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EMA/CHMP/70532/2016
Procedure Management and Committees Support Division

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

Myozyme

alglucosidase alfa

Procedure no: EMEA/H/C/000636/P46/055.1

Note

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

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LIST OF ABBREVIATIONS

AE: adverse event
ALT: alanine aminotransferase
ARRB: Allergic Reaction Review Board
AST: aspartate aminotransferase
CI: confidence interval
CK: creatine kinase
C_{max}: maximal concentration
ECG: electrocardiogram
ECHO: echocardiogram
FA: full analysis
FVC: forced vital capacity
GAA: acid α-glucosidase
GMFCS: Gross Motor Function Classification System
GMFM-88: Gross Motor Function Measure-88
GPE: Global Pharmacovigilance and Epidemiology
IAR: infusion associated-reaction
IgE: immunoglobulin E
IgG: immunoglobulin G
IMP: investigational medicinal product
IV: intravenous
LDH: lactate dehydrogenase
LOCF: last observation carried forward
LVM: left ventricular mass
LVMI: left ventricular mass index
LVM-Z: left ventricular mass Z-score
MedDRA: Medical Dictionary for Regulatory Activities
MEP: maximal expiratory pressure
MIP: maximal inspiratory pressure
PFT: pulmonary function testing
PK: pharmacokinetic
PP: per protocol
PT: preferred term
qow: every other week
qw: every week
rhGAA: recombinant human acid α-glucosidase
SAE: serious adverse event
SMQ: Standardized MedDRA Query
SOC: system organ class
TEAE: treatment emergent adverse events

Introduction

On 29.06.2015, the MAH submitted a completed paediatric study for MYOZYME, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure PAM 055.

A short critical expert overview has also been provided.

On 23.10.2015, the MAH submitted its response to CHMP comment on the Clinical Study Report (CSR) of the Advance study (AGLU09411).

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study AGLU09411 "A Phase 4, open-label, prospective study in patients with Pompe disease to evaluate the efficacy and safety of alglucosidase alfa produced at the 4000L scale" is a stand-alone study.

The MAH confirmed that study ADVANCE (AGLU09411) is not part of an approved Paediatric Investigation Plan. The MAH has not identified any new paediatric information from this study that would need to be added to the EU Product Information.

1.2. Information on the pharmaceutical formulation used in the study

Alglucosidase alfa has been developed as an ERT for the treatment of Pompe disease. Clinical trials have been completed in patients with infantile and late-onset Pompe disease, thus covering the extremes of severity of the disease spectrum.

In the United States (US), alglucosidase alfa is currently manufactured at two different production scales. Alglucosidase alfa manufactured at the 160L scale (initial pilot scale) has a brand name of Myozyme® (alglucosidase alfa) and alglucosidase alfa manufactured at the 4000L (final manufacturing scale) has a brand name of Lumizyme. The present study aimed to clinically assess the efficacy and safety of treatment with alglucosidase alfa produced at the 4000L scale in patients with Pompe disease previously treated with alglucosidase alfa 160L. The data obtained in this study were expected by the MAH to allow greater access to alglucosidase alfa produced in larger quantity at the 4000L scale for patients currently being treated with alglucosidase alfa 160L.

In Europe, alglucosidase alfa (brand name Myozyme) produced at the 4000L scale since 2008.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final reports for:

- AGLU 09411: A phase 4, open-label, prospective study in patients with Pompe disease to evaluate the efficacy and safety of alglucosidase alfa produced at the 4000 L scale.

1.3.2. Clinical study

Description

AGLU 09411 is an open-label, prospective study of US patients aged 1 year or older at time of consent who had a confirmed diagnosis of Pompe disease and were previously treated with alglucosidase alfa 160 L

Methods

Objective(s)

The aim of the study was to evaluate the efficacy and safety of treatment with alglucosidase alfa produced at the 4000 L scale in patients previously treated with 160 L scale alglucosidase alfa.

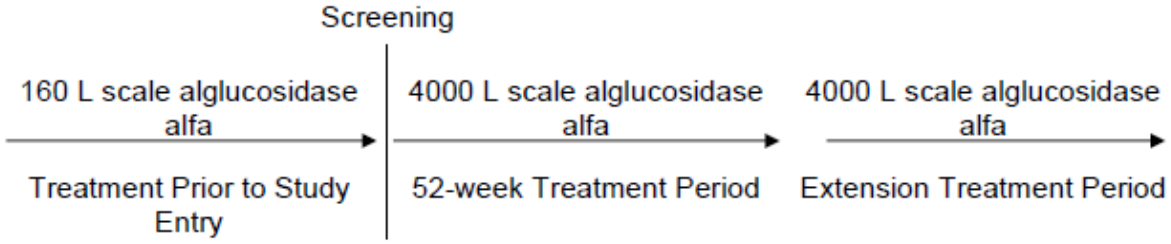
Study design

This was an open-label, prospective study of US patients aged 1 year or older at time of consent who had a confirmed diagnosis of Pompe disease and were previously treated with alglucosidase alfa 160 L.

All eligible patients received an intravenous (IV) infusion of alglucosidase alfa (recombinant human acid α-glucosidase) produced at the 4000 L scale for 52 weeks at the same dose and dose regimen used for their routine treatment prior to the study.

Following the 52-week treatment period, patients had the option to continue treatment with alglucosidase alfa 4000 L in an extension period until the label expansion of Lumizyme was approved by the FDA.

Patients should have remained on a stable dose of alglucosidase alfa for the duration of the study if clinically feasible. If a patient experienced clinical worsening as defined by the primary efficacy objective that was sustained on repeated measurement, the patient may have been managed per the discretion of the Investigator which may have included return to treatment with alglucosidase alfa 160 L.



Study population /Sample size

Screened patients were defined as any patient who signed the informed consent, and who met the inclusion criteria and none of the exclusion criteria:

Main inclusion criteria:

- The patient must have been at least 1 year of age at the time of informed consent.
- The patient had a diagnosis of Pompe disease and must have received treatment with alglucosidase alfa 160 L prior to screening.

- The patient, if female and of childbearing potential, must have had a negative pregnancy test (urine beta-human chorionic gonadotropin) at baseline. Note: all female patients of childbearing potential and sexually mature males must have agreed to use a medically accepted method of contraception throughout the study.

Main exclusion criteria:

- The patient had within the past 3 months prior to screening received or was at time of screening receiving any investigational product other than alglucosidase alfa 160 L or was at time of screening participating in another clinical treatment study.
- The patient, in the opinion of the Investigator, was clinically unstable and would not have been expected to survive to completion of the 52-week treatment period.

Sample size

Sample size of this study was not determined based on statistical power. All eligible patients among those who were receiving alglucosidase alfa 160 L in the US and met eligibility criteria may have enrolled into the study.

Treatments

The investigational medicinal product (IMP) in this study was Alglucosidase alfa an rhGAA produced at the 4000 L manufacturing scale.

All eligible patients were to receive an intravenous (IV) infusion at the same dose and dose regimen used for their routine treatment prior to the study. If clinically feasible, patients should have remained on a stable dosing regimen throughout the duration of the study.

Patients were required to remain in the hospital or the infusion center for observation of AEs for 2 hours after each infusion.

Patients may have had the option for home infusions. Home infusion may have begun after receiving 2 alglucosidase alfa infusions during study participation with infusions monitored in a hospital or an infusion center and no history of moderate or severe infusion associated-reaction IARs or SAEs. Because of the possibility of anaphylactic reactions, personnel competent in recognizing and treating adverse reactions (including anaphylactic reactions) were readily available throughout the home infusion.

Outcomes/endpoints

Efficacy was assessed through echocardiographic evaluation of left ventricular mass (dimensions and function), evaluation of respiratory function, pulmonary function testing, and gross motor function measurement using the GMFM-88 scale.

The GMFM-88 scale was designed to measure gross motor function in children with cerebral palsy and specifically detected quantitative changes in gross motor function. There was no age cut-off for the GMFM-88.

The primary efficacy endpoint of this study was the proportion of patients transitioned to treatment with 4000 L scale alglucosidase alfa who were clinically stable or improved at Week 52, defined as the absence of any of the following definitions of clinical worsening:

• Death due to disease progression or new dependency on invasive ventilation

• Decline in cardiac status from baseline with an increase in LVM-Z of >1 Z-score above a Z-score of 2 (ie, outside the normal range)

• Decline in motor function from baseline as measured by an absolute decrease in GMFM-88 Total Percent Score of ≥8%

• Decline in pulmonary function from baseline with a decrease of ≥15% in absolute value in FVC percent predicted in the sitting position

• Decline in cardiac status, motor function, and pulmonary function had to be confirmed by retest within 4 weeks.

The secondary endpoints of this study were:

• Percent survival at Week 52

• Percent invasive ventilator-free survival at Week 52

• Change from baseline on LVM-Z at Week 52

• Change from baseline on GMFM-88 Total Percent Score at Week 52

• Change from baseline in FVC percent predicted in sitting position at Week 52

Statistical Methods

Four analysis populations were defined for this study: the full analysis (FA) set, per protocol (PP) set, safety set, and PK analysis set. Patients who received at least one infusion of study drug were included in the FA set. All patients in the FA set and who satisfied the following conditions were included in the PP set:

• Received alglucosidase alfa in 4000 L scale only throughout the trial

• Completed the study at Week 52

• The safety set was the same as the FA set. Patients who consented to participate in the PK analysis and provided at least one blood sample pre- and post-infusion were included in the PK Set.

Results were summarized descriptively and no formal hypothesis testing was performed. Categorical variables were summarized using frequency count and percentage distribution. Continuous variables were summarized using number of observations, mean, standard deviation, median, minimum and maximum. For variables with skewed distributions, additional 25th and 75th percentiles and inter-quartile range were also provided. The 95% confidence intervals CI were presented for a selected number of variables as described in the sections below. As appropriate, exact method was used for the derivation of 95% CI.

Results

Recruitment / Number analysed

Study Initiation Date (first patient consented): 09 March 2012

Study Completion Date (last patient completed): 29 December 2014

In total, 114 patients were screened, and 113 patients were treated. Of these, 100 patients (88.5%) completed the Week 52 visit.

Two patients did not meet all inclusion criteria but were treated in the study with the agreement of the Sponsor's Medical Officer: A patient was receiving investigational gene therapy at the time of screening, and a patient was consented prior to 1 year of age although the patient did not receive treatment with alglucosidase alfa 4000 L until after reaching 1 year of age.

Of the 13 patients who discontinued before Week 52, 8 patients discontinued when the study was terminated by the Sponsor upon approval of the Lumizyme label expansion and transitioned to commercial treatment, 2 patients died, and 2 patients refused further treatment in the study and died shortly after withdrawal. One patient was discontinued due to physician decision.

Of the 100 patients who entered the extension phase, 45 patients (39.8%) received study drug within the extension part of the trial for at least 18 months. A total of 55 patients (48.7%) terminated the study before Month 18 of the extension phase. Of these, 4 patients (3.5%) died and 51 (45.1%) discontinued due to transitioned to commercially available alglucosidase alfa either because of physician decision or when the study was terminated by the Sponsor upon approval of the Lumizyme label expansion.

Patient disposition - full analysis population

Parameter	Alglucosidase Alfa 4000 L N (%)
Number of Patients Who Were Screened	114
Number of Patients Who Passed Screening	112
Treated, n (%)	113 (100.0)
Completed Week 52, n (%)	100 (88.5)
Discontinued Before Week 52, n (%)	13 (11.5)
Adverse Events	0
Death	2 (1.8)
Lack of Efficacy	0
Lost to Follow-Up	0
Pregnancy	0
Non-Compliance with Study Drug	0
Progressive Disease	0
Study Terminated by Sponsor	8 (7.1)
Withdraw by Subject	2 (1.8)
Protocol Violation	0
Technical Problems	0
Physician Decision	1 (0.9)
Recovery	0
Refused Further Treatment	0
Other	0
Entered into Extension Phase, n (%)	100 (88.5)
Completed Extension Month 18, n (%)	45 (39.8)
Discontinued Before Extension Month 18, n (%)	55 (48.7)
Adverse Events	0
Death	4 (3.5)
Lack of Efficacy	0
Lost to Follow-Up	0
Pregnancy	0
Non-Compliance with Study Drug	0
Progressive Disease	0
Study Terminated by Sponsor	0
Withdraw by Subject	0
Protocol Violation	0
Technical Problems	0
Physician Decision	0
Recovery	0
Refused Further Treatment	0
Other	51 (45.1)

Note: There were 2 patients who did not meet all inclusion criteria but were treated in the study with the agreement of the Sponsor's Medical Officer: a patient was receiving investigational gene therapy at the time of screening, and a patient was consented prior to 1 year of age, but did not receive Lumizyme until 1 year of age. One patient passed screening but was not treated in the study,because he/she went onto commercial Lumizyme upon FDA approval. Note: Percentages are based on total number of patients treated.

Baseline data

Demography :

The number of male and female patients was comparable at 60 (53.1%) and 53 (46.9%), respectively. The majority of patients were white (71 patients, 62.8%) while 26 (23.0%) patients were Black and 7 (6.2%) were Asian.

The median age at first infusion of Myozyme was 0.6 years (range: 0.0 to 11.4). Of the 113 treated patients, 46 patients received Myozyme treatment prior to 6 months of age, and 26 additional patients were treated between 6 months and < 1 year of age (by definition, a total of 72 [63.6%] patients had classical infantile-onset Pompe disease).

All patients who were 12 months of age or older on alglucosidase alfa 160 L treatment, regardless of phenotype (infantile-onset versus late-onset), were given the opportunity to enroll into this study. The median age at first infusion of alglucosidase alfa 4000 L was 3.8 years (range: 1.0 to 18.7), and the majority of patients (84.1%) were under the age of 8 years at the time of first infusion with alglucosidase alfa 4000 L.

Demography - full analysis population

Parameter	Alglucosidase Alfa 4000L (N=113)
Age (years) at First Infusion of Alglucosidase Alfa 4000L	
n	113
Mean	4.8
Median	3.8
Std. Dev.	3.73
Min., Max.	1.0, 18.7
Age Group (years) at First Infusion of Alglucosidase Alfa 4000L, n (%)	
<2	33 (29.2)
2 - <5	37 (32.7)
5 - <8	25 (22.1)
8 - <12	11 (9.7)
≥12	7 (6.2)
Height (cm)	
n	106
Mean	104.5
Median	100.9
Std. Dev.	25.08
Min., Max.	68.9, 165.9
Weight (kg)	
n	111
Mean	18.7
Median	14.8
Std. Dev.	11.26
Min., Max.	7.3, 69.6
BMI (kg/m^2)	
n	105
Mean	16.3
Median	15.8
Std. Dev.	2.82
Min., Max.	12.0, 28.9

Source: 16-2-4-demo-data [Table 14.1.6]

Parameter	Alglucosidase Alfa 4000L (N=113)
Sex, n (%)	
Male	60 (53.1)
Female	53 (46.9)
Ethnicity, n (%)	
Hispanic or Latino	18 (15.9)
Not Hispanic or Latino	92 (81.4)
Not Reported	1 (0.9)
Unknown	2 (1.8)
Race, n (%)	
American Indian or Alaska Native	0
Asian	7 (6.2)
Black	26 (23.0)
Japanese	0
Native Hawaiian or Other Pacific Islander	0
White	71 (62.8)
Not Reported	2 (1.8)
Unknown	0
Multiple	7 (6.2)
Age (years) at First Infusion of Myozyme	
n	113
Mean	1.7
Median	0.6
Std. Dev.	2.68
Min., Max.	0.0, 11.4
Age Group (years) at First Infusion of Myozyme, n (%)	
<0.5	46 (40.7)
0.5 - <1	26 (23.0)
1 - <5	29 (25.7)
5 - <8	5 (4.4)
8 - <12	7 (6.2)

Pompe disease characteristics at baseline:

The patients experienced the first symptoms of Pompe disease at a median age of 0.3 years (range: 0.0 to 8.9 years), and the median age of being diagnosed with Pompe disease was 0.5 years (range: 0.0 to 8.8 years). The mean duration of disease (as defined as the years since symptom onset to first infusion of Myozyme 160L) was 1.1 years (median, 0.2 years; range: 0 to 11.4 years). Approximately half of the patients had disease duration of less than 0.24 years.

The majority of patients (65 patients, 57.5%) were not currently ambulatory, with 11 of these patients having been ambulatory at some point. Overall, 43 (38.1%) patients were on mechanical ventilator support, with 32 (28.3%) on invasive ventilator support at the Screening Visit. The median duration of dependence on invasive ventilator support was 3.9 years (range: 0.1 to 17.0 years).

Pompe disease characteristics - full analysis population

Parameter	Alglucosidase Alfa 4000L (N=113)
Age at First Symptoms (years)	
n	112
Mean	0.5
Median	0.3
Std. Dev.	1.15
Min., Max.	0.0, 8.9
Duration of Disease (years)[a]	
n	111
Mean	1.1
Median	0.2
Std. Dev.	2.44
Min., Max.	0.0, 11.4
Duration of Disease (years), n (%)	
< 0.24 Years	55 (48.7)
≥ 0.24 Years	56 (49.6)
Age at Initial Diagnosis (years)	
n	113
Mean	0.9
Median	0.5
Std. Dev.	1.40
Min., Max.	0.0, 8.8
Currently Ambulatory, n (%)	
Yes	48 (42.5)
No	65 (57.5)
If No, Ever Ambulatory	11 (9.7)
Currently Using Ambulatory Devices	54 (47.8)
Cane	0
Walker	10 (8.8)
Wheelchair	39 (34.5)
Other[b]	23 (20.4)
Currently on Mechanical Ventilatory Support, n (%)	43 (38.1)
Invasive Ventilation	32 (28.3)
Noninvasive Ventilation	11 (9.7)
No	70 (61.9)
Duration of Dependency on Invasive Ventilatory Support (years)	
n	32
Mean	4.8
Median	3.9
Std. Dev.	4.14
Min., Max.	0.1, 17.0

Source: 16-2-4-demo-data [Table 14.1.7]

a Years from symptom onset to first Myozyme use.

b Other includes: ankle foot orthoses, brace of legs, cruising (not independently ambulating), foot brace, holding someone's hand, kidcart (stroller), knee immobilized, knee orthoses, rifton adapted tricycle, scooter, stander, stroller (adaptive), walker, wheelchair.

Myozyme treatment

Most patients received 20 mg/kg Myozyme qow (81 patients [71.7%]) or 20 mg/kg weekly (13 patients [11.5%]) prior to the study. 10 patients received Myozyme treatment at 40 mg/kg qow prior to entering the study. Mean duration of prior treatment was 3.1 years, ranging from 0.0 to 12.8 years.

Efficacy results

At Week 52, most patients remained on the same alglucosidase alfa dosing regimen that they hadtaken prior to the study

Dosing regimen: Shift from prior Myozyme use to Week 52 – safety population

	Week 52 Dosing Regimen (N=100)							
	10 mg/kg QOW (N=1)	10 mg/kg Weekly (N=1)	20 mg/kg QOW (N=68)	20 mg/kg Weekly (N=10)	30 mg/kg QOW (N=6)	30 mg/kg Weekly (N=2)	40 mg/kg QOW (N=8)	40 mg/kg Weekly (N=4)
Prior Myozyme Use								
10 mg/kg QOW	0	0	0	0	0	0	0	0
10 mg/kg Weekly	0	0	0	1 (10.0)	0	0	0	0
20 mg/kg QOW	1 (100.0)	1 (100.0)	67 (98.5)	1 (10.0)	1 (16.7)	0	0	0
20 mg/kg Weekly	0	0	1 (1.5)	7 (70.0)	0	2 (100.0)	0	2 (50.0)
30 mg/kg QOW	0	0	0	0	3 (50.0)	0	0	0
30 mg/kg Weekly	0	0	0	1 (10.0)	0	0	0	0
40 mg/kg QOW	0	0	0	0	2 (33.3)	0	8 (100.0)	0
40 mg/kg Weekly	0	0	0	0	0	0	0	2 (50.0)

Source: 16-2-5-cdc-data [16.2.5.1 Table 14.3.1.1.4]
Note: Dosing regimen at week 52 is determined based on 4 weeks' observation immediately before week 52.

PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint was the proportion of patients transitioned to treatment with 4000 L scale alglucosidase alfa who were clinically stable or improved at Week 52. At Week 52, 83.7% (95% CI: 75.1%, 90.2%) of patients were clinically stable or improved.

For the 17 patients who declined, the most frequent reasons were GMFM decreased ≥8% (12 of 90 patients [13.3%]), FVC decreased ≥15% (2 of 22 patients [9.1%]), and dependency on invasive ventilator (5 out of 71 patients [7.0%]). Of the patients who declined, 2 patients died prior to 52 weeks on study.

Percentage of patients who were clinically stable or improved after transitioning to 4000L scale Alglucosidase Alfa - full analysis population

	Week 52 (n=104)		
	n/N	%	95% CI[a]
Clinically Stable or Improved [b]	87/104	83.7%	75.1% - 90.2%
Declined [b]	17/104	16.3%	9.8% - 24.9%
Death	2/102	2.0%	0.2% - 6.9%
Dependency on Invasive Ventilator[c]	5/71	7.0%	2.3% - 15.7%
LVMZ[d] Increase 1 Z-score[e]	0/67	0.0%	0.0% - 5.4%
GMFM Decreased ≥ 8%	12/90	13.3%	7.1% - 22.1%
FVC Decreased ≥ 15%	2/22	9.1%	1.1% - 29.2%

Source: 16-2-6-eff-response-data [Table 14.2.1.1.1]

Note: 'Clinically stable or improved' is defined as the absence of 5 conditions: death, new dependency on invasive ventilator, an increase of LVMZ >1 Z-score, a decrease of GMFM total percentage score ≥8%, and a decrease of FVC% predicated at sitting position ≥15%.

a Based on exact binomial distribution.

b Percentage is calculated based on the number of patients who had at least one non-missing data from the components defining the primary efficacy endpoint.

c Patients who were dependent on invasive ventilator at baseline are excluded.

d LVMZ is from M-Mode

e The observed LVMZ also needs to be >2 Z-score indicating the heart is enlarged compared to the normal population.

SECONDARY EFFICACY ENDPOINTS

Percent survival at Week 52

The percent of patients surviving remained steady throughout the study from 3 to 12 months from the first 4000 L infusion. At 12 months, the Kaplan-Meier estimate of survival was 98.1% (95% CI: 92.73, 99.53).

Percent invasive ventilator-free survival at Week 52

The Kaplan-Meier estimate of invasive ventilator-free survival decreased slightly from 3 months (95.1%; 95% CI: 87.38, 98.12) to 12 months (92.4%; 95% CI: 83.89, 96.53) from the first 4000 L infusion.

Change from baseline on LVM-Z at Week 52

The mean LVM Z-score was stable throughout the study, with a mean (SD) change from baseline of -0.5 (1.71) at Week 52.

Change from baseline on GMFM88 Total Percent Score at Week 52

GMFM-88 total score increased from baseline, indicating an improvement in motor function, with a mean (SD) change from baseline in total percent score of 3.7 (17.46) at Week 52.

Change from baseline in FVC percent predicted in sitting position at Week 52

Few patients (22 of 113) were included in the analysis of FVC percent predicted at Week 52 because PFTs were not required for young patients unable to reliably undergo testing and PFTs were unobtainable in patients who received invasive ventilation.

At Week 52, the mean (SD) change from baseline in FVC percent predicted was 2.3 (11.80).

Pharmacokinetic Evaluation in Study AGLU09411

Because participation in PK testing was optional in this study, plasma concentration results are available only for 3 patients. Due to the limited data set, PK results and drug concentrations for these patients are listed only and have not been analysed.

CHMP comments on efficacy:

The objectives of study AGLU09411 was to evaluate the efficacy and safety *of alglucosidase alfa produced in larger quantity in the 4000 L scale in patients previously treated with alglucosidase alfa produced at 160L scale.*

This study is a phase IV prospective open label non comparative study in which all US patients aged 1 year or older at time of consent, who had a confirmed diagnosis of Pompe disease and were previously treated with alglucosidase alfa 160L were eligible regardless of phenotype (infantile-onset versus late-onset Pompe disease).

Proportion of female and male was comparable. The patients experienced the first symptoms of Pompe disease at a median age of 0.3 years, and the median age of being diagnosed with Pompe disease was 0.5 years. Of the 113 treated patients, 72 [63.7%] patients received alglucosidase alfa 160L treatment prior to 1 year of age patients (corresponding to a classical infantile-Pompe disease).

The majority of patients (84.0%) were under the age of 8 years at the time of first infusion with alglucosidase alfa 4000L (median age 3.8 years).

From a statistical point of view, no formal hypothesis testing was performed for this study and results were only descriptive.

113 patients were treated of then, 110 completed then 52-week treatment. 13 patients discontinued for the following reasons: 8 due to study termination, 2 died, 2 refused further treatment and one due to physician decision. All patients entered the extension phase.

The primary endpoint was the percentage of patient transitioned to treatment with 4000L scale alglucosidase alfa who did not met one of the predefined worsening criteria.

The predefined worsening criteria were death due to disease progression or new dependency on invasive ventilation, decline in cardiac status (evaluated by LVM-Z score), decline in motor function from baseline (decrease in GMFM-88 Total Percent Score of ⩾8%) and decline in pulmonary function from baseline (decrease in FVC percent predicted in sitting position ⩾15%).

For the primary efficacy endpoint, 83.7% of patients (87/104 patients; 95% CI: 75.1%, 90.2%) were clinically stable or improved at Week 52. The most frequent reason for decline was GMFM decreased ≥8% (12 of 90 patients [13.3%]).
Only assessment of gross motor function could be obtained in a consistent manner in all study participants (n=90), while pulmonary function testing could not be performed in the majority of patients (n=22), due to either the patient's young age or their dependency on invasive ventilation. Moreover acquisition difficulties of echocardiography data in a number of study participants led to incomplete data sets.

Regarding Pharmacokinetic results, plasma concentration results were only available for 3 patients thus no conclusion can be drawn regarding the comparability of the pharmacokinetic (PK) profile of alglucosidase alfa produced at the 4000 L and 160 L scales.

- ***Safety results***

Extent of exposure

The 113 patients who received alglucosidase alfa 4000L in AGLU09411 study comprise the safety population for this report. All 113 patients were previously treated with Myozyme prior to enrollment into this study.

The median duration of study drug treatment was 929 days (range: 41 to 985 days). A total of 100 patients received at least 52 weeks of treatment. The median number of study drug infusions per patient was 27 infusions (range: 6 to 53 infusions).

Of note, after receiving treatment with alglucosidase alfa 4000L, 2 patients temporarily received treatment with alglucosidase alfa 160L. As per request of the Investigator, a patient received treatment with alglucosidase alfa 160 L from 27 June 2012 to 11 October 2012, and was then returned to treatment with alglucosidase alfa 4000 L. A patient was approved to go on 160 L in January 2014, but did not start on 160 L product until 04 August 2014 through 20 October 2014.

The following patients have received immunomodulation treatment: 4 patients received concomitant methotrexate, 6 patients received concomitant rituximab, and 9 patients received concomitant immunoglobulins for immunomodulation, immune deficiency or immune suppression. A patient received prophylactic ITI treatment during participation in Study AGLU03807.

The majority of patients (81 patients, 71.7%) received 20 mg/kg qow of alglucosidase alfa 4000L.

Table 23 - Number of patients per dose regimen - safety population

Alglucosidase alfa 4000L (N=113)															
10 mg/kg Weekly		20 mg/kg qow		20 mg/kg Weekly		30 mg/kg qow		30 mg/kg Weekly		40 mg/kg qow		40 mg/kg Weekly		Other	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1	0.88	81	71.7	13	11.5	3	2.7	1	0.88	10	8.8	2	1.8	2	1.8

Source: 16-2-7-ae-data [Table 14.3.1.6.3]

Adverse events

Brief summary of adverse events

A total of 2752 treatment emergent adverse events (TEAEs) were reported in 113 patients (overall safety population). All 113 patients reported at least 1 TEAE. An overall summary of TEAEs is presented in Table 2.

Table 2 - Overall Summary of Treatment Emergent Adverse Events – Safety Population

	Alglucosidase Alfa 4000L (N= 113)	
Parameter	Events n	Patients n (%)
Any Adverse Events	2752	113 (100.0)
Discontinued Due to Adverse Events [a]		0
Death		6 (5.3)
Treatment Related Adverse Events	168	38 (33.6)
Serious Adverse Events	287	73 (64.6)
Severe Adverse Events	124	44 (38.9)
Infusion-Associated Reactions	149	35 (31.0)

Source: Table 14.3.1.2.1 in AGLU09411 CSR

Note: Percentages are based on the total number of patients in the corresponding groups.

[a] Other than death

The majority of AEs were non-serious (89.6% of total AEs), mild to moderate in severity (95.5%) and assessed as unrelated to the study drug (93.9%). A majority of treatment-related AEs (88.7%) were IARs and were reported in 35 patients.

One hundred and twenty-four AEs (4.5% of total AEs) were assessed as severe in 44 patients. The only severe TEAEs experienced by more than 5% of patients were pneumonia (12 patients [10.6%]), respiratory distress (9 patients [8.0%]), and respiratory failure (7 patients [6.2%]).

The treatment-emergent adverse events, without regard to causality, are summarised in Table 14.3.1.2.3 of Appendix 16.2.7 “Adverse event data”.

The most frequently reported TEAEs, regardless of relationship to alglucosidase alfa, were pyrexia (234 events in 63 patients [55.8%]), diarrhoea (122 events in 55 patients [48.7%]), upper respiratory tract infection (106 events in 50 patients [44.2%]), vomiting (114 events in 43 patients [38.1%]), cough (107 events in 37 patients [32.7%]), rash (43 events in 32 patients [28.3%]), pneumonia (65 events in 30 patients [26.5%]), rhinorrhoea (42 events in 24 patients [21.2%]), and otitis media (35 events in 23 patients [20.4%]).

Adverse Event by relationship to treatment

There were 168 events that were considered related to alglucosidase alfa in 38 patients (33.6%), of which the most common was pyrexia (11 patients). Related treatment emergent adverse events occurring in ≥2 patients are listed in Table 26 below.

Table 26 - Treatment-emergent adverse events by relationship to treatment and by system organ class and preferred term (related treatment emergent adverse events occurring in ≥2 patients) - safety population

	Alglucosidase Alfa 4000 L (N=113)	
	Not Related	Related
System Organ Class Preferred Term	Patients n (%)	Patients n (%)
Patients with Events	75 (66.4)	38 (33.6)
General disorders and administration site conditions	69 (61.1)	16 (14.2)
Pyrexia	52 (46.0)	11 (9.7)
Chills	2 (1.8)	2 (1.8)
Gastrointestinal disorders	72 (63.7)	12 (10.6)
Vomiting	38 (33.6)	5 (4.4)
Diarrhoea	51 (45.1)	4 (3.5)
Nausea	10 (8.8)	3 (2.7)
Abdominal pain	10 (8.8)	2 (1.8)
Abdominal pain upper	9 (8.0)	2 (1.8)
Investigations	29 (25.7)	10 (8.8)
Blood pressure increased	4 (3.5)	3 (2.7)
Cardiac disorders	26 (23.0)	8 (7.1)
Tachycardia	8 (7.1)	5 (4.4)
Nervous system disorders	29 (25.7)	7 (6.2)
Headache	11 (9.7)	3 (2.7)
Skin and subcutaneous tissue disorders	49 (43.4)	11 (9.7)
Urticaria	4 (3.5)	5 (4.4)
Rash	28 (24.8)	4 (3.5)
Erythema	3 (2.7)	2 (1.8)
Respiratory, thoracic and mediastinal disorders	77 (68.1)	7 (6.2)
Cough	34 (30.1)	3 (2.7)
Wheezing	3 (2.7)	2 (1.8)
Vascular disorders	13 (11.5)	6 (5.3)
Flushing	2 (1.8)	5 (4.4)
Blood and lymphatic system disorders	12 (10.6)	4 (3.5)
Eosinophilia	2 (1.8)	4 (3.5)
Musculoskeletal and connective tissue disorders	43 (38.1)	4 (3.5)

Source: 16-2-7-ae-data [Table 14.3.1.4]

Note: If a patient had more than 1 event for a particular SOC, he/she is counted only once for that SOC

Note: If a patient had more than 1 event for a particular preferred term, he/she is counted only once for that preferred term

Note: Percentages are based on total number of treated patients.

Note: MedDRA Dictionary Version 17.1 was used for coding.

Adverse events by 6-month time interval

The percentage of patients who reported TEAEs was similar across intervals, ranging from 87.0% in the >12 to 18 months interval to 94.7% in the 0 to 6 months interval. There was no consistent trend in TEAE incidence by time interval.

In each time interval (0-6, >6-12, >12-18, >18-24, and >24 months of treatment), the most frequent TEAEs were pyrexia, upper respiratory tract infection, diarrhea, vomiting, and cough.

Adverse events by infusion time period

The majority of the events occurring during the infusion (78/112 events) and up to 2 hours post-infusion (17/35 events) were considered to be IARs. During 2-24 hours post-infusion, the majority of TEAEs were not considered to be IARs (8/62 events) and 1 patient experienced IARs between 24 and 72 hours post-infusion.

The majority of these TEAEs occurred during the infusion or within 24 hours of the infusion. There were a total of 112 events (41.5%) that occurred during the infusion, 35 events (13%) that occurred 0 to 2 hours post-infusion, 62 events (23%) that occurred 2 to 24 hours post-infusion, 43 events (15.9%) that occurred 24 to 48 hours post-infusion, and 18 events (6.7%) that occurred 48 to 72 hours post-infusion.

There were 2 TEAEs that occurred in at least 5% of patients in any given infusion/post-infusion time interval: pyrexia occurred during infusion (12 events in 8 patients [7.1%]), 0-2 hours post-infusion (7 events in 6 patients [5.3%]), and 2 to 24 hours post-infusion (12 events in 10 patients [8.8%]) and diarrhea occurred 2-24 hours post-infusion (7 events in 6 patients [5.3%]).

The most frequent TEAEs that occurred in ≥3 patients by infusion time period were as follows:

• During the infusion: blood pressure increased, erythema, flushing, pyrexia, tachycardia, urticaria, and vomiting

• During the 0-2 hours post-infusion: pyrexia

• During the 2-24 hours post-infusion: diarrhea, vomiting, and pyrexia

• During the 24-48 hours post-infusion: pyrexia

• During the 48-72 hours post-infusion period: pyrexia

Adverse events by gender subgroup

Analysis of AEs by gender did not reveal any meaningful differences in the types of TEAEs experienced between the genders. The 60 (100%) male patients experienced 1,271 TEAEs and 53 (100%) female patients experienced 1,481 TEAEs.

Adverse events by age subgroup

The most frequent TEAEs occurring in at least 5 or more patients in the age group of <2 years were pyrexia, upper respiratory tract infection, diarrhea, vomiting, rhinorrhea, respiratory distress, cough, rash, pneumonia, ear infection, viral infection, nasal congestion, nasopharyngitis and constipation.

The most frequent TEAEs occurring in at least 5 or more patients in the 2-5 year age category were pyrexia, diarrhea, vomiting, cough, upper respiratory tract infection, pneumonia, rash, otitis media, urinary tract infection, pain in extremity, rhinorrhea, respiratory distress, constipation, abdominal pain, gastroenteritis, device occlusion, dehydration, pharyngitis streptococcal, tracheitis, viral infection,

procedural pain, blood creatine phosphokinase MB increase, muscle weakness, headache, nasal congestion, and oropharyngeal pain.

The most frequent TEAEs occurring in at least 5 or more patients in the 5-8 year age category were pyrexia, upper respiratory tract infection, diarrhea, cough, headache, otitis media, abdominal pain upper, tachycardia, viral infection, fall, vomiting, urticaria, and rash.

The most frequent TEAEs occurring in at least 5 or more patients in the 8-12 year age category were pyrexia and diarrhea.

The most frequent TEAE occurring in at least 5 or more patients in the >12 year age category was pneumonia.

Adverse events by dosing regimen

Treatment-emergent AEs are summarized by dosing regimen in 16-2-7-ae-data [Table 14.3.1.6.3]. Few patients were included in the 10 mg/kg Weekly (n=1), 20 mg/kg Weekly (n=13), 30 mg/kg qow (n=3), and 30 mg/kg Weekly (n=1) regimens.

Adverse events by immunogenicity parameters

A summary of safety by immunogenicity parameters, including by seroconversion status and quartiles of peak IgG titer, sustained high antibody titers, and inhibitory antibodies, is presented in Table 29, Table 30, and Table 31.

Table 29 - Summary of safety by seroconversion status, quartiles of peak IgG antibody - safety population

	Negative (N=24)		Positive (N=89)							
			Quartile 1 (0.0 – 400) (n=24)		Quartile 2 (800.0 – 800.0) (n=13)		Quartile 3 (1600.0 – 3200.0) (n=33)		Quartile 4 (6400.0 – 102400.0) (n=19)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Patients with adverse events	598	24 (100.00)	470	24 (100.0)	337	13 (100.0)	731	33 (100.0)	616	19 (100.0)
Patients with serious adverse events	58	14 (58.3)	55	15 (62.5)	15	5 (38.5)	86	23 (69.7)	73	16 (84.2)
Patients with infusion-associated reactions	14	7 (29.2)	9	5 (20.8)	17	2 (15.4)	34	10 (30.3)	75	11 (57.9)

Source: 16-2-7-ae-data [Table 14.3.1.6.4], [Table 14.3.2.1.9], [Table 14.3.2.2.14]
Note: If a patient had more than 1 event for a particular for a particular SOC, he/she is counted only once for that SOC.
Note: If a patient had more than 1 event for a particular preferred term, he/she is counted only once for that preferred term.
Note: Percentages are based on the total number of patients treated in the corresponding groups.
Note: Serious adverse events includes serious infusion-associated reactions.

Table 30 - Summary of safety by status of sustained and elevated IgG titers - safety population

	With Sustained & Elevated Titers (N=5)		Without Sustained & Elevated Titers (N=84)	
System Organ Class Preferred Term	Events n	Patients n (%)	Events n	Patients n (%)
Patients with adverse events	192	5 (100.0)	1962	84 (100.0)
Patients with serious adverse events	28	4 (80.0)	201	55 (65.5)
Patients with infusion-associated reactions	24	3 (60.0)	111	25 (29.8)

Source: 16-2-7-ae-data [Table 14.3.1.6.5], [Table 14.3.2.1.10], [Table 14.3.2.2.15]
Note: If a patient had more than 1 event for a particular SOC, he/she is counted only once for that SOC.
Note: If a patient had more than 1 event for a particular preferred term, he/she is counted only once for that preferred term.
Note: Percentages are based on the total number of patients treated in the corresponding groups.
Note: Serious adverse events include serious infusion-associated reactions.

Table 31 - Summary of safety by status of inhibitory antibody - safety population

	Inhibitory AB for Enzyme Uptake (N=88)				Inhibitory AB for Enzyme Activity (N=88)			
	Negative (N=87)		Positive (N=1)		Negative (N=88)		Positive (N=0)	
Body System Organ Class Preferred Term	Events n	Patients n(%)	Events n	Patients n(%)	Events n	Patients n(%)	Events n	Patients n(%)
Patients with adverse events	2121	87 (100.0)	29	1 (100.0)	2150	88 (100.0)	0	0 (0.0)
Patients with serious adverse events	221	57 (65.5)	5	1 (100.0)	226	58 (65.9)	0	0 (0.0)
Patients with infusion-associated reactions	134	27 (31.0)	1	1 (100.0)	135	28 (31.8)	0	0 (0.0)

Source: 16-2-7-ae-data [Table 14.3.1.6.6], [Table 14.3.2.1.11], [Table 14.3.2.2.16]

Note: If a patient had more than 1 event for a particular SOC, he/she is counted only once for that SOC.
Note: If a patient had more than 1 event for a particular preferred term, he/she is counted only once for that preferred term.
Note: Percentages are based on the total number of patients treated in the corresponding groups.
Note: Serious adverse events include serious infusion-associated reactions.

A total of 28 SAEs were reported for the 4 out of the 5 patients with sustained and elevated titers:

- Patient 10325027 experienced SAEs of chest pain, dyspnea, hyperhidrosis, sinus tachycardia, and urinary tract infection. Of the 5 SAEs reported for this patient, none were considered as IARs. Per 16-2-7-ae-data [Table 14.3.2.2.17.1], the patient experienced 1 additional non-serious IAR of headache. The patient recovered from all the events.

- Patient 10015011 experienced SAEs of oxygen saturation decreased (2 events), abdominal pain, tracheitis, cholecystitis acute, dehydration, diarrhea, dyspnea, intussusception, pyrexia, and respiratory failure. Of the 11 SAEs reported for this patient, 3 were considered as IARs: abdominal pain, diarrhea, and pyrexia. Per 16-2-7-ae-data [Table 14.3.2.2.17.1], the patient experienced 14 additional non-serious IARs of flushing (3 events), urticaria (3 events), dyspnea (2 events), diarrhea, heart rate increased, macule, respiratory distress, tachycardia, and wheezing.

- Patient 10555058 experienced SAEs atelectasis, pneumonia, bradycardia, chest pain, cough, hypotension, left ventricular hypertrophy; all 7 SAEs were considered not related to study treatment. No IARs were reported for Patient 10555058.

- Patient 10015106 experienced SAEs of feeding tube complication, respiratory distress (2 events), pyrexia, cardio-respiratory arrest. Of the 5 SAEs reported for this patient, none were considered as IARs. Per 16-2-7-ae-data [Table 14.3.2.2.17.1], the patient experienced hypertension, tachycardia, pyrexia (2 events), body temperature increased, and tachycardia. See Section 15.3.3 for detailed patient narratives for these 2 patients.

A single patient tested positive for inhibitory antibodies for enzyme uptake at baseline. This patient had a baseline titer of 25 600, a peak titer of 102 400 (at Week 30), and a last titer of 25 600 at Week 117. This patient reported the following 5 SAEs: pneumonia (2 events), pneumonia parainfluenza viral, sepsis, and device related infection. The 2 events of pneumonia and the event of pneumonia parainfluenza viral sepsis were considered severe in intensity and both sepsis and device related infection were considered moderate and not related to study treatment. The patient had recovered from the events, with sequelae for the event of pneumonia parainfluenza viral.

Death and study discontinuations for safety reasons

One hundred patients completed AGLU09411 study.

There were no AEs leading to discontinuation from the study.

Two patients temporarily received alglucosidase alfa 160L during the trial.

Six patients (5.3%) died during the study. All of the deaths were unrelated to alglucosidase alfa 4000L treatment and were due to disease progression (respiratory failure and pneumonia; cardio-respiratory

arrest and cerebral ischemia; respiratory failure (2); respiratory distress; cardiac arrest). In addition, 2 patients (10015106, 10735032) died shortly after withdrawal (from unknown cause and respiratory failure, respectively).

Other serious adverse events

A total of 287 treatment-emergent SAEs (10.4% of total AEs) were experienced by 73 patients during the study.

All SAEs experienced during treatment with alglucosidase alfa are summarized by relationship to treatment in Table 14.3.2.1.4 of Appendix 16.2.7 “Adverse event data”.

The majority of SAEs were unrelated to study drug. Eight patients (7.1%) experienced SAEs considered related to the study drug: a Patient (abdominal pain, diarrhoea, and pyrexia), another (vomiting), (self-injurious ideation), (pyrexia [2 events], chills [2 events], rhonchi, tremor), another patient (gross motor delay [2 events]), another patient (oedema peripheral), another patient (left ventricular hypertrophy identified as an ECG finding, however was not associated with changes in ECHO or changes in clinical signs or symptoms; the event was assessed by the investigator as due to decreased response to treatment), and another patient (chills, pyrexia, nausea). All of these events were considered IARs except for the events of gross motor delay (2 events) and left ventricular hypertrophy.

Of the 73 patients who experienced SAEs, 39 (34.5%) patients experienced severe events, 31 (27.4%) patients experienced moderate events, and 3 (2.7%) patients experienced mild events. The majority of SAEs were resolved.

SAEs by 6-month time intervals

During the first 6 months in the study, 33 of 113 patients (29.2%) reported SAEs. During the later time intervals, 36 of 107 patients (33.6%) reported SAEs from >6 to 12 months, 33 of 100 patients (33.0%) reported SAEs from >12 to 18 months, 26 of 91 patients (28.6%) reported SAEs from >18 to 24 months, and 28 of 83 patients (33.7%) reported SAEs after 24 months on treatment.

The most frequent SAEs reported in at least 5 patients occurring in each interval were:

• 0 to 6 month: pyrexia (5 [4.4%] patients), respiratory distress (6 [5.3%] patients), and pneumonia (5 [4.4%] patients)

• >6 to 12 months: pneumonia (10 [9.3%] patients) and respiratory distress (7 [6.5%] patients)

• >12 to 18 months: pneumonia (4 [4.0%] patients)

• >18 to 24 months: pneumonia (7 [7.7%] patients) and Respiratory distress (5 [5.5%] patients)

• >24 months: pneumonia (5 [6.0%] patients)

As presented in 16-2-7-ae-data [Table 14.3.2.1.4], all of the SAEs of pneumonia were considered unrelated to alglucosidase alfa.

SAEs by infusion time period

Thirty-seven SAEs were experienced by 26 patients during infusion or up to 72 hours post-infusion. Of the 37 SAEs, more events were experienced during infusion or between 2-24 hours post-infusion (15 events [40.5%] in 11 patients [9.7%]) compared to the other infusion time periods.

The only SAEs occurring in ≥2 patients during any infusion time period were supraventricular tachycardia (48-72 hours post-infusion), pyrexia (0-2 hours post-infusion), and respiratory failure (0-2 hours post-infusion). The SAEs experienced during infusion and up to 72 hours post-infusion are consistent with the known safety profile of alglucosidase alfa.

The majority of the AEs occurring during the infusion and up to 2 hours post-infusion were considered to be IARs. During 2-24 hours post-infusion, the majority of AEs were not considered to be IARs and there were no IARs reported between 24 and 48 hours post-infusion and 2 IARs between 48 and 72 hours post-infusion (16-2-7-ae-data [Table 14.3.2.2.2]).

Serious adverse events by gender subgroup

Analysis of SAEs by gender did not reveal any meaningful differences in the types of SAEs experienced. Out of 60 male patients, 38 (63.3%) patients had 155 events. Out of 53 female patients, 35 (66%) patients had 132 events.

Serious adverse events by age subgroup

Events across age categories were consistent with the manifestations and complications of the underlying Pompe disease or the known safety profile of alglucosidase alfa in this patient population.

Serious adverse events by dosing regimen

Serious adverse events are summarized by dosing regimen in 16-2-7-ae-data [Table 14.3.2.1.8]. Analysis of SAEs by dosing regimen did not reveal any meaningful differences in the types of SAEs experienced.

Other significant adverse events

Infusion-associated reactions

An IAR was defined by Genzyme as any events occurring on the day of infusion and up to 48 hours (2 days) after infusion.

One hundred and forty-nine (149) IARs (at any severity grade) were reported in 35 patients.

The most frequent IARs occurring in ≥2 patients were: pyrexia, tachycardia, urticaria, flushing, and vomiting.

Of the 35 patients with IARs, all were mild or moderate in intensity and the majority of IARs were considered non-serious.

Of the patients who experienced IARs, the majority of patients were IgG positive with a peak titer range of 200 to 102 400. None of the patients experiencing IARs tested positive for IgE antibodies. Of the patients who were seronegative at baseline, 10 patients seroconverted, of which, 2 patients had IARs: Patient 10405047 seroconverted at Study Day 225, and had a peak titer of 400 at Weeks 64 and 78; and Patient 10735048 seroconverted at Study Day 87, and had a peak titer of 800 at Weeks 64 and 78 and a last titer of 400 at Week 52.

Eight patients experienced an IAR with the Day 1 infusion: a patient (IgG titer range at time of IARs: 3200 to 12 800), another patient (not seropositive at time of IAR), another patient (IgG titer at time of IAR not available), another patient (IgG titer at time of IAR: 25600-25600), another patient (IgG titer at time of IAR: 3200), another patient (not seropositive at time of IAR), another patient (not seropositive at time of IAR), another patient (IgG titer at time of IAR: 1600). Two of these patients had received immunomodulation treatment: 10015011 and 10665015.

IARs by 6-month time interval

During the first 6 months in the study, 22 of 113 patients (19.5%) had IARs. During the later time intervals, 13 of 107 patients (12.1%) had IARs from >6 to 12 months, 11 of 100 patients (11.0%) had IARs from >12 to 18 months, 12 of 91 patients (13.2%) had IARs from >18 to 24 months, and 13 of 83 patients (15.7%) had IARs after 24 months on treatment.

First 6 months on treatment, the most frequent IARs occurring in ≥2 patients were: pyrexia, vomiting, tachycardia, nausea, urticaria, headache, flushing, abdominal pain, diarrhea, chills, blood pressure increased, and wheezing. During the >6 to 12-month time interval, the IARs occurring in ≥2 patients were: pyrexia, cough, urticaria, and flushing. During the >12 to 18-month interval, no IARs were reported in more than 1 patient. During the >18 to 24-month time interval, the IARs occurring in ≥2 patients were: pyrexia, urticaria, headache, and abdominal pain upper.

After 24 months on treatment, the only IAR reported in more than 1 patient was urticaria.

IARs by infusion time interval

The majority of IARs were experienced during infusion or within 24 hours post-infusion. There were no events assessed as IARs between 24 and 48 hours.

There were 2 events assessed as IARs between 48 and 72 hours.

The most frequent IARs occurring in ≥2 patients during infusion were: urticaria, pyrexia, flushing, nausea, vomiting, headache, throat irritation, tachycardia, blood pressure increased, and erythema.

One IAR occurred in ≥2 patients during 0-2 hour's post-infusion: pyrexia, and 1 IAR occurred in ≥2 patients during 2-24 hours post-infusion: diarrhea. There were no IARs experienced in patients during 24-48 hours post-infusion.

IARs by Infusion Rate

There does not appear to be an association between IARs and infusion rate from >0 to ≤3 mg/kg/hr to >7 mg/kg/hr. Twelve patients (10.6%) experienced IARs at infusion rates of >0 to ≤3 mg/kg/hr. Eight patients (7.1%) each experienced IARs at infusion rates of >3 to ≤5 mg/kg/hr and >5 to ≤7 mg/kg/hr. Six patients (5.3%) experienced IARs at an infusion rate of >7 mg/kg/hr.

There were 4 serious IARs in 1 patient (0.9%) that occurred at the >7 mg/kg/hr infusion rate.

A total of 6 patients experienced an IAR at an infusion at rate >7 mg/kg/hr; these patients are listed in Table 35 with the IARs they experienced at an infusion rate >7 mg/kg/hr, IARs they experienced after completion of an infusion associated with IAR at an infusion rate >7 mg/kg/hr, and their immunogenicity results. All 6 patients continued to receive study treatment for the duration of the study. All of the IARs were of mild or moderate intensity and the outcome was recovered, and no consistent relationship with immunogenicity results was apparent. Pyrexia (4 events, 1 patient) was the most frequent of the 25 events reported for these 6 patients.

Table 35 - Infusion-associated reactions and immunogenicity results for patients with IAR at infusion rate >7 mg/kg/hr

Infusion Associated Reaction	Serious Adverse Event	Intensity	Relationship to Study Treatment	Outcome	Immunogenicity Results
Patient 10015011					
Flushing	No	Moderate	Possibly related	Recovered	Tested positive for complement activation, negative for IgE antibodies. The patient was seropositive at screening for IgG antibodies (titer=12,800) and reached a peak titer of 51,200 at Week 126.
Dyspnoea	No	Moderate	Possibly related	Recovered	
Macule	No	Moderate	Possibly related	Recovered	
Wheezing	No	Moderate	Possibly related	Recovered	
Patient 10015106					
Body temperature increased	No	Mild	Possibly related	Recovered	Results for complement activation and IgE antibodies were not provided for this patient. The patient was seropositive at screening for IgG antibodies (titer=102,400) and reached a peak titer during treatment with study drug of 51,200 at Week 6.
Patient 10345030					
Oropharyngeal pain	No	Mild	Possibly related	Recovered	Tested negative for complement activation and for IgE antibodies. The patient was seropositive for IgG antibodies at the first assessment at Week 4 (titer=800) and reached a peak titer of 6,400 at Week 132.
Throat tightness	No	Mild	Possibly related	Recovered	
Throat tightness	No	Mild	Possibly related	Recovered	
Patient 10375051					
Chills	Yes	Moderate	Related	Recovered	Tested positive for complement activation, negative for IgE antibodies. The patient was seropositive at screening for IgG antibodies (titer=51,200) and reached a peak titer of 102,400 at Week 20.
Pyrexia	Yes	Moderate	Related	Recovered	
Tremor	Yes	Moderate	Related	Recovered	
Chills	Yes	Moderate	Possibly related	Recovered	
Pyrexia	Yes	Moderate	Possibly related	Recovered	
Ronchi	Yes	Moderate	Possibly related	Recovered	
Pyrexia	No	Mild	Related	Recovered	
Tremor	No	Mild	Related	Recovered	
Pyrexia	No	Mild	Related	Recovered	
Patient 10535084					
Urticaria	No	Mild	Related	Recovered	Results for complement activation and IgE antibodies were not provided for this patient. The patient was seropositive at screening for IgG antibodies (titer=1,600) and reached a peak titer of 3,200 at Week 21.

Infusion Associated Reaction	Serious Adverse Event	Intensity	Relationship to Study Treatment	Outcome	Immunogenicity Results
Patient 10735048					
Erythema	No	Mild	Possibly related	Recovered	Results for complement activation and IgE antibodies were not provided for this patient. The patient was seronegative at screening for IgG antibodies and reached a peak titer of 800 at Week 64.
Blood pressure increased	No	Mild	Possibly related	Recovered	
Erythema	No	Mild	Possibly related	Recovered	
Erythema	No	Mild	Possibly related	Recovered	
Urticaria	No	Mild	Possibly related	Recovered	
Arthralgia	No	Mild	Possibly related	Recovered	
Hyperhidrosis	No	Mild	Possibly related	Recovered	

Source: 16-2-7-ae-data [Table 14.3.2.2.17.1] and 16-2-5-cdc-data [16.2.5.1 Listings 16.2.5.1], 16-2-7-other-safety [Listings 16.2.8.7], [Listings 16.2.8.8], [Listings16.2.8.9]
Note: IARs with missing onset time or infusion rate information are excluded from the table.
Note: For patients with IARs that occurred during infusion at a rate >7 mg/kg/hr, the table also includes associated IARs that occurred after such infusion was stopped or completed.

Infusion-associated reactions by gender subgroup

A summary of IARs by gender is presented in 16-2-7-ae-data [Table 14.3.2.2.12]. Analysis of IARs by gender did not reveal any meaningful differences in the types of IARs experienced. Out of 60 male patients, 19 (31.7%) patients had 70 events. Out of 53 female patients, 16 (30.2%) patients had 79 events.

Infusion-associated reactions by age subgroup

A summary of IARs by age at first infusion is presented in 16-2-7-ae-data [Table 14.3.2.2.11]. The IARs occurring in 2 or more patients in the <2 years category were: pyrexia and tachycardia. The IARs occurring in 2 or more patients in the 2 to 5 years category were: diarrhea, urticaria, flushing and pyrexia. The IARs occurring in 2 or more patients in the 5 to 8 years category were: abdominal pain upper, pyrexia, cough, flushing, and urticaria. The IARs occurring in 2 patients or more patients in the 8 to 12 years category were: nausea and rash. No IARs were experienced by 2 or more patients in the >12 years category.

Infusion-associated reactions by dosing regimen

A summary of IARs by dosing regimen is presented in 16-2-7-ae-data [Table 14.3.2.2.13]. The majority of patients (81 out of 113 patients) were receiving the 20 mg/kg qow dosing regimen. Due to the small size of the 10 mg/kg qw, 20 mg/kg qw, 30 mg/kg qow, and 30 mg/kg qw, 40 mg/kg qow, and 40 mg/kg qw and the “Others” group which included a number of different dose and frequency combinations (see Table 23), it is difficult to draw any conclusions; therefore, these groups are not further discussed by the MAH.

The IARs occurring in ≥2 patients in the 20 mg/kg qow dosing regimen group were: pyrexia, tachycardia, diarrhea, flushing, vomiting, urticaria, blood pressure increased, rhonchi, headache, erythema, and cough.

Potential infusion reactions and potential delayed reactions

Potential infusion reactions were defined in the SAP as: all AEs occurring during an infusion or within 2 hours after the completion of an infusion will be considered as potential IARs. This definition for potential IARs does not rely on the Investigators' assessment of an AE's relationship to the study treatment.

During the infusion period or within 2 hours after completion of infusion, 49 (43.4%) out of 113 patients reported 147 potential infusion reactions (Table 36) regardless of causality. A total of 35 out of 113 (31%) patients experienced IARs 16-2-7-ae-data [Table 14.3.2.2.1] and the majority occurred during infusion or within 24 hours post-infusion. There were no IARs reported between 24 and 48 hours. Two events of diarrhea in 1 patient were reported between 48 and 72 hours post infusion [Table 14.3.2.2.2].

The potential infusion reactions occurring in ≥2 patients regardless of causal relationship were: sinus tachycardia, tachycardia, catheter site extravasation, extravasation, body temperature increased, respiratory failure, wheezing, erythema, vomiting, nausea, chest pain, chills, pyrexia, urinary tract infection, blood pressure increased, headache, anxiety, dyspnea, rhonchi, throat irritation, urticaria, flushing, and cough. The events of potential IARs regardless of causality occurring up to 2 hours post-infusion are consistent with the previous alglucosidase alfa experience as described in the product prescribing information.

Potential delayed reactions were defined in the SAP as: all AEs which occur between 2 to 48 hours after an infusion. This is irrespective of the Investigator's assessment of an AE's relationship to the study drug. Potential delayed reactions are summarized by infusion time periods in 16-2-7-ae-data [Table 14.3.2.2.10] and listed by patient in [Table 14.3.2.2.17.2]. Refer to Section 11.3.4.1 as well as [Table 14.3.2.2.2] for analysis of IARs by infusion time intervals.

A total of 69 (61.1%) of 113 patients reported 231 potential delayed reactions occurring between 2-48 hours post-infusion. The majority of events were assessed as not related or unlikely related to treatment and were considered to be related to the underlying complications and manifestations of Pompe disease in this patient population. The potential delayed reactions occurring in ≥2 patients regardless of causal relationship were: vomiting, diarrhea, bradycardia, constipation, pyrexia, bacterial tracheitis, device related infection, ear infection, hordeolum, nasopharyngitis, otitis media, pneumonia, tracheitis, upper respiratory tract infection, urinary tract infection, oxygen saturation decreased, pain in extremity, headache, cough, hemoptysis, respiratory distress, rash, anemia, tachycardia, nausea, secretion discharge, and pseudomonas infection.

Fifteen patients experienced 26 events which were assessed as possibly related or related to treatment and occurred on the same day of infusion or up to 72 hours post-infusion (16-2-7-ae-data [Table 14.3.2.2.17.2]). The majority of these events occurred on the same day or 2-24 hours post-infusion including diarrhea, vomiting, abdominal pain/discomfort, urticaria, arthralgia, arthropathy, myopathy, cough, eyelid ptosis, edema, edema peripheral, rash, electrocardiogram ST segment elevation, heart valve incompetence, electrocardiogram abnormal, right ventricular hypertrophy, hematuria, and pyrexia. Events occurring ≥48 hours post-infusion included pulmonary function test decreased, pyrexia, and diarrhea.

Anaphylactic and significant allergic reactions

Four patients experienced reactions which met the composite criteria of the standard MedDRA query for anaphylaxis. Upon review of these AEs for these 4 patients, 3 patients experienced IARs suggestive of allergic reactions. The summaries of all 4 cases are listed below:

Patient	Adverse reactions SMQ Anaphylaxis	Intensity	Causality	Seriousness	Outcome	Immunology
	Flushing, dyspnea, respiratory distress, urticaria, and wheezing that were considered of moderate intensity, and urticaria and dyspnea assessed as an IAR	Mild	Possibly related	Non-serious	Resolved	This patient had a screening titer of 12 800 and an anti-rhGAA IgG antibody peak titer of 51 200 (reached at Week 126); the last titer was 51 200. The patient was IgE-negative, but tested positive for complement activation at Week 0 and Week 36.
	Erythema, pruritus, and cough assessed as an IAR	Mild	Possibly related	Non-serious	Resolved	The patient had an anti-rhGAA IgG antibody peak titer of 200 (at Weeks 49 and 53); the last titer was 200.
	Cough	Mild	Not related	Non-serious	Resolved	This case represents an IAR of erythema and is not considered to be an allergic reaction. The patient had a peak titer of 800 (at Weeks 64 and 78); the last titer was 400.
	Erythema assessed as an IAR		Possibly related			
	Tachypnea, wheezing, and blood pressure decreased assessed as an IAR	Moderate	Possibly related	Non-serious	Resolved	The patient had a screening titer of 6400 and a peak titer of 25 600 (at Weeks 4 and 8); the last titer was 3200.

A patient was included previously in the interim clinical study report listing of potential anaphylactic reaction but excluded in the final clinical study report listing because both events of cough and hypotension started at 11:08 AM on 13 Dec 2012, before the closest infusion at 11:48 AM the same day.

Immune-mediated reactions

Twelve patients were identified to have experienced 14 events that satisfied the search criteria as described in 16-2-7-ae-data [Table 14.3.2.3]. Adverse events included lymphadenopathy, influenza like illness, arthralgia, arthropathy, myalgia, proteinuria and skin lesion. All of the events were considered non-serious and mild in intensity except for one event of moderate intensity for influenza like illness. All patients recovered from the events with the exception of the events of arthropathy, proteinuria, and arthralgia.

Two patients experienced mild, non-serious adverse events of skin lesions, which occurred under the tracheostomy tie in 1 patient which was assessed as unrelated to treatment.
Five patients experienced events of arthralgia or arthropathy, which resolved. All events of arthralgia/arthropathy were assessed as unrelated to alglucosidase alfa treatment except for 1 event in a patient and 1 event in another patient which were assessed as IARs.
A patient experienced a mild, non-serious, unrelated event of lymphadenopathy and recovered from the event.

A patient experienced a mild, non-serious, unrelated event of myalgia and recovered from the event.

A patient experienced a moderate, non-serious, unrelated event of influenza like symptoms. A patient experienced a single event of mild, non-serious proteinuria at Week 38, assessed as unlikely related to alglucosidase alfa treatment and recorded as not resolved.

Upon review of the cases described above meeting the search criteria, no patients were considered to have experienced an immune-mediated reaction.

Hearing loss

Five (4.4%) patients had TEAEs of hearing loss: conductive deafness, deafness, deafness unilateral, mixed deafness, and deafness neurosensory in 1 patient each (16-2-7-ae-data [Table 14.3.2.4]).

None of the events were SAEs [Table 14.3.2.1.12]. Deafness unilateral was mild and resolved while the other events were moderate in intensity and were recorded as not resolved. None of the events were considered related to study drug. Occurrence of some degree of hearing loss in Pompe disease patients while being treated with ERT has been reported in the literature (Prater SN, 2012).

Immunogenicity

Anti-rhGAA IgG antibodies

Patients with sustained and elevated IgG titres were defined as those who have a peak titre ≥25,600 and a last titre which is equal to the peak titre or is 1 dilution level lower than the peak titre; 5 out of 77 patients at baseline who were seropositive had sustained and elevated IgG titres. A total of 28 SAEs were reported for the 4 out of the 5 patients with sustained and elevated titres.

IgG seroconversion and time to seroconversion

Of the 113 patients, 77 tested seropositive at baseline and 24 of the 36 patients who were seronegative at baseline remained negative throughout the entire study period. Twelve patients seroconverted after study entry.

For patients who were seronegative at baseline and seroconverted, the median time for IgG conversion from date of first infusion was 113 days (range: 21.0 to 643.0 days) and the median titer value at seroconversion was 100 (range: 100.0 to 1600.0)

IgG peak titer and time to peak titer

The mean time from first infusion to first occurrence of IgG peak titre for patients who tested seronegative at baseline was 362.7 days (range: 21.0 to 826.0 days) and the mean time for patients who tested seropositive at baseline was 178.4 days (range: 14.0 to 924.0 days). The overall median IgG peak titre was 1,600 (range: 0 to 102,400; n=113) for patients who were ever IgG positive. The median IgG peak titre for the patients who tested IgG-negative at baseline was 400 (range: 100 to 1,600), markedly lower than the median IgG peak titre for patients seropositive at baseline 1,600 (range: 0 to 102,400). The median time from first infusion to first occurrence of IgG peak titre for patients who were seronegative at baseline was 117.5 days (range: 0 to 686 days) on study treatment, and titre levels did not increase markedly over the course of the study.

IgG titer over time

There were 36 patients who were seronegative at baseline. At Week 52, 24 out of the 36 patients remained seronegative at the end of the study period. For the 77 patients who were seropositive at baseline, titer levels did not increase markedly over the course of the study. The range for titer at Week 52 was 0.0 to 51 200; the median last titer was 800 for the patients who were seropositive at baseline. The range for titer at extension 18 months was 0.0 to 102 400.

Patients with sustained high IgG antibody, decreasing titer, or tolerization

Of the 113 patients, 7 patients (6.2%) tolerised, 27 (23.9%) patients had diminishing IgG antibodies over the course of the study, and 24 (21.2%) of patients remained seronegative throughout the study period. Only 5 (4.4%) of the 113 patients met the protocol defined criteria for high sustained antibody titres.

Neutralizing antibodies of enzyme activity or uptake

One patient (10595046) tested positive for enzyme uptake inhibition at Day 1 and Weeks 4 and 52.

No patients ever tested positive for inhibitory enzyme activity throughout the study.

Additional laboratory tests for moderate, severe, or recurrent infusion-associated reactions suggestive of hypersensitivity reaction

Six patients were tested for both complement activation and serum tryptase; 4 patients tested positive for complement activation and all serum tryptase results were within the normal range (≤12.5 μg/L). Eight patients were tested for anti-rhGAA IgE antibodies and all were negative.

Circulating immune complex

In the event that a patient exhibited evidence of symptoms suggestive of immune complex disease (eg, proteinuria), circulating immune complex was tested. No patients were tested for circulating immune complexes.

Laboratory parameters

Individual patient changes in laboratory values

Chemistry

Laboratory assessment shift from baseline in normality status for chemistry values is summarized in 16-2-8-clin-lab-data [Table 14.3.4.1.2].

For selected laboratory assessments, little change was observed from Week 26 to Week 52 in results classified by the central lab to be at the panic level or requiring notifying the site or patient by telephone call: ALT (Week 26: 63, Week 52: 64), alkaline phosphatase (AP) (Week 26: 0, Week 52: 1), AST (Week 26: 70, Week 52: 71), calcium (Week 26: 1, Week 52: 1), CK (Week 26: 73, Week 52: 71), CK-MB (Week 26: 0, Week 52: 0), GGT (Week 26: 3, Week 52: 3), LDH (Week 26: 47, Week 52: 52), and serum glucose (Week 26: 0, Week 52: 0).

Hematology

Laboratory assessment shift from baseline in normality status for hematology assessments is summarized in 16-2-8-clin-lab-data [Table 14.3.4.1.4].

Results for selected hematology assessments were classified by the central lab to be at the panic level or requiring notifying the site or patient by telephone call: hemoglobin (Week 26: 0, Week 52: 0),

leukocytes (Week 26: 2, Week 52: 3), neutrophils (Week 26: 0, Week 52: 0), and platelet (Week 26: 1, Week 52: 1).

Urinalysis

Laboratory assessment shift from baseline in normality status is summarized in 16-2-8-clin-lab-data [Table 14.3.4.1.6].

No urinalysis results were classified by the central lab to be at the panic level or requiring notifying the site or patient by telephone call at Week 52.

Individual clinically relevant abnormalities in laboratory values

Chemistry

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

Chemistry laboratory results reaching panic values or requiring immediate notification were reported as an SAE in 1 patient. Patient's 10655000 AST values were at immediate notification levels at screening and at Week 26 and increased to high panic level at Weeks 36 and 52. The SAE was not related to alglucosidase alfa treatment, which were assessed as unlikely related to alglucosidase alfa treatment. The patient had SAEs of ALT increased, GGT increased, and blood albumin decreased at the same time, which were assessed as not related to alglucosidase alfa treatment. These laboratory values did not reach immediate notification or high panic levels.

Chemistry laboratory results reaching panic values or requiring immediate notification were reported as non-serious AEs in 8 patients:

Patient	Adverse Event	AE Intensity	Causality	Outcome
	Increasing CK at Week 52	Mild	Unlikely related	Not resolved. CK values were at high panic levels at screening through Extension 18 months.
	Increase of ALT at Weeks 52 and 131	Mild	Unlikely related	The patient recovered from the event on Week 52, but the event at Week 131 was reported as not resolved. ALT values were at immediate notification or high panic levels at screening through extension 18 months.
	Increase of AST at Weeks 52 and 131	Mild	Unlikely related	The patient recovered from the event on Week 52, but the event at Week 131 was reported as not resolved. AST values were at immediate notification levels at screening through extension 18 months.
	Increase of CK-MB at Week 78 (but the laboratory values did not reach immediate notification)	Mild	Unlikely related	Not resolved.
	Increasing CK at Week 38	Mild	Unlikely related	Not resolved. CK values were at high panic levels at screening through Extension 18 months.
	Increase of ALT at Week 52	Mild	Unlikely related	The patient recovered from the event. ALT values were at high panic levels at screening through Extension 18 months.
	Increase of AST at Week 52	Mild	Unlikely related	The patient recovered from the event. AST values were at high panic levels at screening through Extension 18 months.
	Increasing LDH at Week 52	Mild	Unlikely	The patient recovered from the event. LDH

			related	values were at high panic levels at screening through Extension 18 months.
	Increase of CK-MB at Week 78 (but the laboratory values did not reach immediate notification or high panic levels)	Mild	Unlikely related	Not resolved.
	Increased CK at Week 104	Moderate	Unrelated	Not resolved. CK values were at immediate notification or high panic levels at screening through Extension 12 months.
	Increased CK MB at Week 104 (but the laboratory values did not reach immediate notification or high panic levels)	Moderate	Unrelated	Not resolved.
	Elevated ALT at Week 104	Moderate	Unlikely related	Not resolved. ALT values were at immediate notification or high panic levels at screening through Extension 12 months.
	Elevated AST at Week 104	Moderate	Unlikely related	Not resolved. AST values were at high panic levels at screening through extension 12 months.
	Elevated LDH at Week 104	Mild	Unlikely related	Not resolved. LDH values were at high panic levels at screening through Extension 12 months.
	Abnormal ALT at Week 42	Severe	Unrelated	Not resolved. ALT values were high panic at screening and an unscheduled visit and immediate notification at another unscheduled visit.
	Abnormal AST at Week 42	Severe	Unrelated	Not resolved. AST values were at high panic levels at screening and 2 unscheduled visits.
	Abnormal CK at Week 42	Severe	Unrelated	Not resolved. CK values were at high panic levels at screening and 2 unscheduled visits.
	Abnormal LDH at Week 42	Severe	Unrelated	Not resolved. LDH values were at high panic levels at screening and 2 unscheduled visits.
	Increased of CK at Week 51	Mild	Unlikely related	Not resolved. CK values were at immediate notification levels at an unscheduled visit and Week 38, 52 and Extension 12 months.
	Increased CK MB at Week 51 (but the laboratory values did not reach immediate notification or high panic levels)	Mild	Unlikely related	The patient recovered from the event.
	Increased AST at Week 105	Mild	Unlikely related	Not resolved. AST values were at high panic levels at screening through Extension 18 months.
	Increase of AST at Week 105	Mild	Unlikely related	Not resolved.
	Elevated CK at Week 104	Mild	Unrelated	Not resolved. CK values were at high panic levels at screening through extension 18 months and LFTs were elevated at Day 547 during the Extension.
	Elevated GGT at Week 38	Mild	Unlikely related	Not resolved. GGT values were at immediate notification levels from screening through extension 12 months and at high panic levels at Extension 6 and 12 months.
	Elevated AP at Week 52	Mild	Unlikely related	The patient recovered from the event. AP values were at high panic values at Week 52.

In addition, 1 SAE of hypoglycemia was reported for a patient at Week 15 (moderate in severity and unlikely related to alglucosidase alfa treatment) and non-serious AE of hypoglycaemia was recorded in a patient at Week 52 (mild in severity and not related to alglucosidase alfa treatment), another patient at Week 98 (moderate in severity and not related to alglucosidase alfa treatment), and another patient (mild in severity and not related to alglucosidase alfa treatment).

Hematology

Hematology laboratory results reaching panic values or requiring immediate notification were reported as non-serious AEs in 3 patients:

- For a patient, neutrophil and leukocyte values reached immediate notification level at Week 26, and the patient had non-serious AEs of neutrophil count increased and white blood cell count increased at the same time. Both events resolved and were considered unlikely related to study drug.

- For a patient, elevated platelets were at immediate notification levels at screening and at Week 26 and hematocrit and hemoglobin were at low panic levels at Week 26. The patient had a non-serious AEs of platelet count increased and hemoglobin decreased on Day 183 and a non-serious AE of anemia on Day 19. The 3 events were considered not related to the study drug and were recorded as ongoing.

- For a patient, decreased neutrophils were at low telephone notification levels at Week 26. The patient had a non-serious AE of mild neutropenia on Day 190 that was considered not related to the study drug and was recorded as ongoing.

Urinalysis

For 2 patients, AEs of elevated urine creatinine were reported: (Week 52), (Week 52), and another patient (Week 38). All events were assessed as being mild in severity and unlikely related to alglucosidase alfa treatment.

A non-serious AE of proteinuria was reported in a patient at Week 38 (mild in severity and unlikely related to alglucosidase treatment). The event was recorded as not resolved.

A non-serious AE of protein urine was reported in a patient at Week 104 (mild in severity and not related to alglucosidase treatment). The event was recorded as not resolved.

A non-serious AE of protein urine present was reported in a patient at Week 131 (mild in severity and unlikely related to alglucosidase treatment). The event was recorded as not resolved.

Vital signs, physical findings, and other safety observations

Vital signs

At Week 52, mean changes from baseline (standard deviation, number of patients) were: diastolic blood pressure 3.0 mmHg (12.46, n = 99), systolic blood pressure 2.5 mmHg (15.07, n = 99), heart rate -2.9 beats/min (19.48, n = 99), respiratory rate 1.0 breaths/min (7.01, n = 99), and temperature 0.0°C (0.54, n = 95).

Physical exam

Physical examination findings are listed by patient in 16-2-7-other-safety [Listing 16.2.8.1]. Height and weight are summarized by study visit in [Table 14.3.5.2.1] and listed in [Listing 16.2.8.2].

Electrocardiogram results

Of the 36 patients who had normal ECG values at baseline, 23 had normal values at Week 52. Nine patients with initially abnormal but not clinically significant results at baseline and 6 patients with clinically significant abnormal results at baseline showed normal ECG results at Week 52. Three patients had abnormal values that were not considered clinically significant and 10 patients had clinically significant abnormalities at Week 52. In addition, 3 of 13 patients who had abnormal ECG values that were not clinically significant at baseline and 25 of 35 patients who had clinically significant abnormalities at baseline had abnormal values at Week 52.

Adverse events associated with abnormal ECG findings are presented in the TEAE section. Arrhythmias may persist in Pompe disease patients despite improvement in cardiomyopathy and the conduction system while receiving enzyme replacement therapy (McDowell R, 2008). They may, at least in part, be related to myocardial fibrosis and/or ventricular remodeling associated with progressive long-term pathological changes in the heart (Prater SN, 2012).

CHMP comments on safety:

One of the objectives of study AGLU09411 was to determine the safety and immunogenicity profile of alglucosidase alfa produced at the 4000 L scale.

The safety population of study AGLU09411 included 113 patients, all previously treated with alglucosidase alfa at the 160L scale. When clinically feasible, patients continued to be treated at the same dose and dose regimen (every week or every other week) used for their routine treatment with 160 L alglucosidase alfa prior to screening and remained on a stable dose for the duration of the treatment period.

One hundred patients (88.5%) completed the study. There were no AEs leading to discontinuation from the study. Six patients (5.3%) died during the study due to disease progression.

Two patients (2.9-year-old female and 5.7-year-old male infantile-onset Pompe patients) temporarily received treatment with alglucosidase alfa 160L. However, the precise reasons for treatment switching and the consequences of the action taken in these two patients remain unclear.

No clear explanation has been found in the following case narratives which described in the 1st patient:

- SAEs of abdominal pain, diarrhoea and dehydration (thereafter "The patient's alglucosidase alfa 4000 L treatment was switched to alglucosidase alfa 160 L on 27 June 2012 [Week 11]");

- SAEs of dyspnea and oxygen saturation decreased (thereafter "The alglucosidase alfa 4000 L infusion was restarted on 18 October 2012 [Week 27]")

No mention regarding the switch has been retrieved in the case narratives for SAEs in the 2nd patient.

The MAH is requested to discuss about these aspects.

All patients experienced AEs. A total of 2752 AEs were reported during the 52-week study. The majority of AEs were non-serious (89.6% of total AEs), assessed as mild to moderate in severity (95.5%), and unrelated to the treatment (93.9%). Thirty-eight patients (33.6% of total patients)

experienced 168 AEs (6.1% of total AEs) that were assessed by the investigator as related to alglucosidase alfa, of which the most common was pyrexia. Regardless of causality, AEs belonged to the main following SOCs: Infections and infestations (23.0%), Respiratory, thoracic and mediastinal disorders (15.1%), Gastrointestinal disorders (14.1%), and General disorders and administration site conditions (13.5%).

One hundred and forty-nine treatment-related AEs (88.7%) were characterized as IARs in 35 patients (31.0%). The majority of treatment-related IARs were non-serious, all were mild or moderate in severity; among the 35 patients who experienced treatment-related IARs 29 recovered, 1 patient was recovering and 5 patients did not recover with AEs reported as ongoing (including 1 patient who also had resolved AE of worsening ptosis with sequelae).

No specific trend in the occurrence of AEs with alglucosidase alfa 4000L by 6-month time interval, infusion time period or gender subgroup was found. Events across age categories were consistent with the manifestations and complications of the underlying Pompe disease or the known safety profile of alglucosidase alfa in this patient population. Analysis of AEs by dosing regimen did not reveal any meaningful differences in the types of AEs experienced but no conclusion could be drawn since few patients were included in the 10 mg/kg Weekly (n=1), 20 mg/kg Weekly (n=13), 30 mg/kg qow (n=3), and 30 mg/kg Weekly (n=1) regimens.

Four cases of anaphylactic/allergic reactions (characterized as IARs) were reported but 1 patient experienced an IAR of erythema which was not considered to be an allergic reaction.

No patients were identified to have experienced an immune-mediated reaction.

There was no treatment-related case of hearing loss.

Five out of 77 patients at baseline who were seropositive for anti-rhGAA IgG antibodies had sustained and elevated IgG titres.

The small number of patients having sustained high antibody titers or testing positive for inhibitory antibodies, prevent from drawing any definite conclusion on AEs by immunogenicity parameters. There was no consistent relationship between incidence of AEs, SAEs, and IARs when stratified by seroconversion status and the quartiles of peak IgG titer. Considering that only 2 patients experiencing IARs seroconverted, we concur that no conclusions can be made regarding the relationship between time to seroconversion and onset of IARs. No consistent relationship between titer levels, peak titers, and occurrence of IARs has been evidenced.

There was one case of enzyme uptake inhibition at 3 timepoints, and no patient tested positive for enzyme activity inhibition. IgE testing was performed in 8 patients, which was negative. Complement activation and serum tryptase testing were performed in 6 patients, of which 4 patients tested positive for complement activation and all serum tryptase results were normal. No patients were tested for circulating immune complexes.

No concerning trends in laboratory parameters, vital signs, physical exam and ECG parameters have been identified.

Based on the data provided by the MAH dealing with the final results of study AGLU09411, no new safety concerns have been identified with alglucosidase alfa at the 4000L scale as compared to previous studies and experiences in infantile- and late-onset Pompe patients treated with alglucosidase alfa 160 L at a dose of 20 mg/kg qow. However, the MAH should provide clarifications on the underlying reasons for switching temporarily 2 patients from alglucosidase alfa 4000L to 160 L during the study and the consequences in these patients.

The assessment of AEs by immunogenicity parameters is hampered by the small number of patients having sustained high antibody titers or tested for other immunogenicity parameters.

Regarding patients who received other dosing regimen, no relevant comparative assessment of AEs frequency and immunogenicity could be made due to the small number of patients included in these groups.

1.3.3. Discussion on clinical aspects

The data submitted by the MAH is an observational study without comparator arm and non a priori formal hypothesis testing. The aim of this study was to assess efficacy and safety of a treatment with alglucosidase alfa produced at the 4000 L scale in patients previously treated with 160 L scale alglucosidase alfa.

Due to the design of study AGLU07510 which included any patient aged over 1 year with Pompe disease previously treated with alglucosidase alfa produced at the 160 L scale, the gross motor, respiratory and cardiac functions at baseline in the study population were heterogeneous.

The majority of patients (84.0%) were under the age of 8 years at the time of first infusion with alglucosidase alfa 4000L and 63.7% received alglucosidase alfa 160L treatment prior to 1 year of age.

Regarding the primary endpoint, it appears that 83.7% of patients (87/104 patients; 95% CI: 75.1%, 90.2%) transitioned to treatment with 4000L scale alglucosidase alfa were clinically stable or improved at Week 52. The most frequent reason for decline was GMFM decreased ≥8% (12 of 90 patients [13.3%]). Nevertheless, due to the patients' age and dependency on invasive ventilation, pulmonary function testing could not be performed and majority of echocardiography data are incomplete.

Thus, given the absence of comparative arm and the heterogeneity of the population at baseline it is difficult to draw any firm conclusion on this study. Moreover no comparison of those results to previous clinical trials and no extrapolation to all subtypes of Pompe disease can be done.

During AGLU09411 study, treatment-related AEs (mainly IARs) were reported in 38 out of 113 patients treated with alglucosidase alfa produced at the 4000 L scale. Based on the data provided by the MAH regarding the final results of study AGLU07510, no new safety concerns have been identified as compared to previous studies and experiences in infantile- and late-onset Pompe patients treated with alglucosidase alfa 160 L at a dose of 20 mg/kg qow. However, the MAH should provide clarifications on the underlying reasons for switching temporarily 2 patients from alglucosidase alfa 4000L to 160 L during the study and the consequences in these patients.

The assessment of AEs by immunogenicity parameters is hampered by the small number of patients having sustained high antibody titers or tested for other immunogenicity parameters, which prevent from any definite conclusion.

Regarding patients who received other dosing regimen, no relevant comparative assessment of AEs frequency and immunogenicity could be drawn, due to the small number of patients included in these groups.

2. CHMP overall conclusion and recommendation

☒ Fulfilled

Due to the design of study AGLU07510, the absence of comparative arm, the heterogeneity of the population at baseline no firm conclusion can be drawn on this study and to compare those result to previous clinical trials and extrapolate them to all subtypes of Pompe disease.

Based on the data provided by the MAH regarding the final results of study AGLU07510, no new safety concerns have been identified as compared to previous studies and experiences in infantile- and late-onset Pompe patients treated with alglucosidase alfa 160 L at a dose of 20 mg/kg qow. The additional clarifications provided on the underlying reasons for switching temporarily 2 patients from alglucosidase alfa 4000L to 160 L during the study and the consequences in these patients did not raise any new safety concern.

Due to the small number of patients having sustained high antibody titers or tested for other immunogenicity parameters, no definite conclusion could be drawn regarding AEs by immunogenicity parameters. As regards patients who received other dosing regimen, no relevant comparative assessment of AEs frequency and immunogenicity could be performed, due to the small number of patients included in these groups.

3. Additional clarification requested

The MAH should discuss about the underlying reasons for switching temporarily 2 patients from alglucosidase alfa 4000L to 160 L during the study and the consequences in these patients as the reporting information in the corresponding case narratives remains unclear on these aspects.

MAH responses to Request for supplementary information

Both patients (10015011 and 10585007) received temporary treatment with alglucosidase alfa 160L while enrolled in the ADVANCE study (AGLU09411). The treatment change was based on requests by the investigator and in accordance with the study protocol rescue criteria: *if a patient experienced clinical worsening as defined by the primary efficacy objective that is sustained on repeated measurement, the patient may be managed per the discretion of the Investigator which may include return to treatment with 160 L alglucosidase alfa.*

As noted in the final clinical study report, Patient 10015011 was enrolled in the ADVANCE study (AGLU09411) and initiated alglucosidase alfa 4000 L treatment on 12 April 2012. The investigator requested a switch in treatment after reporting related serious adverse event (SAE) of diarrhoea. However, the patient had a relevant medical history of recurrent *Clostridium difficile* colitis, fecal transplant, bloody stools, gastric dysmotility, recurrent constipation and recurrent diarrhea, that provides an alternate explanation for the reported events. Furthermore, according to Data Safety and Monitoring Board, there were multiple alternative explanations for the patient's diarrhea, including recurrent *C. difficile* infections and post gastroenteritis feeding intolerance. Patient received treatment with alglucosidase alfa 160 L from 27 June 2012 to 11 October 2012. The patient was again returned to treatment with alglucosidase alfa 4000 L on 18 October 2012 per request of the Investigator. After switching back to 4000 L patient continued in the study till 11 September 2014.

Patient 10585007 was enrolled in the ADVANCE study (AGLU09411) and received his first infusion of alglucosidase alfa 4000 L treatment on 16 April 2012. The investigator requested a switch in treatment

to 160 L after reporting 2 related SAEs of worsening of gross motor function decline and non-serious related events of right ventricular hypertrophy, abnormal electrocardiogram and heart valve incompetence. The patient had a relevant medical history of hypertrophic cardiomyopathy, invasive mechanical ventilation, bilateral diaphragmatic palsy and supraventricular tachycardia. The patient received treatment with alglucosidase alfa 160 L from 04 August 2014 to 20 October 2014. All the above mentioned AEs remained ongoing till the study end even after switching to alglucosidase alfa 160 L treatment. The patient was switched back to the commercially available alglucosidase alfa 4000 L when the ADVANCE study (AGLU09411) was terminated following approval of alglucosidase alfa 4000L in the US for all Pompe patients.

In conclusion, as discussed above, both patients switched treatment based on investigator request and in accordance with the rescue criteria outlined in the ADVANCE study (AGLU09411) clinical study protocol. The benefit –risk assessment of alglucosidase alfa was not affected by the above 2 cases and the safety profile of alglucosidase alfa 4000 L observed in this study is consistent with the previous alglucosidase alfa experience as described in the alglucosidase alfa product labels.

CHMP comments on MAH's response:

The clarification provided does not raise any new safety concerns.