (122.92)	
	Median	0.0	
	Minimum-maximum	0 - 330	
	Pain on exertion or exertion	1 (12.5)	
	End of 12-month treatment		
	Number of subjects	7	6
	Mean (standard deviation)	1.6 (3.74)	-63.3 (128.01)
	Median	0.0	0.0
	Minimum-maximum	0 - 10	-320 - 0
	Intermittent or irregular pain	1 (12.5)	
Severity of bone pain	Baseline		
	Number of subjects	8	
	Mean (standard deviation)	1.94 (2.542)	
	Median	1.00	
	Minimum-maximum	0.0 - 6.5	
	End of 12-month treatment		
	Number of subjects	8	8
	Mean (standard deviation)	0.88 (1.727)	-1.06 (1.860)
	Median	0.00	-0.50
	Minimum-maximum	0.0 - 5.0	-5.0 - 1.0
Number of bone crisis (times)	Baseline		
	Number of subjects	8	
	Mean (standard deviation)	0.0 (0.00)	
	Median	0.0	
	Minimum-maximum	0 - 0	
	End of 12-month treatment		
	Number of subjects	7	7
	Mean (standard deviation)	0.0 (0.00)	0.0 (0.00)
	Median	0.0	0.0
	Minimum-maximum	0 - 0	0 - 0

Note: for bone pain occurring after walking or related to exertion, frequency and duration of bone pain were classified as "pain on exertion or exertion"; for intermittent, irregular, and occasional bone pain, frequency and duration of bone pain were categorized as "intermittent or irregular pain"; for persistent pain, frequency of bone pain was defined as 30 times/month and duration of bone pain was categorized as "persistent bone pain".

Source: Table 14.2.3.2

The efficacy criteria for success included improved and stable hematologic parameters (primary efficacy endpoint), organ volumes, and bone disease that are defined below. The spleen volume assessments did not apply to patients who have had a total splenectomy.

Overview of Predefined Success Criteria:

- Hematological Parameters:
    - Hemoglobin level ≥ 110 g/L

AND

- Increase platelet counts sufficiently to prevent surgical, obstetrical, and spontaneous bleeding:
    - Nonsplenectomized patients with thrombocytopenia > 50×109/L should increase 1.5- to 2-fold from baseline,
    - Nonsplenectomized patients with thrombocytopenia < 50×109/L should increase 1.5-fold from baseline,
    - Splenectomized patients with thrombocytopenia should normalize in 1 year.
- Organ Volume
    - If applicable, spleen volume (in MN) should decrease by 30%-50% from screening.

      AND
    - If applicable, liver volume (in MN) should decrease by 20%-30% from screening.
- Bone Disease
    - Reduction or remission in bone pain.

      AND
    - Remission in bone crises.

As shown above, the study's success criteria encompassed 6 critical endpoints, including haematological parameters, organ volume, and bone disease. Of the paediatric population, 4 participants (50%) met all six predefined targets. Seven (7) participants (87.5%) achieved the success threshold for haematological parameters, 5 participants (62.5%) met the criteria for organ volume, and 7 participants (87.5%) reached the predefined benchmarks for bone disease.

Assessment of the response

The MAH has submitted a separate analysis of the data of the 8 included paediatric patients, as requested. The discussion on clinical aspects is updated based on this response.

Conclusion

Issue resolved.