Amsterdam, 19 August 2022
EMA/718122/2022
Human Medicines 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/P46/059

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	21/06/2022	21/06/2022
☐	CHMP Rapporteur Assessment Report	25/07/2022	06/07/2022
☐	CHMP members comments	08/08/2022	n/a
☐	Updated CHMP Rapporteur Assessment Report	11/08/2022	n/a
☒	CHMP adoption of conclusions:	19/08/2022	19/08/2022

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LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AEs:	adverse events
BLA:	Biologic License Application
CRIM:	cross-reacting immunologic material
ECG:	electrocardiogram
ERT:	enzyme replacement therapy
GAA:	acid α-glucosidase
GCP:	Good Clinical Practice
GMFM-88:	Gross Motor Function Measure-88
IARs:	infusion-associated reactions
IgE:	immunoglobulin E
IgG:	immunoglobulin G
IOPD:	infantile-onset Pompe disease
IQ:	intelligence quotient
LOPD:	late-onset Pompe disease
PEDI:	Pediatric Evaluation of Disability Inventory
PTs:	preferred terms
rhGAA:	recombinant human acid α-glucosidase
SAE:	serious adverse event
SD:	standard deviation
SMQ:	standardized Medical Dictionary for Regulatory Activities queries
SOC:	system organ class
TEAEs:	treatment-emergent adverse events

1. Introduction

On 30 May 2022, the MAH submitted a completed paediatric study for alglucosidase alfa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s) specific obligation(s).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that AGLU03606/LTS12869 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

N/A

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

AGLU03606/LTS12869 : A Long-Term Study to Evaluate Growth and Development Outcomes in Patients with Infantile-Onset Pompe Disease Who Are Receiving Alglucosidase Alfa Long-Term Growth and Development Study of Alglucosidase Alfa.

2.3.2. Clinical study

AGLU03606/LTS12869

Description

Methods

AGLU03606/LTS12869 was a Phase IV multicenter study of patients with IOPD who began alglucosidase alfa treatment prior to 1 year of age. Patients were followed in this study for up to 10 years.

Study participants

Main inclusion Criteria:

Confirmed diagnosis of Pompe disease as determined by deficient endogenous GAA activity or GAA mutation analysis.

The patient must be <1 year of age at time of study enrolment (and receive alglucosidase alfa treatment before 1 year of age),

Or the patient must be between 1 year and 24 months of age and must have initiated alglucosidase alfa treatment prior to turning 1 year of age.

Exclusion criteria

The patient is participating in another clinical study using alglucosidase alfa or any investigational therapy.

Treatments

The study drug details are outlined in Table 1

TABLE 1- OVERVIEW OF STUDY INTERVENTION(S) ADMINISTERED

Intervention label	Myozyme®/ Lumizyme®
Intervention name	Alglucosidase alfa
Type	Drug
Dose formulation	Intravenous infusion
Unit dose strength(s)	20 mg/kg of body weight
Dosage level(s)	Every 2 weeks
Route of administration	Intravenous
Packaging and labeling	Commercial product as prescribed by the treating physician was used. Alglucosidase alfa was not provided by the Sponsor as part of the study.

Objective(s)

The overall objective was to evaluate long-term growth and development of patients with infantile onset Pompe disease who begin treatment with alglucosidase alfa before 1 year of age. Patients were followed for a 10-year period.

An additional objective was to collect long-term safety data on patients with infantile-onset Pompe disease. As an exploratory objective, the effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4) was evaluated.

Outcomes/endpoints

Efficacy: The following efficacy assessments were performed at scheduled visits during the study:

- Growth as measured by recumbent length/height, weight and head circumference
- Motor development and function, as measured by changes in the motor subscale of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), Gross Motor Function Measure (GMFM-88) and Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI)
- Cognitive Development, as measured by the cognitive and language subscales of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), change in the Brief IQ score of the Leiter International Performance Scale – Revised (Leiter-R) and/or the change in the Nonverbal IQ score of the Leiter International Performance Scale – 3rd Edition (Leiter-3) (starting at the final assessment of the Bayley-III before 42 months of age).

For patients treated with alglucosidase alfa prior to age 1 (prior to study entry), available retrospective growth and development data were collected. Parameters for retrospective data

collection included available standard-of-care growth (height, weight, head circumference) and motor milestone information (e.g., head support, sitting, standing, and walking ability) from the time of treatment initiation.

Safety: The following safety assessments were performed during the study: AE monitoring, laboratory tests (clinical chemistry, hematology and urinalysis), anti-rhGAA antibody (immunoglobulin G [IgG]) collection, neuroimaging (at the discretion of the Investigator), vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examinations, electrocardiograms (ECGs), hearing testing and visual screening.

Additional safety evaluations included the assessment of: (1) immunoglobulin E (IgE), serum tryptase, complement activation and skin testing, when clinically indicated following moderate, severe, or recurrent IARs suggestive of hypersensitivity; and (2) circulating immune complex detection when clinically indicated by symptoms suggestive of immune complex disease.

Inhibitory antibody (activity and uptake) were to be assessed when clinically indicated (e.g., requirement for new invasive ventilator use, plateau or decline in response in the presence of adequate dosing).

Sample size

No formal statistical sample size calculation was performed. The number of patients followed in this study was not limited prospectively.

Randomisation and blinding

Not Applicable

Statistical Methods

The statistical analysis of all growth and development parameters and other efficacy outcomes and safety measurements were conducted on all patients who received alglucosidase alfa. All data collected in this study were documented using summary tables, figures and patient data listings.

For categorical variables, frequencies and percentages were presented. For continuous variables, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) were presented.

Besides standard safety analyses of the incidence of AEs and SAEs, additional analyses were carried out to examine the trends in incidence and prevalence of AEs, SAEs and other relevant safety parameters over time. Key safety analyses were also carried out by gender.

Results

Participant flow

A total of 12 patients were screened, enrolled, and treated in the study. Eleven patients (91.7%) discontinued the study due to withdrawal of consent (6 patients [50.0%]), death (3 patients [25.0%]), and non-compliance with the study drug (2 patients [16.7%]) (**TABLE 2**).

TABLE 2- PATIENT DISPOSITION

Disposition	Alglucosidase Alfa (N=12)
Screened patients	12
Enrolled patients [a]	12 (100%)

Treated patients [b]	12 (100%)
Patients who completed study [c]	1 (8.3%)
Number of subject who discontinued [c]	11 (91.7%)
Primary reason for withdrawal [c]	
Adverse experience(s)	0
Non-compliant	2 (16.7%)
Wishes to withdraw	6 (50.0%)
Lost to follow-up	0
Death	3 (25.0%)
Other	0
Status at last study contact [c]	
Alive	9 (75.0%)
Dead	3 (25.0%)

Note: [a] Percentages are calculated using the number of screened patients as denominator. [b] Percentages are calculated using the number of enrolled patients as denominator. [c] Percentages are calculated using the number of treated patients as denominator.

Recruitment

Study initiation date: 26 August 2008 (first patient signed informed consent).

Study completion date: 23 November 2021 (last patient last visit).

This study was conducted at 3 centres that enrolled patients in the United States.

Baseline data

The baseline for this study was defined as the value measured at the screening/baseline visit prior to the first infusion during the study.

The median age of patients at first Pompe diagnosis was 3.11 months, and 4.01 months at the time of first alglucosidase alfa infusion (Table 4). Of the 12 patients, 5 patients (41.7%) were male and 7 patients (58.3%) were female. Seven patients (58.3%) were White and 5 (41.7%) were Black; most were not Hispanic or Latino (11 patients [91.7%]).

Nine patients (75.0%) were CRIM positive, 2 patients (16.7%) were CRIM negative, and for 1 patient (8.3%) CRIM status was not evaluated.

Demographics and patient characteristics at baseline – Full analysis set

Parameter	Alglucosidase Alfa (N = 12)
Age (months) at signing of informed consent	

Parameter	Alglucosidase Alfa (N = 12)
Number	12
Mean (SD)	11.558 (6.226)
Median	11.400
Min : Max	3.55 : 22.80
Age group, n (%)	
Mean (SD)	4.102 (2.828)
Median	4.010
Min : Max	0.23:9.76
Age (months) at first Pompe diagnosis	
Number	12
Mean (SD)	3.510 (2.685)
Median	3.105
Min : Max	0.03 : 9.56
Age (months) at first Pompe symptoms	
Number	12
Mean (SD)	2.210 (2.732)
Median	1.430
Min : Max	0.03 : 9.17
Time (months) from first Pompe symptoms to first alglucosidase alfa infusion*	
Number	12
Mean (SD)	1.924 (2.228)
Median	1.115
Min : Max	0.23 : 7.85
Time (months) from Pompe diagnosis to first alglucosidase alfa infusion*	
Number	12
Mean (SD)	0.624 (0.507)
Median	0.445
Min : Max	0.10 : 1.41
Gender, n (%)	
Male	5 (41.7%)
Female	7 (58.3%)
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black	5 (41.7%)
Native Hawaiian or Other Pacific Islander	0
White	E (58.3%)
Ethnicity, n (%)	
Hispanic or Latino	

Parameter	Alglucosidase Alfa (N = 12)
Not Hispanic or Latino	1 (8.3%)
Weight at baseline (kg)	
Number	12
Mean (SD)	8.42 (2.61)
Median	8.45
Min : Max	5.0 : 12.8
Weight at baseline (percentile)	
Number	12
Mean (SD)	35.27 (37.25)
Median	19.70
Min : Max	0.2 : 89.8
Recumbent length/height at baseline (cm)	
Number	12
Mean (SD)	72.95 (10.24)
Median	70.90
Min : Max	57.2 : 95.0
Recumbent length/height at baseline (percentile)	
Number	12
Mean (SD)	38.06 (41.64)
Median	16.67
Min : Max	0.3 : 99.9
Body Mass Index (BMI) at baseline (kg/m^2)	
Number	12
Mean (SD)	15.52 (2.02)
Median	15.40
Min : Max	12.8 : 18.4
Head circumference at baseline (cm)	
Number	12
Mean (SD)	45.20 (3.61)
Median	44.80
Min : Max	39.6 : 50.8
Head circumference at baseline (percentile)	
Number	12
Mean (SD)	51.07 (38.44)
Median	40.24
Min : Max	6.3 : 100.
CRIM Status, n (%)	

Parameter	Alglucosidase Alfa (N = 12)
Positive	9 (75%)
Negative	2 (16.7%)
Not tested	1 (8.3%)

Note: * Patients may have received alglucosidase alfa prior to study entry
1) Percentages are based on all enrolled patients who receive at least one infusion in study.
2) Age for category = (Date of category – Birth Date + 1)/30.4375 rounded to the nearest hundredth.

Medical history and concurrent illnesses

Eleven patients (91.7%) reported at least 1 pre-specified medical or surgical history, of which, most patients reported current cardiovascular events (8 patients [66.7%])

The most frequently reported medical history included failure to thrive and hypotonia (8 patients [66.7%] each); feeding difficulties, muscle weakness in upper and lower extremities, and delayed motor milestones (7 patients [58.3%] each), and congestive heart failure (6 patients [50.0%]). Prior to alglucosidase alfa administration, there was evidence of left ventricular hypertrophy noted in all 12 patients (100.0%) and cardiac involvement (cardiomegaly) diagnosed by chest X-Ray in 8 patients (66.7%).

Prior, concomitant, or post-intervention therapy

Concomitant medications/therapies were defined as all medications taken by the patient for AEs, pre-infusion medications, and medications for long-term disease management.

All 12 patients (100%) reported use of prior and concomitant medications. The most frequently reported prior medications (>75%) by therapeutic class included antiemetics and antinauseants, antipruritics, incl. all antihistamines, anesthetics etc; anti-Parkinson drugs, psycholeptics, antihistamines for systemic use (12 patients [100%] each); other alimentary tract and metabolism products, analgesics (11 patients [91.7%] each).

Number analysed

The full analysis set was used for all analyses, as all 12 enrolled patients received at least 1 infusion of alglucosidase alfa

Efficacy results

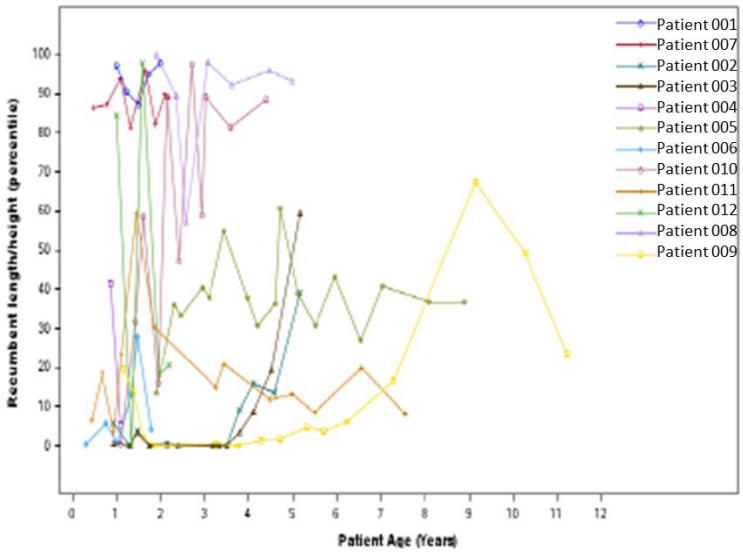
Primary efficacy endpoint

Physical growth

Physical growth was measured by changes in recumbent length/height, weight, and head circumference.

At the last available assessment, all patients had recumbent length/height and head circumference above the 3rd percentile. Eleven patients had maintained or improved weight for age percentiles (above the 3rd percentile) while 1 patient remained below the 3rd percentile at the last available assessment. Physical growth parameters for 2 CRIM negative patients were above the 3rd percentile over the course of the study.

FIGURE 1 PHYSICAL GROWTH – SPAGHETTI PLOT OF RECUMBENT LENGTH/HEIGHT (PERCENTILE) OVER TIME BY AGE – FULL ANALYSIS SET



Note: For the calculation of percentiles, the 2006 WHO growth chart reference population is used for patients <24 months old, while the 2000 CDC growth chart reference population is used for patients >2 years old.
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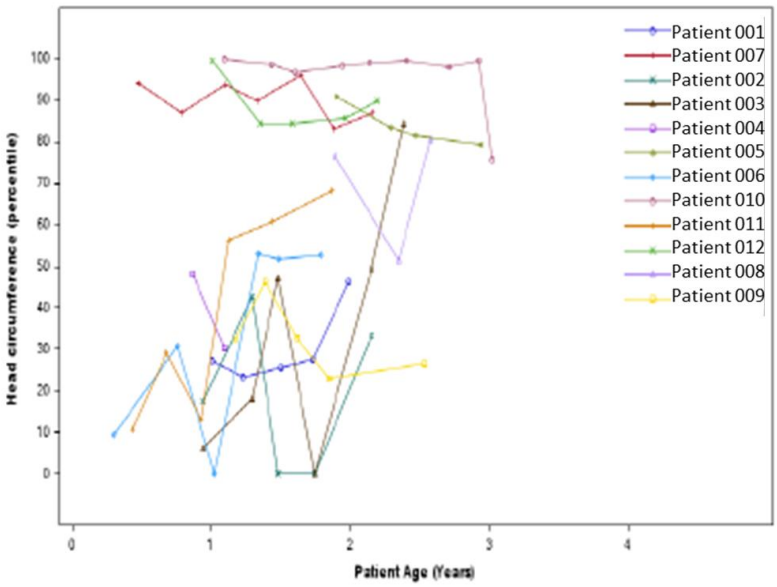
FIGURE 2 PHYSICAL GROWTH – SPAGHETTI PLOT OF HEAD CIRCUMFERENCE (PERCENTILE) OVER TIME BY AGE – FULL ANALYSIS SET



Note: For the calculation of percentiles, the 2006 WHO growth chart reference population is used for patients <24 months old, while the 2000 CDC growth chart reference population is used for patients >2 years old.
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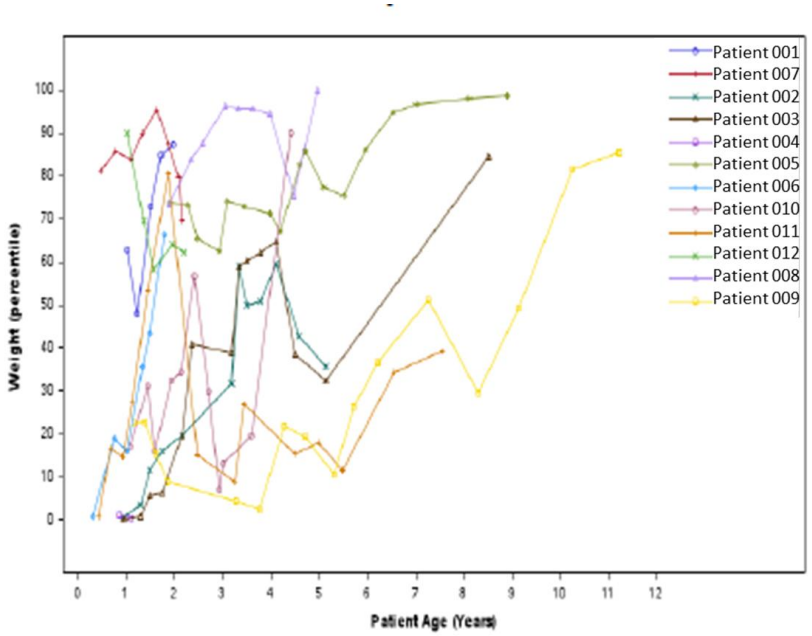
FIGURE 3PHYSICAL GROWTH – SPAGHETTI PLOT OF WEIGHT (PERCENTILE) OVER TIME BY AGE – FULL ANALYSIS SET



Note: For the calculation of percentiles, the 2006 WHO growth chart reference population is used for patients <24 months old, while the 2000 CDC growth chart reference population is used for patients >2 years old.
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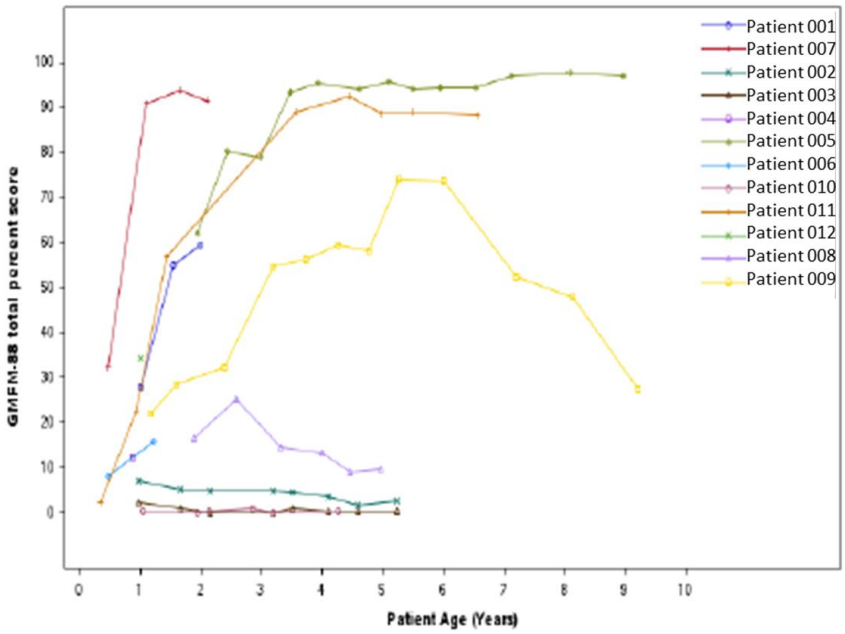
Motor development

GMFM-88 Total Percent Score

The GMFM-88 was developed specifically to detect quantitative changes in gross motor function through the evaluation of 88 items that represent motor functions typically performed by children without motor impairment by 5 years of age. Total scores range from 0 to 100, with higher scores indicating greater motor skills. The GMFM-88 was administered by a trained physical therapist.

Of the 12 patients, 10 patients had GMFM-88 data at more than 1 time point. Changes in GMFM-88 scores were observed over the course of the study, which ranged from nearly 10 months (2 patients) to nearly 8 years (1 patient). Compared to baseline, 6 patients had improved GMFM-88 total percent scores at the last available assessment ranging from 5.45 to 85.88-point increase. Of the 2 patients with CRIM negative status, 1 had improved GMFM-88 total percent score by 31.67-points and the other patient had a decline in score by -6.85-points.

FIGURE 4 GMFM-88 – SPAGHETTI PLOT OF TOTAL PERCENT SCORE OVER TIME BY AGE – FULL ANALYSIS SET



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Pompe PEDI Functional Skills Scale

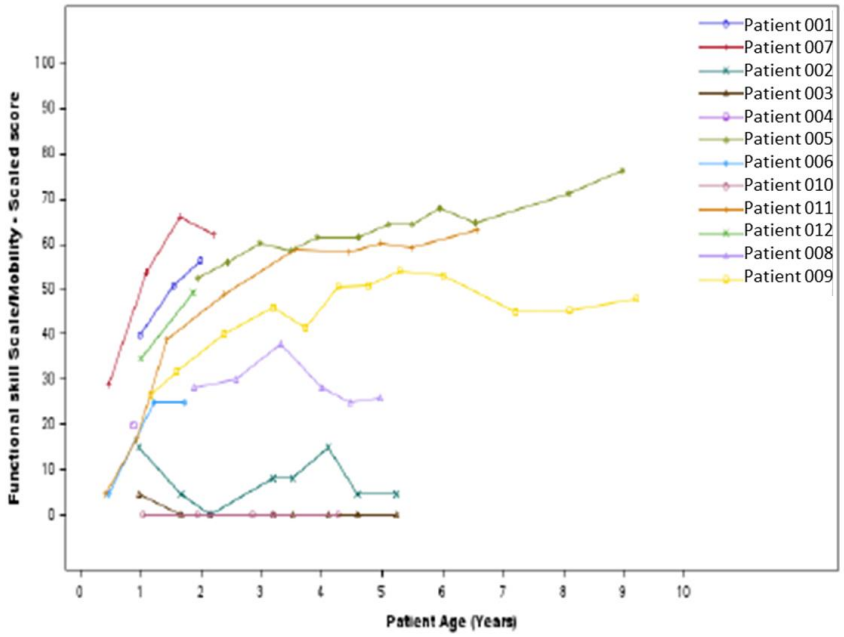
The Pompe PEDI is a caregiver reported measure of clinically relevant functional skills for children with Pompe disease. A trained physical therapist administered the Pompe PEDI to the patients' parents/caregivers. Results for the Mobility, Self-care, and Social domains were reported as scaled scores, which were calculated from the raw scores and transformed to a 0 to 100 scale, with higher scores indicating better function

- Pompe PEDI Functional Skills Scale, **Mobility**

Of the 12 patients, 11 had multiple assessments for comparison across time ranging from 10 months (1 patient) to 8 years (1 patient). At the last available assessment, 7 patients had improvement in Pompe PEDI Functional Skills Scale Mobility domain, 3 patients had a decrease in scores from baseline while 1 patient experienced no change from the lowest possible score. The patient with only the baseline assessment had a Pompe PEDI Functional Skills Scale Mobility scaled score of 19.75.

One patient with CRIM negative status showed improvement in Pompe PEDI Functional Skills Scale Mobility domain while the other patient had a slight decrease in score from baseline

FIGURE 5 POMPE PEDI SCORE: FUNCTIONAL SKILLS SCALE/MOBILITY – SPAGHETTI PLOT OF SCALED SCORE OVER TIME BY AGE – FULL ANALYSIS SET



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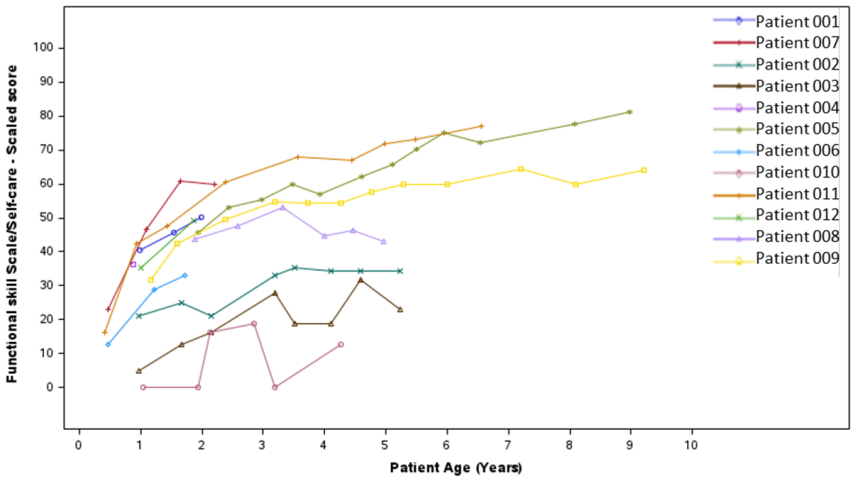
- Pompe PEDI Functional Skills Scale, **Self-care**

Of the 12 patients, 11 patients had multiple assessment points for the Pompe PEDI to compare Self-care skills over time; time ranged from 10 months (1 patient) to 8 years (1 patient).

Compared to baseline, all patients had improvement in Pompe PEDI Functional Skills Scale Self-care domain scaled score at the last available assessment except for 1 patient (CRIM negative) who had a slight decline in score from baseline.

FIGURE 6 POMPE PEDI SCORE: FUNCTIONAL SKILLS SCALE/SELF-CARE – SPAGHETTI PLOT OF SCALED SCORE OVER TIME BY AGE – FULL ANALYSIS SET



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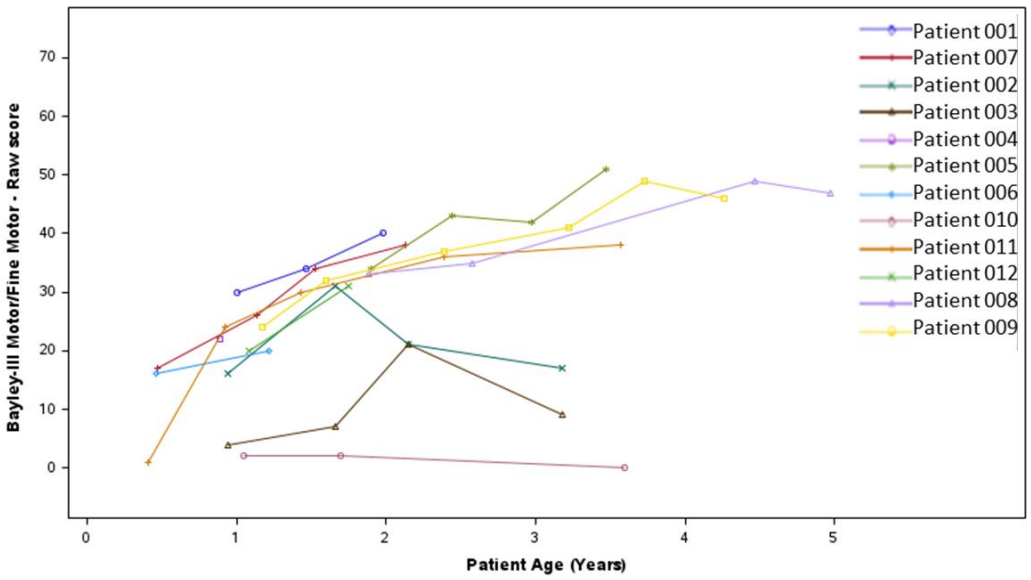
Bayley-III Fine Motor Raw Scores

The Bayley-III is a standardized assessment of infant and child development utilized to assess cognitive, language, and motor development. The Bayley-III was administered to patients up to 42 months of age or until the maximum score on each of the scales had been obtained. Data were reported by change in raw score on the 5 administered subtests (cognitive, receptive language, expressive language, fine motor, and gross motor). Normative scores for the cognitive, language, and motor scales were also reported, with attention to scores that fall within 2 SDs of the composite score mean (mean = 100, SD = 15). Composite scores that fell below 70 were classified as 'Extremely Low' by the Bayley-III.

Eleven of 12 patients had Bayley-III Fine Motor data at multiple assessments. At the last available assessment at which the Bayley-III was administered (per protocol), 10 patients had an improvement in Bayley-III Fine Motor raw score, and 1 patient had a decrease in score from baseline. Both CRIM negative patients had an improvement in Bayley-III Fine Motor raw score from baseline.

FIGURE 7 BAYLEY-III: MOTOR SCALE/FINE MOTOR- SPAGHETTI PLOT OF RAW SCORE OVER TIME BY AGE – FULL ANALYSIS SET



Footnote: Maximum raw score for Bayley-III: Motor scale/Fine motor is 51
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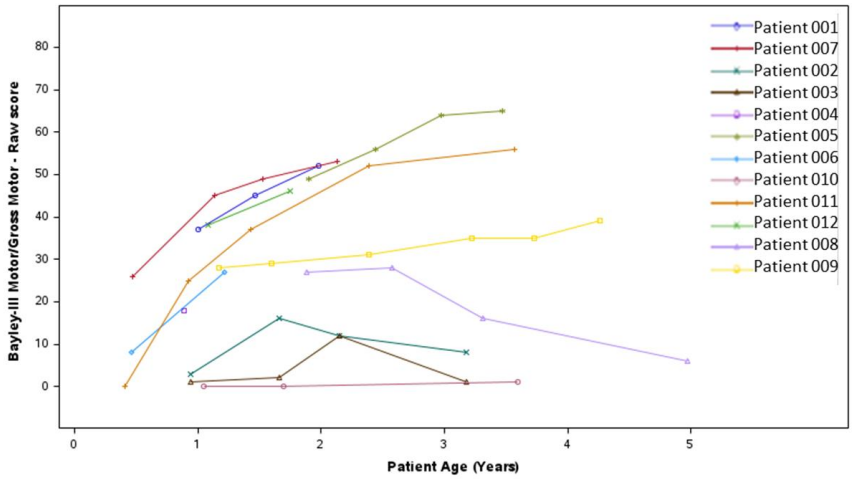
Bayley-III Gross Motor Raw Scores

Eleven of 12 patients had Bayley-III Gross Motor data at multiple time points. The maximum raw score for Bayley-III Gross Motor scale was 65. At the last available assessment of the Bayley-III (per protocol), 9 patients had an improvement in Bayley-III Gross Motor Raw score and 1 patient had no change in score from baseline. One patient with CRIM negative status had a decrease in Bayley-III Gross Motor Raw score by 21-points observed over 156 weeks; this was the largest raw score decrease observed on the Bayley-III in the study.

FIGURE 8 BAYLEY-III: MOTOR SCALE/GROSS MOTOR- SPAGHETTI PLOT OF RAW SCORE OVER TIME BY AGE – FULL ANALYSIS SET



Footnote: Maximum raw score for Bayley-III: Motor scale/Gross motor is 65
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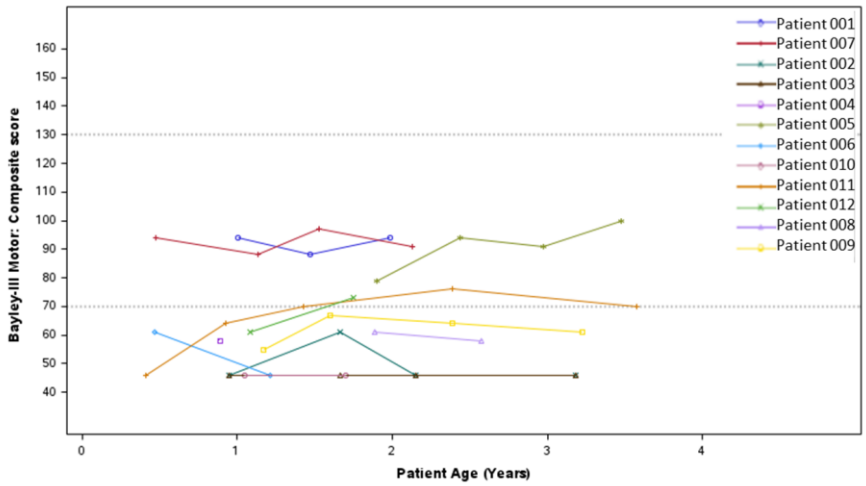
Bayley-III Motor Composite Score

The Bayley-III composite scores are norm-reference scores scaled to a metric with a mean of 100 and SD of 15, and range from 40 to 160. Scores below 70 indicate performance greater than 2 SDs below the mean and are classified as 'Extremely Low'.

At the last available assessment when the Bayley-III was assessed, 3 patients had Bayley-III motor composite scores above 85; 2 patients had a score between ≥70 and ≤85 suggesting mild or moderate impairment while 7 patients had scores <70 suggesting severe impairment in motor skills. One CRIM negative patient had Bayley-III motor composite score above 85 while the other had a score of 58.

FIGURE 9 BAYLEY-III: MOTOR SCALE – SPAGHETTI PLOT OF COMPOSITE SCORE OVER TIME BY AGE – FULL ANALYSIS SET



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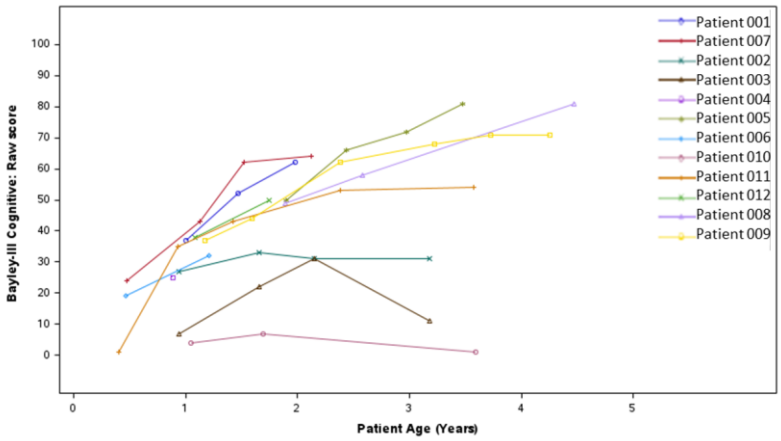
Cognitive development

Bayley-III Cognitive Raw Score

Eleven patients had Bayley-III cognitive raw score data at multiple assessments. All patients, with the exception of 1, showed improvement in Bayley-III cognitive raw score over the course of the study. One patient with a score of 4 at baseline had a declined score at the last available assessment by 3-points. The maximum raw score for Bayley-III cognitive scale was 81. Both CRIM negative patients had improved Bayley-III cognitive raw score from baseline.

FIGURE 10 BAYLEY-III: COGNITIVE SCALE – SPAGHETTI PLOT OF RAW SCORE OVER TIME BY AGE – FULL ANALYSIS SET



Maximum raw score for Bayley-III: Cognitive scale is 81
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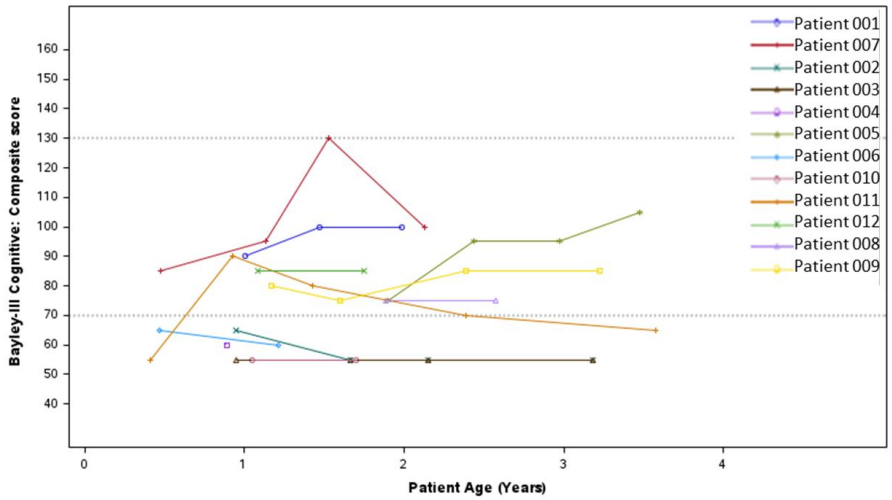
Bayley-III Cognitive Composite Score

At the last available assessment, 3 patients had Bayley-III cognitive composite scores (>85), while 2 patients had a score between ≥70 and ≤85 suggesting low average/borderline performance in cognitive function in these patients. Seven patients had cognitive composite scores <70, indicating extremely low performance (Figure 11). One CRIM negative patient had Bayley-III cognitive composite score of 100 while the other had a score between ≥70 and ≤85.

FIGURE 11BAYLEY-III: COGNITIVE SCALE – SPAGHETTI PLOT OF COMPOSITE SCORE OVER TIME BY AGE – FULL ANALYSIS SET



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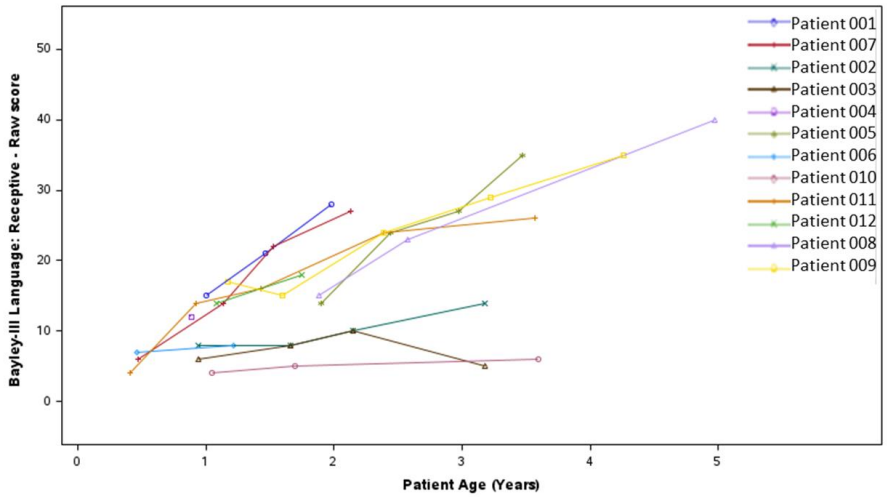
OUT=REPORT/OUTPUT/eff_spag_cong_bayley03_f_g_i.rtf (15APR2022 – 11:12)

Bayley-III Receptive Language Raw

The Bayley-III Receptive Language subtests were completed at multiple time points by 11 of 12 patients. At the last available assessment, all 11 patients showed improvement in Bayley-III language/receptive raw score from baseline. The maximum raw score for Bayley-III language scale/receptive was 40.

FIGURE 12 BAYLEY-III: LANGUAGE SCALE/RECEPTIVE- SPAGHETTI PLOT OF RAW SCORE OVER TIME BY AGE – FULL ANALYSIS SET

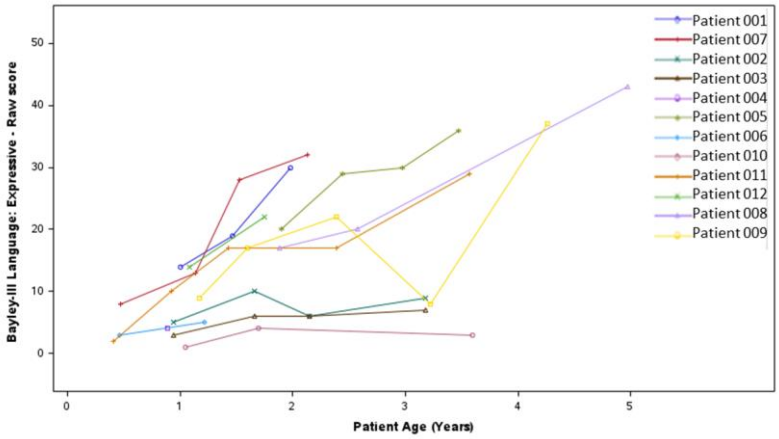


Footnote: Maximum raw score for Bayley-III: Language scale/Receptive is 40
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/eff_spaghetti_f_g.sasOUT=REPORT/OUTPUT/eff_spag_lang_rec_bayley01_f_g_i.r tf (15APR2022 – 11:12)

Bayley-III Expressive Language Raw

Eleven of 12 patients had Bayley-III Expressive Language scores at multiple assessments. At the last available assessment, all 11 patients showed improvement in Bayley-III Expressive Language raw score from baseline. The maximum raw score for Bayley-III language scale/expressive was 43.

FIGURE 13 BAYLEY-III: LANGUAGE SCALE/EXPRESSIVE- SPAGHETTI PLOT OF RAW SCORE OVER TIME BY AGE – FULL ANALYSIS SET

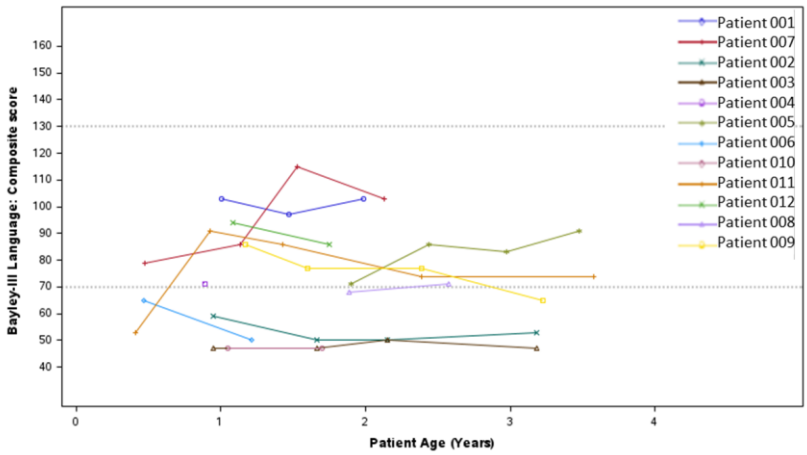


Footnote: Maximum raw score for Bayley-III: Language scale/Expressive is 43
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/eff_spaghetti_f_g.sasOUT=REPORT/OUTPUT/eff_spag_lang_exp_bayley01_f_g_i. rtf (15APR2022 – 11:12)

Bayley-III Language Composite Score

At the last available assessment, 4 patients had Bayley-III language composite scores above 85; 3 patients had scores between ≥70 and ≤85 suggesting low average/borderline performance in language skills while 5 patients had scores <70 suggesting extremely low performance in these patients. One CRIM negative patient had Bayley-III language composite score of 103 and the other patient had a score between ≥70 and ≤85

FIGURE 14 BAYLEY-III: LANGUAGE SCALE – SPAGHETTI PLOT OF COMPOSITE SCORE OVER TIME BY AGE – FULL ANALYSIS SET



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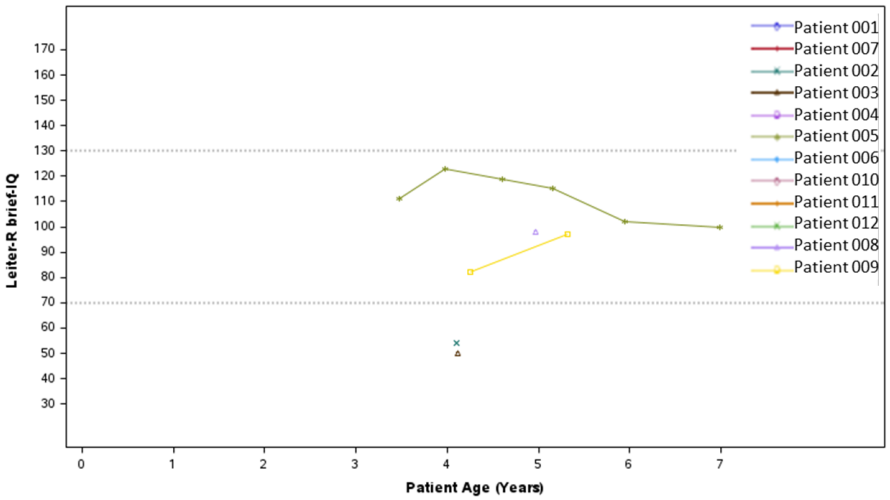
OUT=REPORT/OUTPUT/eff_spag_lang_bayley03_f_g_i.rtf (15APR2022 – 11:12)

Leiter-R Brief IQ

The modified Leiter-R Scale was administered by a trained clinician to assess intellectual ability. The Leiter-R was administered to patients starting at the last assessment of the Bayley-III

Cognitive and Language Scales prior to the patient reaching 42 months of age. During the study, the Leiter-R was replaced by the Leiter-3 (due to upgrade from developer). Leiter-R Brief IQ scores were available only for 5 patients, of which 2 had the Leiter-R for multiple time points. The Leiter-R captured a range of Brief IQ scores, with 2 patients falling below 70 and 3 patients had scores between 70 and 130 (within 2 SDs from the mean).

FIGURE 15 LEITER-R – SPAGHETTI PLOT OF BRIEF IQ OVER TIME BY AGE – FULL ANALYSIS SET

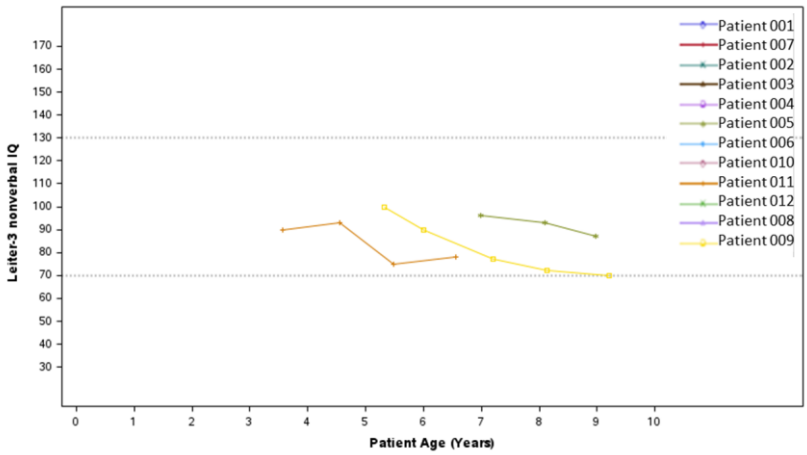


PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/eff_spaghetti_f_g.sas
OUT=REPORT/OUTPUT/eff_spag_leiterr_iq_f_g_i.rtf (15APR2022 – 11:12)

Leiter-3 Nonverbal IQ

Leiter-3 Nonverbal IQ scores were available only for 3 patients, only 2 of which had assessments at multiple time points. All 3 patients had scores above 90 at the first assessment but the scores decreased gradually over the course of the study, but did not fall below 70.

FIGURE 16 LEITER-3 – SPAGHETTI PLOT OF NONVERBAL IQ OVER TIME BY AGE – FULL ANALYSIS SET



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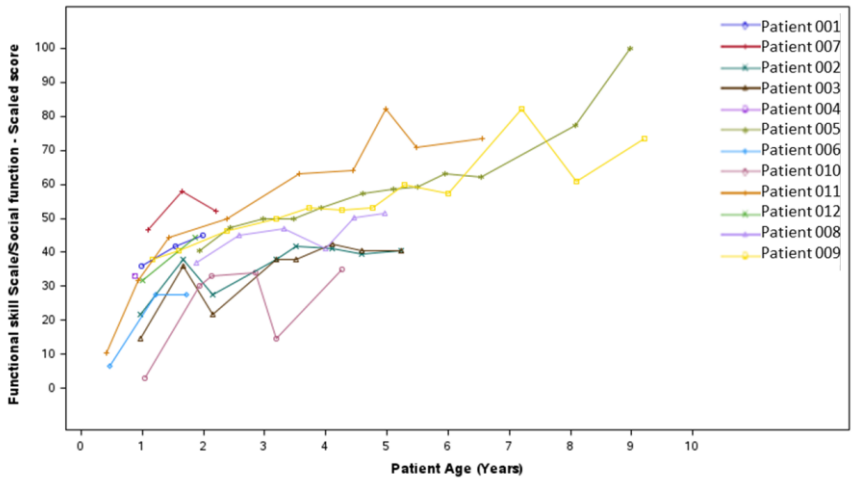
OUT=REPORT/OUTPUT/eff_spag_leiter3_iq_f_g_i.rtf (15APR2022 – 11:12)

Pompe PEDI, Functional Skills Scale, Social Function

Compared to baseline, or the earliest completed Pompe PEDI Functional Skills Scale Social Function domain completion, all patients showed improvement in score (for social function) from baseline. The maximum functional skill scale score for social function was 100.

FIGURE 17 POMPE PEDI SCORE: FUNCTIONAL SKILLS SCALE/SOCIAL FUNCTION – SPAGHETTI PLOT OF SCALED SCORE OVER TIME BY AGE – FULL ANALYSIS SET



PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/eff_spaghetti_f_g.sas
OUT=REPORT/OUTPUT/eff_spag_pedi_soci_f_g_i.rtf (15APR2022 – 11:12)

CHMP comments on efficacy:

The objectives of this Phase IV AGLU03606/LTS12869 open-label study was to evaluate long-term growth and development of patients with infantile-onset Pompe disease who began treatment with alglucosidase alfa before 1 year of age at the dose of 20 mg/kg every 2 weeks. Patients were followed in this study for up to 10 years.

Long-term growth was assessed by change of length/height, weight, and head circumference.

Long term motor and cognitive development was evaluated using the Motor Scale of the Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley-III) (up to 42 months of age), the Gross Motor Function Measure-88 (GMFM-88), the Pompe Pediatric Evaluation of Disability Inventory (PEDI), the Brief intelligence quotient (IQ) score of the Leiter International Performance Scale – Revised (Leiter-R) or the change in the Nonverbal IQ score of the Leiter International Performance Scale 3rd Edition (Leiter-3).

All 12 patients were only included in the USA and were treated with the commercial product as prescribed by the treating physician (i.e., Lumizyme).

Overall, 12 patients were included in the FAS population. Only 1 patient completed the study, 11 patients (91.7%) discontinued due to withdrawal of consent (6 patients), death (3 patients), and non-compliance (2 patients).

The mean (SD) duration of alglucosidase alfa exposure was 4.43 (3.46) years (range: 0.5 to 10.1 years).

Regarding growth, most patients maintained or improved their scores and all patients had height and head circumference above the 3rd percentile at last evaluation.

Regarding motor development, 10 patients had GMFM-88 data of which 6 improved their score and 3 had a decrease. Of the 11 patients with multiple assessments, 7 patients had improvement in Pompe PEDI Functional Skills Scale Mobility domain and 3 patients had a decrease.

Regarding cognitive development, of the 11 patients with multiple assessments, at last available assessment, 3 patients had Bayley-III cognitive composite scores >85, 2 patients had score between ≥ 70 and ≤85, suggesting low average/borderline performance in cognitive function and 7 patients had composite scores <70, indicating extremely low performance. Leiter-R Brief IQ and Leiter-3 Nonverbal IQ scores were available only for 2 patients with multiple evaluation.

Considering the size of the population (12 patients) the number of patients who discontinued the study (11), the mean duration of treatment (4.43 years) and the observational nature of the study, it is difficult to draw any firm conclusion regarding the effect of alglucosidase alfa on long term growth and development of IOPD patients. However, taking into account the rarity and the seriousness of the pathology, the benefit of alglucosidase alfa in patients with IOPD remains positive.

Safety results

- ***Safety results***

Extent of exposure

All 12 (100%) enrolled patients in the study were included in the Full Analysis Set.

The mean (SD) duration of alglucosidase alfa exposure was 4.43 (3.46) years (range: 0.5 to 10.1 years) and mean (SD) total number of alglucosidase alfa infusions was 124.3 (102.5). Further details on exposure are presented in 5.3.5.2 Study LTS12869, Appendix 16.2.5 Dosing and drug concentration data [16.2.5.1.1.1]

Adverse events

Brief summary of adverse events

A total of 28 pre-treatment AEs were experienced by 8 patients (66.7%) enrolled in the study.

A total of 512 AEs were experienced by 12 patients enrolled in the study. Eleven patients (91.7%) had treatment-emergent adverse events (TEAEs), of which 4 patients (33.3%) had related TEAEs and 7 patients (58.3%) had unrelated TEAEs. Nine patients (75.0%) had at least 1 treatment-emergent SAE. No treatment-related treatment-emergent SAEs were reported. No patients discontinued treatment with the study drug due to TEAE (Table 10). The most frequently (>50%) reported TEAEs by preferred terms (PTs) were pyrexia (10 patients [83.3%]); pneumonia and cough (8 patients [66.7%] each); atelectasis and vomiting (7 patients [58.3%] each) (16-2-7-ae-data [16.2.7.1.3]).

A by-patient listing of AEs is provided in 16-2-7-ae-data [16.2.7.1.12].

Table 10 - Overview of adverse event profile: Treatment-emergent adverse events - Full analysis set

	Alglucosidase Alfa (N=12)	
Adverse Event Categories	**Event, n**	**Patients, n (%)**
Any Adverse Events	512	12 (100%)
Any Treatment-Emergent Adverse Events (TEAEs)	484	11 (91.7%)
TEAEs related to the study drug	63	4 (33.3%)
TEAEs unrelated to the study drug	421	7 (58.3%)
TEAEs by severity	484	11 (91.7%)
Mild	292	1 (8.3%)
Moderate	145	1 (8.3%)
Severe	47	9 (75.0%)
TEAEs by gender	484	11 (91.7%)
Male	190	5 (41.7%)
Female	294	6 (50.0%)
Any treatment-emergent SAE	85	9 (75.0%)
Any treatment-emergent SAE considered related to study drug	0	0
Any protocol-defined infusion-associated reactions	61	4 (33.3%)
Any TEAE leading to treatment adjusted	11	4 (33.3%)
Any TEAE leading to treatment interrupted	56	6 (50.0%)
Any TEAE leading to permanent treatment discontinuation	0	0
Any TEAE leading to death	4	3 (25.0%)

Note: 1) If a patient has more than one occurrence of an AE, the most severe occurrence of the AE will be used in the severity.
2) If a patient has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the relationship to treatment.
3) TEAE: Treatment-emergent adverse event. Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose.
4) Related AEs are defined as possible, probable, or definitely related. Unrelated AEs are defined as unlikely or not related. If the assessment of the relationship of the AE to study drug is missing, the event will be considered related to the study drug.
5) Patient percentages are based on the full analysis set.
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/ae_ovr_f_t.sas OUT=REPORT/OUTPUT/ae_ovr_f_t_i.rtf (10MAR2022 - 10:44)

Display of adverse events

Project Code / Study Number / Analysis: GZ419829 / AGLU03606-LTS12869 / CSR

16.2.7 Adverse event data

16.2.7.1 Adverse events

16.2.7.1.3 Number (%) of patients with TEAE(s) by primary SOC and PT - Full analysis set

System Organ Class (SOC) Preferred Term (PT)	Alglucosidase Alfa (N=12) Events, n	Patients, n (%)
Any treatment emergent adverse event	484	11 (91.7%)
Infections and infestations	93	11 (91.7%)
Pneumonia	27	8 (66.7%)
Otitis media	11	6 (50.0%)
Upper respiratory tract infection	13	5 (41.7%)
Vascular device infection	5	5 (41.7%)
Pneumonia aspiration	4	3 (25.0%)
Urinary tract infection	4	2 (16.7%)
Ear infection	2	2 (16.7%)
Influenza	2	2 (16.7%)
Bacteraemia	2	1 (8.3%)
Device related sepsis	2	1 (8.3%)
Oral candidiasis	2	1 (8.3%)
Pharyngitis streptococcal	2	1 (8.3%)
Rhinitis	2	1 (8.3%)
Viral upper respiratory tract infection	2	1 (8.3%)
Bronchitis	1	1 (8.3%)
Catheter site infection	1	1 (8.3%)
Fungal skin infection	1	1 (8.3%)
Gastroenteritis	1	1 (8.3%)
Medical device site infection	1	1 (8.3%)
Pneumonia bacterial	1	1 (8.3%)
Pseudomonas infection	1	1 (8.3%)
Rash pustular	1	1 (8.3%)
Respiratory syncytial virus bronchiolitis	1	1 (8.3%)
Respiratory tract infection	1	1 (8.3%)
Sepsis	1	1 (8.3%)
Viral pharyngitis	1	1 (8.3%)
Vulvovaginal candidiasis	1	1 (8.3%)
Blood and lymphatic system disorders	1	1 (8.3%)
Iron deficiency anaemia	1	1 (8.3%)
Immune system disorders	2	2 (16.7%)
Allergy to animal	1	1 (8.3%)
Multiple allergies	1	1 (8.3%)
Metabolism and nutrition disorders	16	4 (33.3%)
Feeding disorder	3	2 (16.7%)
Dehydration	2	2 (16.7%)
Hypokalaemia	5	1 (8.3%)
Diabetes mellitus	2	1 (8.3%)
Acidosis	1	1 (8.3%)
Hypoglycaemia	1	1 (8.3%)
Hyponatraemia	1	1 (8.3%)
Hypophosphataemia	1	1 (8.3%)
Nervous system disorders	11	6 (50.0%)
Hypoglycaemic seizure	2	2 (16.7%)
Hypotonia	2	2 (16.7%)
Seizure	2	2 (16.7%)
Areflexia	1	1 (8.3%)
Encephalopathy	1	1 (8.3%)
Focal dyscognitive seizures	1	1 (8.3%)
Neurological decompensation	1	1 (8.3%)
White matter lesion	1	1 (8.3%)
Eye disorders	9	6 (50.0%)
Eye discharge	2	2 (16.7%)
Eyelid ptosis	2	2 (16.7%)
Papilloedema	2	2 (16.7%)
Chalazion	1	1 (8.3%)
Eye swelling	1	1 (8.3%)
Visual acuity reduced	1	1 (8.3%)
Ear and labyrinth disorders	7	6 (50.0%)
Deafness neurosensory	4	4 (33.3%)
Deafness	1	1 (8.3%)
External ear disorder	1	1 (8.3%)
Middle ear effusion	1	1 (8.3%)
Cardiac disorders	21	6 (50.0%)
Tachycardia	18	4 (33.3%)
Cardio-respiratory arrest	1	1 (8.3%)
Right ventricular hypertrophy	1	1 (8.3%)
Sinus tachycardia	1	1 (8.3%)
Vascular disorders	4	4 (33.3%)
Flushing	2	2 (16.7%)
Hypotension	2	2 (16.7%)
Respiratory, thoracic and mediastinal disorders	126	10 (83.3%)
Cough	28	8 (66.7%)
Atelectasis	11	7 (58.3%)
Rhinorrhoea	16	5 (41.7%)
Respiratory failure	11	5 (41.7%)
Dyspnoea	6	4 (33.3%)
Respiratory distress	5	4 (33.3%)
Wheezing	5	3 (25.0%)
Hypercapnia	4	3 (25.0%)
Hypoxia	5	2 (16.7%)
Asthma	2	2 (16.7%)
Nasal congestion	2	2 (16.7%)
Sinus congestion	2	2 (16.7%)
Upper respiratory tract congestion	3	1 (8.3%)
Aspiration	2	1 (8.3%)
Bronchial secretion retention	2	1 (8.3%)
Hypoventilation	2	1 (8.3%)
Rhonchi	2	1 (8.3%)
Sneezing	2	1 (8.3%)
Velopharyngeal incompetence	2	1 (8.3%)
Apnoea	1	1 (8.3%)
Bronchospasm	1	1 (8.3%)
Chronic respiratory failure	1	1 (8.3%)
Dysphonia	1	1 (8.3%)
Epistaxis	1	1 (8.3%)
Increased upper airway secretion	1	1 (8.3%)
Oropharyngeal pain	1	1 (8.3%)
Pleural effusion	1	1 (8.3%)
Pneumonitis	1	1 (8.3%)
Productive cough	1	1 (8.3%)
Pulmonary hypertension	1	1 (8.3%)
Pulmonary oedema	1	1 (8.3%)
Respiratory tract congestion	1	1 (8.3%)
Stridor	1	1 (8.3%)
Gastrointestinal disorders	28	9 (75.0%)
Vomiting	11	7 (58.3%)
Diarrhoea	6	4 (33.3%)
Constipation	2	2 (16.7%)
Teething	2	1 (8.3%)
Dental caries	1	1 (8.3%)
Dysphagia	1	1 (8.3%)
Gingival swelling	1	1 (8.3%)

System Organ Class (SOC) Preferred Term (PT)	Alglucosidase Alfa (N=12) Events, n	 Patients, n (%)
Mouth ulceration	1	1 (8.3%)
Post-tussive vomiting	1	1 (8.3%)
Salivary hypersecretion	1	1 (8.3%)
Swollen tongue	1	1 (8.3%)
Skin and subcutaneous tissue disorders	58	8 (66.7%)
Rash	20	4 (33.3%)
Urticaria	19	3 (25.0%)
Dermatitis diaper	5	3 (25.0%)
Erythema	3	3 (25.0%)
Dry skin	2	2 (16.7%)
Hair growth abnormal	2	2 (16.7%)
Angioedema	2	1 (8.3%)
Decubitus ulcer	1	1 (8.3%)
Dermatitis contact	1	1 (8.3%)
Papule	1	1 (8.3%)
Rash papular	1	1 (8.3%)
Skin disorder	1	1 (8.3%)
Musculoskeletal and connective tissue disorders	5	9 (75.0%)
Arthralgia	3	3 (25.0%)
Muscular weakness	3	2 (16.7%)
Extremity contracture	2	2 (16.7%)
Joint contracture	2	2 (16.7%)
Foot deformity	1	1 (8.3%)
Myopathy	1	1 (8.3%)
Pain in extremity	1	1 (8.3%)
Scoliosis	1	1 (8.3%)
Spinal deformity	1	1 (8.3%)
Renal and urinary disorders	1	1 (8.3%)
Nephrolithiasis	1	1 (8.3%)
Reproductive system and breast disorders	1	1 (8.3%)
Balanoposthitis	1	1 (8.3%)
Congenital, familial and genetic disorders	1	1 (8.3%)
Glycogen storage disease type II	1	1 (8.3%)
General disorders and administration site conditions	58	10 (83.3%)
Pyrexia	44	10 (83.3%)
Pain	6	4 (33.3%)
Asthenia	2	2 (16.7%)
Catheter site rash	1	1 (8.3%)
Mass	1	1 (8.3%)
Swelling	1	1 (8.3%)
Swelling face	1	1 (8.3%)
Unevaluable event	1	1 (8.3%)
Vascular device occlusion	1	1 (8.3%)
Investigations	23	8 (66.7%)
Oxygen saturation decreased	6	2 (16.7%)
Body temperature increased	2	2 (16.7%)
Clostridium test positive	2	1 (8.3%)
Audiogram abnormal	1	1 (8.3%)
Bacterial test positive	1	1 (8.3%)
Blood potassium decreased	1	1 (8.3%)
Blood urine present	1	1 (8.3%)
Electrocardiogram QRS complex prolonged	1	1 (8.3%)
Electrocardiogram QT prolonged	1	1 (8.3%)
Electrocardiogram T wave inversion	1	1 (8.3%)
Fungal test positive	1	1 (8.3%)
Haematocrit decreased	1	1 (8.3%)
Haemoglobin decreased	1	1 (8.3%)
Pseudomonas test positive	1	1 (8.3%)
Tympanometry abnormal	1	1 (8.3%)
Urine output decreased	1	1 (8.3%)
Injury, poisoning and procedural complications	5	5 (41.7%)
Anaesthetic complication	1	1 (8.3%)
Femur fracture	1	1 (8.3%)
Joint dislocation	1	1 (8.3%)
Procedural pain	1	1 (8.3%)
Stoma site haemorrhage	1	1 (8.3%)
Product issues	4	3 (25.0%)
Device malfunction	4	3 (25.0%)

Note : 1) MedDRA 24.1 is used.
2) If a patient had more than 1 event for a particular SOC, the patient is counted only once for that SOC.
3) If a patient had more than 1 event for a particular PT, the patient is counted only once for that PT.
4) Patient percentages are calculated using the number of all enrolled patients who receive at least one infusion as denominator.
5) Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose.

Adverse events by severity

Overall, the majority of TEAEs experienced during the study were considered to be of mild intensity (292 events). A total of 145 TEAEs were moderate in intensity, and 47 were severe (16-2-7-ae-data [16.2.7.1.8]). The most frequently reported severe TEAEs were atelectasis and respiratory failure (5 patients [41.7%] each), and pneumonia (4 patients [33.3%]).

Treatment-related TEAEs

One patient (8.3%) reported TEAEs which were considered as possibly related to the study drug; 2 patients (16.7%) reported TEAEs which were considered as probably related to the study drug. One patient (8.3%) reported TEAEs of urticaria and rash, which were considered as definitely related to the study drug (Table 11).

Table 11 - Related treatment-emergent adverse events by SOC and PT by relationship to the study drug - Full analysis set

	Alglucosidase Alfa (N=12)					
	Possible		Probable		Definite	
System Organ Class (SOC) Preferred Term (PT)	Event, n	Patients, n (%)	Event, n	Patients, n (%)	Event, n	Patients, n (%)
Any TEAE	20	1 (8.3%)	13	2(16.7%)	30	1 (8.3%)
Cardiac disorders	8	1 (8.3%)	3	1 (8.3%)	0	0
Tachycardia	8	1 (8.3%)	3	1 (8.3%)	0	0
Vascular disorders	1	1 (8.3%)	0	0	0	0
Flushing	1	1 (8.3%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1	1 (8.3%)	0	0	0	0
Cough	1	1 (8.3%)	0	0	0	0
Gastrointestinal disorders	2	1 (8.3%)	1	1 (8.3%)	0	0
Vomiting	2	1 (8.3%)	1	1 (8.3%)	0	0
Skin and subcutaneous tissue disorders	2	1 (8.3%)	5	2(16.7%)	30	1 (8.3%)
Urticaria	2	1 (8.3%)	2	1 (8.3%)	15	1 (8.3%)
Rash	0	0	1	1 (8.3%)	15	1 (8.3%)
Angioedema	0	0	2	1 (8.3%)	0	0
General disorders and administration site conditions	4	1 (8.3%)	1	1 (8.3%)	0	0
Pyrexia	3	0	1	1 (8.3%)	0	0
Swelling face	1	1 (8.3%)	0	0	0	0
Investigations	2	0	3	1 (8.3%)	0	0
Oxygen saturation decreased	2	0	2	1 (8.3%)	0	0
Body temperature increased	0	0	1	1 (8.3%)	0	0

Note : 1) If a patient has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the relationship to treatment summary table.
2) Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose.
3) MedDRA 24.1 is used.
4) If a patient had more than 1 event for a particular SOC, the patient is counted only once for that SOC and if a patient had more than 1 event for a particular PT, the patient is counted only once for that PT.
5) Patient percentages are based on the full analysis set.
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/ae_socpt_f_t.sas OUT=REPORT/OUTPUT/ae_socpt_teae_rel_rel_f_t_i.rtf (10MAR2022 - 10:46)

Treatment-emergent adverse events by anti-drug antibody status

Of 8 patients with positive ADA titer, 2 patients had low ADA titer (100-800), 3 patients had intermediate ADA titer (1600-6400), and 3 patients had high ADA titer (≥12800) (Table 12).

A total of 154 TEAEs were reported in 2 patients with intermediate ADA titer. The most frequently (>50%) reported TEAEs in these patients were pneumonia, upper respiratory tract infection, tachycardia, cough, erythema, atelectasis, hypercapnia, hypoxia, wheezing, vomiting, and pyrexia (2 patients [66.7%] each).

Eighty-five TEAEs were reported in 3 patients with high ADA titer. The most frequently (>50%) reported TEAEs in these patients were pneumonia and pyrexia (3 patients [100%] each); cough, atelectasis, respiratory failure, and dyspnoea (2 patients [66.7%] each).

Protocol-defined IARs are described in detail in Section 5.2.2.7.1.

Table 12 - TEAE(s) by ADA status, peak ADA categories, and by primary SOC and PT - Full analysis set

System Organ Class (SOC) Preferred Term (PT)	Negative (N=4)		Positive (N=8)					
			100-800 (N=2)		1600-6400 (N=3)		≥12800 (N=3)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Any TEAE	157	4 (100%)	88	2 (100%)	154	2 (66.7%)	85	3 (100%)
Infections and infestations	37	4 (100%)	10	2 (100%)	30	2 (66.7%)	16	3 (100%)
Pneumonia	8	2 (50.0%)	4	1 (50.0%)	10	2 (66.7%)	5	3 (100%)
Otitis media	6	4 (100%)	1	1 (50.0%)	4	1 (33.3%)	0	0
Upper respiratory tract infection	3	2 (50.0%)	1	1 (50.0%)	9	2 (66.7%)	0	0
Vascular device infection	2	2 (50.0%)	1	1 (50.0%)	1	1 (33.3%)	1	1 (33.3%)
Pneumonia aspiration	2	1 (25.0%)	1	1 (50.0%)	0	0	1	1 (33.3%)
Urinary tract infection	3	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Ear infection	1	1 (25.0%)	0	0	0	0	1	1 (33.3%)
Influenza	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Bacteraemia	2	1 (25.0%)	0	0	0	0	0	0
Device related sepsis	0	0	0	0	0	0	2	1 (33.3%)
Oral candidiasis	0	0	0	0	2	1 (33.3%)	0	0
Pharyngitis streptococcal	0	0	2	1 (50.0%)	0	0	0	0
Rhinitis	0	0	0	0	0	0	2	1 (33.3%)
Viral upper respiratory tract infection	2	1 (25.0%)	0	0	0	0	0	0
Bronchitis	1	1 (25.0%)	0	0	0	0	0	0
Catheter site infection	0	0	0	0	0	0	1	1 (33.3%)
Fungal skin infection	1	1 (25.0%)	0	0	0	0	0	0
Gastroenteritis	0	0	0	0	1	1 (33.3%)	0	0
Medical device site infection	1	1 (25.0%)	0	0	0	0	0	0
Pneumonia bacterial	1	1 (25.0%)	0	0	0	0	0	0
Pseudomonas infection	1	1 (25.0%)	0	0	0	0	0	0
Rash pustular	0	0	0	0	0	0	1	1 (33.3%)
Respiratory syncytial virus bronchiolitis	0	0	0	0	0	0	1	1 (33.3%)
Respiratory tract infection	1	1 (25.0%)	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	1	1 (33.3%)
Viral pharyngitis	0	0	0	0	1	1 (33.3%)	0	0
Vulvovaginal candidiasis	1	1 (25.0%)	0	0	0	0	0	0
Blood and lymphatic system disorders	1	1 (25.0%)	0	0	0	0	0	0
Iron deficiency anaemia	1	1 (25.0%)	0	0	0	0	0	0
Immune system disorders	2	2 (50.0%)	0	0	0	0	0	0
Allergy to animal	1	1 (25.0%)	0	0	0	0	0	0
Multiple allergies	1	1 (25.0%)	0	0	0	0	0	0
Metabolism and nutrition disorders	9	1 (25.0%)	0	0	5	2 (66.7%)	2	1 (33.3%)
Feeding disorder	0	0	0	0	1	1 (33.3%)	2	1 (33.3%)
Dehydration	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Hypokalaemia	5	1 (25.0%)	0	0	0	0	0	0
Visual acuity reduced	0	0	0	0	1	1 (33.3%)	0	0
Ear and labyrinth disorders	3	3 (75.0%)	2	1 (50.0%)	1	1 (33.3%)	1	1 (33.3%)
Deafness neurosensory	2	2 (50.0%)	1	1 (50.0%)	1	1 (33.3%)	0	0
Deafness	0	0	0	0	0	0	1	1 (33.3%)
External ear disorder	0	0	1	1 (50.0%)	0	0	0	0
Middle ear effusion	1	1 (25.0%)	0	0	0	0	0	0
Cardiac disorders	3	3 (75.0%)	0	0	6	2 (66.7%)	12	1 (33.3%)
Tachycardia	1	1 (25.0%)	0	0	6	2 (66.7%)	11	1 (33.3%)
Cardio-respiratory arrest	0	0	0	0	0	0	1	1 (33.3%)
Right ventricular hypertrophy	1	1 (25.0%)	0	0	0	0	0	0
Sinus tachycardia	1	1 (25.0%)	0	0	0	0	0	0
Vascular disorders	1	1 (25.0%)	1	1 (50.0%)	2	2 (66.7%)	0	0
Flushing	0	0	1	1 (50.0%)	1	1 (33.3%)	0	0
Hypotension	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Respiratory, thoracic and mediastinal disorders	29	4 (100%)	14	1 (50.0%)	61	2 (66.7%)	22	3 (100%)
Cough	6	3 (75.0%)	3	1 (50.0%)	16	2 (66.7%)	3	2 (66.7%)
Atelectasis	4	2 (50.0%)	2	1 (50.0%)	2	2 (66.7%)	3	2 (66.7%)
Rhinorrhoea	4	3 (75.0%)	0	0	11	1 (33.3%)	1	1 (33.3%)
Respiratory failure	3	2 (50.0%)	0	0	2	1 (33.3%)	6	2 (66.7%)
Dyspnoea	0	0	1	1 (50.0%)	1	1 (33.3%)	4	2 (66.7%)
Respiratory distress	1	1 (25.0%)	1	1 (50.0%)	2	1 (33.3%)	1	1 (33.3%)
Wheezing	1	1 (25.0%)	0	0	4	2 (66.7%)	0	0
Hypercapnia	0	0	2	1 (50.0%)	2	2 (66.7%)	0	0
Hypoxia	0	0	0	0	5	2 (66.7%)	0	0
Asthma	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Nasal congestion	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Sinus congestion	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Upper respiratory tract congestion	0	0	0	0	0	0	3	1 (33.3%)
Aspiration	0	0	0	0	2	1 (33.3%)	0	0
Bronchial secretion retention	2	1 (25.0%)	0	0	0	0	0	0
Hypoventilation	0	0	2	1 (50.0%)	0	0	0	0
Rhonchi	0	0	0	0	2	1 (33.3%)	0	0
Sneezing	0	0	0	0	2	1 (33.3%)	0	0
Velopharyngeal incompetence	0	0	0	0	2	1 (33.3%)	0	0
Apnoea	0	0	0	0	1	1 (33.3%)	0	0
Bronchospasm	0	0	0	0	0	0	1	1 (33.3%)
Chronic respiratory failure	0	0	1	1 (50.0%)	0	0	0	0
Dysphonia	1	1 (25.0%)	0	0	0	0	0	0
Epistaxis	0	0	0	0	1	1 (33.3%)	0	0

System Organ Class (SOC) Preferred Term (PT)	Negative (N=4)		Positive (N=8) 100-800 (N=2)		1600-6400 (N=3)		≥12800 (N=3)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Increased upper airway secretion	0	0	0	0	1	1 (33.3%)	0	0
Oropharyngeal pain	0	0	1	1 (50.0%)	0	0	0	0
Pleural effusion	0	0	0	0	1	1 (33.3%)	0	0
Pneumonitis	1	1 (25.0%)	0	0	0	0	0	0
Productive cough	1	1 (25.0%)	0	0	0	0	0	0
Pulmonary hypertension	1	1 (25.0%)	0	0	0	0	0	0
Pulmonary oedema	1	1 (25.0%)	0	0	0	0	0	0
Respiratory tract congestion	0	0	1	1 (50.0%)	0	0	0	0
Stridor	0	0	0	0	1	1 (33.3%)	0	0
Gastrointestinal disorders	11	3 (75.0%)	7	2 (100%)	8	2 (66.7%)	2	2 (66.7%)
Vomiting	4	2 (50.0%)	2	2 (100%)	4	2 (66.7%)	1	1 (33.3%)
Diarrhoea	4	2 (50.0%)	1	1 (50.0%)	1	1 (33.3%)	0	0
Constipation	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Teething	0	0	2	1 (50.0%)	0	0	0	0
Dental caries	1	1 (25.0%)	0	0	0	0	0	0
Dysphagia	0	0	0	0	1	1 (33.3%)	0	0
Gingival swelling	0	0	0	0	0	0	1	1 (33.3%)
Mouth ulceration	0	0	0	0	1	1 (33.3%)	0	0
Post-tussive vomiting	0	0	1	1 (50.0%)	0	0	0	0
Salivary hypersecretion	1	1 (25.0%)	0	0	0	0	0	0
Swollen tongue	0	0	1	1 (50.0%)	0	0	0	0
Skin and subcutaneous tissue disorders	11	3 (75.0%)	33	2 (100%)	8	2 (66.7%)	6	1 (33.3%
Rash	1	1 (25.0%)	16	2 (100%)	3	1 (33.3%)	0	0
Urticaria	0	0	15	1 (50.0%)	1	1 (33.3%)	3	1 (33.3%
Dermatitis diaper	4	2 (50.0%)	1	1 (50.0%)	0	0	0	0
Erythema	1	1 (25.0%)	0	0	2	2 (66.7%)	0	0
Dry skin	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Hair growth abnormal	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Angioedema	0	0	0	0	0	0	2	1 (33.3%
Decubitus ulcer	0	0	0	0	0	0	1	1 (33.3%
Dermatitis contact	1	1 (25.0%)	0	0	0	0	0	0
Papule	1	1 (25.0%)	0	0	0	0	0	0
Rash papular	0	0	1	1 (50.0%)	0	0	0	0
Skin disorder	1	1 (25.0%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	7	4 (100%)	3	2 (100%)	4	2 (66.7%)	1	1 (33.3%
Arthralgia	2	2 (50.0%)	0	0	1	1 (33.3%)	0	0
Muscular weakness	2	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Extremity contracture	1	1 (25.0%)	0	0	1	1 (33.3%)	0	0
Joint contracture	1	1 (25.0%)	1	1 (50.0%)	0	0	0	0
Foot deformity	1	1 (25.0%)	0	0	0	0	0	0
Myopathy	0	0	1	1 (50.0%)	0	0	0	0
Pain in extremity	0	0	0	0	1	1 (33.3%)	0	0
Scoliosis	0	0	0	0	0	0	1	1 (33.3%)
Spinal deformity	0	0	1	1 (50.0%)	0	0	0	0
Renal and urinary disorders	1	1 (25.0%)	0	0	0	0	0	0
Nephrolithiasis	1	1 (25.0%)	0	0	0	0	0	0
Reproductive system and breast disorders	1	1 (25.0%)	0	0	0	0	0	0
Balanoposthitis	1	1 (25.0%)	0	0	0	0	0	0
Congenital, familial and genetic disorders	0	0	1	1 (50.0%)	0	0	0	0
Glycogen storage disease type II	0	0	1	1 (50.0%)	0	0	0	0
General disorders and administration site conditions	18	4 (100%)	11	1 (50.0%)	14	2 (66.7%)	15	3 (100%)
Pyrexia	12	4 (100%)	8	1 (50.0%)	10	2 (66.7%)	14	3 (100%)
Pain	2	1 (25.0%)	2	1 (50.0%)	1	1 (33.3%)	1	1 (33.3%)
Asthenia	2	2 (50.0%)	0	0	0	0	0	0
Catheter site rash	0	0	1	1 (50.0%)	0	0	0	0
Mass	1	1 (25.0%)	0	0	0	0	0	0
Swelling	0	0	0	0	1	1 (33.3%)	0	0
Swelling face	0	0	0	0	1	1 (33.3%)	0	0
Unevaluable event	0	0	0	0	1	1 (33.3%)	0	0
Vascular device occlusion	1	1 (25.0%)	0	0	0	0	0	0
Investigations	9	3 (75.0%)	4	2 (100%)	4	2 (66.7%)	6	1 (33.3%)
Oxygen saturation decreased	0	0	0	0	1	1 (33.3%)	5	1 (33.3%)
Body temperature increased	1	1 (25.0%)	0	0	0	0	1	1 (33.3%)
Clostridium test positive	0	0	2	1 (50.0%)	0	0	0	0
Audiogram abnormal	1	1 (25.0%)	0	0	0	0	0	0
Bacterial test positive	1	1 (25.0%)	0	0	0	0	0	0
Blood potassium decreased	0	0	0	0	1	1 (33.3%)	0	0
Blood urine present	1	1 (25.0%)	0	0	0	0	0	0
Electrocardiogram QRS complex prolonged	1	1 (25.0%)	0	0	0	0	0	0
Electrocardiogram QT prolonged	0	0	0	0	1	1 (33.3%)	0	0
Electrocardiogram T wave inversion	0	0	1	1 (50.0%)	0	0	0	0
Fungal test positive	0	0	0	0	1	1 (33.3%)	0	0
Haematocrit decreased	1	1 (25.0%)	0	0	0	0	0	0
Haemoglobin decreased	1	1 (25.0%)	0	0	0	0	0	0
Pseudomonas test positive	1	1 (25.0%)	0	0	0	0	0	0
Tympanometry abnormal	1	1 (25.0%)	0	0	0	0	0	0
Urine output decreased	0	0	1	1 (50.0%)	0	0	0	0
Injury, poisoning and procedural complications	2	2 (50.0%)	1	1 (50.0%)	2	2 (66.7%)	0	0
Anaesthetic complication	1	1 (25.0%)	0	0	0	0	0	0
Femur fracture	0	0	0	0	1	1 (33.3%)	0	0
Joint dislocation	0	0	1	1 (50.0%)	0	0	0	0
Procedural pain	0	0	0	0	1	1 (33.3%)	0	0
Stoma site haemorrhage	1	1 (25.0%)	0	0	0	0	0	0
Product issues	2	2 (50.0%)	0	0	0	0	2	1 (33.3%)
Device malfunction	2	2 (50.0%)	0	0	0	0	2	1 (33.3%)

Note : 1) Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose.
2) MedDRA 24.1 is used.
3) If a patient had more than 1 event for a particular SOC, the patient is counted only once for that SOC.
4) If a patient had more than 1 event for a particular PT, the patient is counted only once for that PT.
5) Patient percentages are based on the full analysis set.
6) Negative: Patients with ADA always negative from first alglucosidase alfa infusion in study.
7) Positive: Patients with ADA ever positive from first alglucosidase alfa infusion in study.

Deaths, serious adverse events, and other significant adverse events

Death

Three (25.0%) patients (all 3 patients were CRIM positive) died during the study; these fatal TEAEs included respiratory failure, glycogen storage disease type II, and cardio-respiratory arrest. All fatal TEAEs were considered unrelated to the study drug (Table 10 and Table 13).

Further details are provided in the patient narratives (8-3-3-narratives-death).

Table 13 - Listing of deaths - Full analysis set

Date of death	Age (months) at death	Cause of death	Any AE leading to death	Autopsy performed	Autopsy result
2010-04-27	17.94	RESPIRATORY FAILURE RELATED TO UNDERLYING POMPE DISEASE	Y	N	
2012-01-24	23.49	POMPE DISEASE AND COMPLICATIONS THEREOF	Y	Y	COMPLICATIONS OF POMPE DISEASE
2015-08-01	53.36	CARDIOPULMONARY ARREST	Y	N	

Note: Age at death = (Date of death - Date of birth + 1) / 30.4375, rounded to the nearest hundredth.
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/ae_dth_f_1.sas OUT=REPORT/OUTPUT/ae_dth_f_1_1.rtf (10MAR2022 - 10:56)

Serious adverse events

A total of 85 treatment-emergent SAEs were reported by 9 patients (75.0%) during the study. The most frequently (>50%) reported SAEs by System Organ Class (SOC) were respiratory, thoracic and mediastinal disorders and infections and infestations (8 patients [66.7%] each) and by PT was pneumonia (7 patients [58.3%]). One patient with CRIM negative status reported SAEs of atelectasis, respiratory distress, and respiratory failure; another CRIM negative patient had SAEs of bacteraemia, pyrexia, hypotension, pulmonary hypertension, and respiratory failure. (16-2-7-ae-data [16.2.7.1.4]). No SAEs were considered as related to the study drug ([16.2.7.1.5]).

Further details are provided in the patient narratives (8-3-3-narratives-sae).

Adverse events leading to treatment discontinuation

No TEAEs leading to permanent discontinuation of the study drug were reported (16-2-7-ae-data [16.2.7.1.17]).

Adverse events of special interest

Adverse events of special interest (AESI) included protocol-defined IARs, algorithm-defined potential IAR, potential immune mediated reactions, anaphylaxis, and hypersensitivity events.

Protocol-defined infusion-associated reactions

Infusion-associated reactions are defined as AEs that occurred during the infusion or within up to 24 hours after the start of infusion and were considered as related or possibly related to the ERT by the Investigator or the Sponsor. At the discretion of the Investigator, AEs occurring ≥24 hours after the start of the infusion that were assessed as related may also have been considered IARs.

A total of 58 protocol-defined IARs were reported by 4 patients (33.3%) during the infusion with the most frequently reported IARs of urticaria (3 patients [25.0%]); rash, vomiting, and tachycardia (2

patients [16.7%] each). Protocol-defined IARs of tachycardia, vomiting, and swelling face were reported by 1 patient (8.3%) day after the infusion (16-2-7-ae-data [16.2.7.1.6]). Further details are provided in the patient narratives (8-3-3-list-narratives). The peak ADA titer value of these 4 patients were: 800 (2 patients), 3200 (1 patient), and 12800 (1 patient) (16-2-8-clin-lab-data [16.2.8.2.6]).

A by-patient listing of IARs is provided in 16-2-7-ae-data [16.2.7.1.13].

Algorithm-defined potential IAR

An alternative definition of IAR which does not rely on the Investigator's assessment of an AE's relationship to the treatment was also employed. It included potential IARs (all AEs started on the day of infusion and those started the day following the infusion).

A total of 107 algorithm-defined potential IARs were reported by 11 patients (91.7%) during the infusion with the most frequently reported IARs of cough (4 patients [33.3%]); urticaria, upper respiratory tract infection, and device malfunction (3 patients [25.0%] each); rash, vomiting, ear infection, flushing, arthralgia, pyrexia, body temperature increased, and tachycardia (2 patients [16.7%] each). Thirty-one algorithm-defined potential IARs were reported by 7 patients (58.3%) the day after the infusion with the most frequently reported IARs of pyrexia (4 patients [33.3%]); vascular device infection, and vomiting (2 patients [16.7%] each) (16-2-7-ae-data [16.2.7.1.7]). A by-patient listing of IARs is provided in 16-2-7-ae-data [16.2.7.1.13].

Potential immune mediated reactions

Standardized Medical Dictionary for Regulatory Activities query (SMQ) criteria were used to identify TEAEs that were potentially immune mediated reactions and those identified are listed in 16-2-7-ae-data [16.2.7.1.15].

During the study, 3 patients met composite criteria of the SMQ for potential immune mediated reactions. Of these, 1 patient had mild TEAEs of oral ulceration and arthralgia while 2 patients (1 patient was CRIM negative) had arthralgia. Further details are provided in the patient narratives (8-3-3-narratives-sae).

Anaphylaxis

Standard MedDRA query criteria used to identify TEAEs that were potentially associated with symptoms of anaphylactic reactions and those identified are listed in 16-2-7-ae-data [16.2.7.1.14].

During the study, 1 patient (with peak ADA titer 3200) met composite criteria of the SMQ for anaphylaxis. The patient experienced 3 TEAEs that matched anaphylaxis SMQ, flushing (mild), urticaria (moderate), and cough (mild) all on Day 1954. All of the events were considered recovered/resolved. The events were considered possibly related to the study drug, which was interrupted as a result of the events. Further details are provided in the patient narratives (8-3-3-narratives-sae).

Hypersensitivity

Standard MedDRA query criteria for hypersensitivity used to identify TEAEs that were potentially associated with symptoms of hypersensitivity and those identified are listed in 16-2-7-ae-data [16.2.7.1.16].

Overall, 11 patients experienced 89 TEAEs that met the criteria of the SMQ for hypersensitivity reactions. The most frequent TEAEs meeting the criteria for hypersensitivity included rash and urticaria. The majority of the events were mild or moderate in intensity. Of the 2 CRIM negative patients, 1 had TEAEs of bronchospasm, respiratory distress, respiratory failure, and gingival swelling and the other CRIM negative patient had respiratory failure that met the criteria of the SMQ for hypersensitivity.

Further details are provided in the patient narratives (8-3-3-list-narratives).

Clinical laboratory evaluations

Laboratory value over time and individual participant changes in laboratory values

Descriptive statistics across visits on treatment for clinical parameters are provided in 16-2-8-clin-lab-data. Summaries of change from baseline in biochemistry, hematology, and urinalysis parameters are presented in [16.2.8.1.1], [16.2.8.1.2], and [16.2.8.1.3], respectively.

The potentially clinically significant abnormalities (PCSA) for clinical laboratory tests are summarized in 16-2-8-clin-lab-data [16.2.8.1.4].

Hematology

A by-patient listing of hematology parameters is provided in 16-2-8-clin-lab-data [16.2.8.1.6].

Clinically significant values for hematology were reported for 2 patients. One patient had abnormal hematocrit and hemoglobin values at baseline and events of decreased hemoglobin and hematocrit (both mild) were reported. The events were considered as not related to the study drug by the Investigator. Another patient had abnormal hematocrit, hemoglobin, platelet count, erythrocyte count, basophils, lymphocyte count, and neutrophil count at Week 468.

Clinical chemistry

A by-patient listing of clinical chemistry parameters is provided in 16-2-8-clin-lab-data [16.2.8.1.5].

Clinically significant values for clinical chemistry were reported for 2 patients. One patient had abnormal alanine aminotransferase, aspartate aminotransferase, and creatine kinase values at baseline. Another patient had abnormal sodium and glucose levels at Week 364 and was reported with an SAE of diabetes mellitus. The event was considered as not related to the study drug by the Investigator.

Urinalysis

A by-patient listing of urinalysis is provided in 16-2-8-clin-lab-data [16.2.8.1.7]. Clinically significant values for urinalysis were reported for 1 patient. The patient had abnormal urine bacteria and urine occult blood values at Week 208 and AEs of bacterial test positive and blood urine present (both mild) unrelated to the study drug were reported.

Vital signs, ECG, physical findings, and other safety observations

Vital signs

A by-patient listing of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) by visit and time point is provided in 16-2-7-other-safety [16.2.7.1.1]. The PCSA for vital signs are summarized in [16.2.7.1.2].

Clinically significant vital sign assessments were recorded for 2 patients. For 1 patient who had increased heart rate at Week 12 post infusion, an event of tachycardia (moderate) probably related to the study drug was reported. The patient also had increased heart rate and body temperature at Week 68 and events of tachycardia (moderate) and pyrexia (mild) probably related to the study drug were reported. Both the events resolved on the same day. Another patient had increased body temperature at Week 80 and the event of pyrexia (moderate) not related to the study drug was reported.

Electrocardiograms

Individual patient ECG results with clinically significant abnormalities are provided in 16-2-7-other-safety [16.2.7.3.3]. Summaries of ECG parameters and PCSA for ECG are provided in [16.2.7.3.1], [16.2.7.3.2], and [16.2.7.3.4], respectively.

Conduction abnormalities, left ventricular hypertrophy, and to a lesser extent right ventricular hypertrophy were prevalent at baseline and decreased over time. Abnormal sinus node rhythm and arrhythmias occurred throughout follow-up (16-2-7-other-safety [16.2.7.3.3]).

Physical examination findings

All physical examination results are listed for each patient in 16-2-7-other-safety [16.2.7.2.1].

Findings from physical examinations generally reflected the various manifestations of Pompe disease, including abnormalities in neurological; head, eyes, ears, nose, and throat; skin, extremities/joints; abdomen, heart, lungs; and general appearance in the majority of patients.

Other observations related to safety

Neuroimaging assessment

Three patients in the study had abnormal magnetic resonance imaging findings mostly related to white matter changes. These abnormal findings are summarized in 16-2-7-other-safety [16.2.7.4.1].

Hearing testing

Tympanometry assessments were abnormal from baseline for the majority of patients (16-2-7-other-safety [16.2.7.5.1]). Audiometry revealed abnormalities in most of the patients at baseline and at Weeks 52, 104, 156, 208, 260, and 416 [16.2.7.5.2].

Visual screening

By-patient listings of visual testing are provided in 16-2-7-other-safety [16.2.7.6.1], [16.2.7.6.2], [16.2.7.6.3], [16.2.7.6.4], [16.2.7.6.5], and [16.2.7.6.6].

Abnormal visual assessments reported in the study (16-2-7-other-safety [16.2.7.6.1]) were:

• Conjunctival melanosis: 1 patient (baseline, Week 52, study completion/discontinuation visit)

• Ptosis: 2 patients (at Weeks 52–156/not recorded thereafter, and Weeks 156–260)

• Left eyelid bruising from recent trauma (1 patient), right eye posterior synechiae versus persistent vasculature (1 patient) (at Week 52).

Immunogenicity

Of the 12 patients with baseline ADA status, 8 patients (66.7%) with positive titer had persistent ADA response. Of these, 3 patients (25.0%) had high ADA response (Table 14).

The overall median peak titer from time of study entry for the IgG positive patients was 3805.5 (range of 800 to 25600) (Table 15). Three (1 patient was CRIM negative) of 8 patients had a peak titer of ≥ 12800.

The overall median last titer was 800 (range of 100 to 12800) (Table 16) for the patients who were IgG positive. Only 1 of 8 patients had a last titer of ≥12800. Most patients showed decreased titers by last assessment (16-2-8-clin-lab-data [16.2.8.2.5]).

A by-patient listing of anti-rhGAA ADA data is provided in 16-2-8-clin-lab-data [16.2.8.2.6] and neutralizing antibody testing data is provided in [16.2.8.2.8]. Individual plots of anti-alglucosidase alfa titers over time for patients with at least 1 antibody positive titer is provided in [16.2.8.2.7].

Table 15 - Alglucosidase alfa ADA peak titer by baseline ADA status - Full analysis set

Characteristic/Statistic	NEGATIVE (N=2)	POSITIVE (N=8)
Time (in days) from seroconversion to first alglucosidase alfa ADA peak titer		
Number	0	NA
Mean (SD)		
Median		
Q1 : Q3		
Min : Max		
ADA peak titer for patients ever ADA positive		
Number	0	8
Geometric Mean		3805.5
Geometric SD		3.8
Median		3200.0
Q1 : Q3		1200.0 : 12800.0
Min : Max		800 : 25600
Number (%) of patients in ADA peak titer categories:		
Number	2	8
Always negative	2 (100%)	NA
100-800	0	2 (25.0%)
1600-6400	0	3 (37.5%)
≥12800	0	3 (37.5%)
ADA peak titer for patients ever ADA positive		
Number	0	8
Geometric Mean		3805.5
Geometric SD		3.8
Median		3200.0
Q1 : Q3		1200.0 : 12800.0
Min : Max		800 : 25600
Number (%) of patients in ADA peak titer categories:		
Number	2	8
Always negative	2 (100%)	NA
100-800	0	2 (25.0%)
1600-6400	0	3 (37.5%)
≥12800	0	3 (37.5%)

Peak titer refers to the first occurrence of the maximum titer value from first study infusion to the end of the study.
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/lab_is_titer_f_t.sas OUT=REPORT/OUTPUT/lab_is_titer_peak_f_t_i.rtf (10MAR2022 - 10:46)

Table 16 - Alglucosidase alfa ADA last titer by baseline ADA status - Full analysis set

Characteristic/Statistic	NEGATIVE (N=2)	POSITIVE (N=8)
ADA last titer for patients ever IgG positive		
Number*	0	8
Geometric Mean		872.4
Geometric SD		5.6
Median		800.0
Q1 : Q3		200.0 : 4000.0
Min : Max		100 : 12800
Number (%) of patients in ADA last titer categories:		
Number	0	8
≤800	0	5 (62.5%)
1600-6400	0	2 (25.0%)
≥12800	0	1 (12.5%)

Note: *Only patients with non-zero last titers are included.
PGM=PRODOPS/GZ419829/AGLU03606/CSR/REPORT/PGM/lab_is_titer_f_t.sas OUT=REPORT/OUTPUT/lab_is_titer_last_f_t_i.rtf (10MAR2022 - 10:46)

Complement Activation, Serum Tryptase, and Serum Immunoglobulin E Antibody Testing

No patients met the protocol criteria for immunology testing due to IARs. However, 1 patient tested positive for complement activation and was within normal range for serum tryptase (16-2-8-clin-lab-data [16.2.8.2.9]).

One patient had a positive result for intradermal skin testing (wheal longest diameter of 7 mm, and erythema longest diameter of 12 mm) (16-2-8-clin-lab-data [16.2.8.2.10]).

CHMP comments on safety:

The secondary objective of this Phase 4 long-term study of growth and development outcomes in patients with infantile-onset Pompe disease (IOPD) receiving alglucosidase alfa (AGLU03606/LTS12869) was to collect long-term safety data. This study was ongoing during the last PBRER for alglucosidase alfa. The 12 participants were already enrolled at that time.

*According to the currently submitted data, the **safety population** of AGLU03606/LTS12869 study was the same as the full analysis set which included the 12 patients who began alglucosidase alfa (Myozyme®) infusions prior to 1 year of age at a dose of 20 mg/kg every 2 weeks and were followed for up to 10 years.*

Only a single patient completed the study. There were no TEAEs leading to permanent discontinuation of the study drug. Primary reasons for study discontinuation were mainly wishes to withdraw by parents/guardians (half of patients – from Day 393 to Day 2876), death in 3 patients (25.0%) and non-compliance with study drug in 2 patients (16.7% - both discontinued at Day 2851).

In the 3 patients (all CRIM positive, <2 years old) who died during the study, cause of death was either reported as respiratory insufficiency/failure due to underlying Pompe disease on Day 218, Pompe disease and complications on Day 538, or cardio-respiratory arrest on Day 1228. The deaths were assessed as unrelated to alglucosidase alfa by the investigators. No safety concern could be identified from the available reported information.

All patients but one experienced TEAEs, i.e., a total of 484 TEAEs reported during the study. The majority of TEAEs were non-serious (427/484, 88.2% of total TEAEs), and mild to moderate in severity (437/484, 90.3%) all but two patients (81.8% of patients) experienced TEAEs assessed as severe.
Regardless of causality, TEAEs belonged to the main following SOCs: Infections and infestations (all patients); Respiratory, thoracic and mediastinal disorders; General disorders and administration site conditions (10/11 patients each); Musculoskeletal and connective tissue disorders (9/11); Skin and subcutaneous tissue disorders, Investigations (8/11 each); Ear and labyrinth disorders, Nervous system disorders, Cardiac disorders, Eye disorders (6/11 each); Injury, poisoning and procedural

complications (5/11); Vascular disorders, Metabolism and nutrition disorders (4/11); Product issues (3/11). Most events were consistent with the manifestations and complications of the underlying Pompe disease or device related issues.
According to available information from the MAH, 63 TEAEs (13.0%), all non-serious, were related to alglucosidase alfa in 4 patients. No laboratory-related TEAEs were reported. All but 2 of the related TEAEs were characterized as protocol-defined IARs (96.8%). The related TEAEs were all listed/reflected in Myozyme PI: tachycardia, flushing, cough*, vomiting, urticaria*, rash, angioedema, pyrexia, swelling face, oxygen saturation decreased, and body temperature increased. *anaphylaxis*

*Among **AESI**, the potential immune mediated reactions of ulceration (1) and arthralgia (3) identified in 3 patients were all assessed as unrelated to study drug by the investigator.*

*No safety issue in **physical findings, ECG parameters** and **other safety observations** have been identified. The changes observed during the study were generally consistent with manifestations of the underlying Pompe disease.*

*All patients had baseline **ADA status**, of which 8 with positive titers had persistent ADA response (incl. 3 with high ADA response ⩾12800, 3 with intermediate ADA titer 1600-6400, and 2 with low ADA titer 100-800). No patient had tolerized ADA response. One patient tested positive for complement activation and skin testing. Neutralizing antibody testing were performed in 3 patients (1 at withdrawal from the study, 1 at W26, and the remaining at W12) which were negative.*

Based on the data provided by the MAH dealing with the final results of study AGLU03606/LTS12869, notably including reviews of case narrative information, no new safety concerns have been identified with alglucosidase alfa as compared to previous studies and experiences in IOPD patients treated with alglucosidase alfa at a dose of 20 mg/kg qow. No safety issue which could alter the known safety profile of alglucosidase alfa in IOPD patient population has been found. However, very few patients (12) were enrolled in this study, hampering any meaningful conclusion.

2.3.3. Discussion on clinical aspects

Considering the size of the population (12 patients) the number of patients who discontinued the study (11), the mean duration of treatment (4.43 years), the observational nature of the study, and the paucity of the data, it is difficult to draw any firm conclusion regarding the effect of alglucosidase alfa on long term growth and development of IOPD patients.
The treatment-related AEs reported in 4 patients treated with alglucosidase alfa were consistent with its known safety profile. Based on the data provided by the MAH regarding the final results of this study, no new safety concerns have been identified as compared to previous studies and experiences in infantile-onset Pompe patients treated with alglucosidase alfa at a dose of 20 mg/kg qow.

Taking into account the rarity and the seriousness of the pathology, the known safety profile of alglucosidase alfa, the benefit/risk ratio of alglucosidase alfa at a dose of 20 mg/kg qow remains positive in patients with IOPD.

3. Rapporteur's overall conclusion and recommendation

Based on the data provided by the MAH regarding the final results of study AGLU03606/LTS12869 - IOPD study, no new safety concerns have been identified as compared to previous studies and experiences in IOPD patients treated with alglucosidase alfa at a dose of 20 mg/kg qow.

☒ **Fulfilled:**

No regulatory action required.