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Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease

Laura E. Case [a], Carl Bjartmar [b], Claire Morgan [b], Robin Casey [c], Joel Charrow [d], John P. Clancy [e], Majed Dasouki [f], Stephanie DeArmey [a], Khan Nedd [g], Mary Nevins [h], Heidi Peters [i], Dawn Phillips [b], Zachary Spigelman [j], Cynthia Tifft [k], Priya S. Kishnani [a,*]

[a] *Duke University Medical Center, Durham, North Carolina, USA*
[b] *Genzyme, a sanofi company, Cambridge, Massachusetts, USA*
[c] *Alberta Children's Hospital, Alberta, Canada*
[d] *Ann and Robert H. Lurie Children's Hospital of Chicago, IL, USA*
[e] *Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA*
[f] *University of Kansas Medical Center, Kansas City, Kansas, USA*
[g] *Infusion Associates, Grand Rapids, Michigan, USA*
[h] *Adirondack Pediatrics, Glens Falls, New York, USA*
[i] *The Royal Children's Hospital, Victoria, Australia*
[j] *Parker Hill Oncology & Hematology, PC, Roxbury Crossing, Massachusetts, USA*
[k] *Children's National Medical Center, District of Columbia, USA*

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Abstract

Emerging phenotypes in long-term survivors with Pompe disease on standard enzyme replacement therapy (ERT) (alglucosidase alfa 20 mg/kg/2 weeks) can include patients with worsening motor function. Whether higher doses of ERT improve skeletal function in these patients has not been systematically studied. This exploratory, randomized, open-label, 52-week study examined the safety and efficacy of 2 ERT regimens of alglucosidase alfa (20 mg/kg/week or 40 mg/kg/2 weeks) in 13 patients with Pompe disease and clinical decline or a lack of improvement on standard ERT: late-onset (n = 4), infantile-onset (n = 9). Cross-reactive immunologic material assay-negative patients were excluded. Eleven of 13 patients completed the study. Trends for improvement were seen in total gross motor function, but not mobility; however, 6 (late-onset, 2; infantile-onset, 4) of 11 patients (55%) who met the entry criteria of motor decline (late-onset, 4; infantile-onset, 7) showed improvement in motor and/or mobility skills. No between-regimen differences in efficacy emerged. Two case studies highlight the benefits of increased ERT dose in patients with Pompe disease experiencing clinical decline. Both alternative regimens were generally well tolerated. This study was limited by the small sample size, which is not uncommon for small clinical studies of rare diseases. Additionally, the study did not include direct assessment of muscle pathology, which may have identified potential causes of decreased response to ERT. Results were inconclusive but suggest that increased ERT dose may be beneficial in some patients with Pompe disease experiencing motor decline. Controlled studies are needed to clarify the benefits and risks of this strategy.

Keywords: Alglucosidase alfa; Enzyme replacement therapy; Infantile onset; Late onset; Pompe disease; Clinical decline; Dose

1. Introduction

Pompe disease, a rare autosomal recessive neuromuscular disorder caused by a deficiency of the lysosomal enzyme acid α-glucosidase (GAA), results in glycogen accumulation in various organs, primarily muscle tissue [1]. Infantile-onset Pompe disease represents the most severe form, with early death due to cardiorespiratory failure within the first year of life [2]. The main clinical manifestations of Pompe disease include profound hypotonia/generalized muscle weakness, respiratory distress, and marked hypertrophic cardiomyopathy [3]. The only available treatment for Pompe disease, alglucosidase alfa (Genzyme, a Sanofi company, Cambridge, MA), targets the underlying cause by replacing the deficient GAA enzyme; and the recommended dosage is 20 mg/kg/2 weeks [4].

In infants with Pompe disease, alglucosidase alfa treatment has been shown to extend overall survival and invasive

* Corresponding author. Medical Genetics, Duke University Medical Center, 905 South LaSalle Street, GSRB1, Durham, NC 27710, USA. Tel.: +1 919 684 2036; fax: +1 919 684 8944.
E-mail address: priya.kishnani@duke.edu (P.S. Kishnani).

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ventilation-free survival, reverse cardiomyopathy, and permit children to achieve gross motor milestones, including independent walking, not observed in untreated cohorts where the median age of death was less than 9 months [3,5,6]. However, with increased long-term survival on alglucosidase alfa, an emerging phenotype characterized by progressive weakness and decreased motor function has been identified in patients with infantile-onset Pompe disease that initially responded well to enzyme replacement therapy (ERT) with alglucosidase alfa [7,8]. The emergence of this phenotype has raised the question of whether the currently approved ERT regimen (alglucosidase alfa 20 mg/kg/2 weeks) eventually may be insufficient in some patients, even in those who initially responded well to treatment.

We report on an open-label study (ClinicalTrials.gov, NCT00483379) including 2 detailed case reports that examine the efficacy and safety of alternative regimens of alglucosidase alfa in patients with late-onset and infantile-onset Pompe disease who experienced clinical decline or a lack of improvement despite continuation of ERT at the dose recommended in the package insert of 20 mg/kg/2 weeks. Together, these results suggest that controlled studies are warranted to establish the effects of alternative ERT regimens of alglucosidase alfa in Pompe disease and the development of new treatment approaches to allow for a continued clinical benefit.

2. Patients and methods

We first report on an open-label study of 13 cases that evaluated the safety and efficacy of alternative regimens of alglucosidase alfa (20 mg/kg/week or 40 mg/kg/2 weeks) in patients with late-onset or infantile-onset Pompe disease who experienced clinical decline or lack of improvement while receiving the recommended ERT dose of 20 mg/kg/2 weeks for ≥6 months. Patients <18 years of age who were cross-reactive immunologic material (CRIM) - negative were excluded. After reviewing results from this cohort, we subsequently selected 2 patients in the infantile-onset group (<18 years of age) for further review to elucidate examples in which patients who exhibited suboptimal treatment response with standard ERT may benefit from dose adjustments of alglucosidase alfa.

2.1. Open-label study design

This open-label, randomized, exploratory, 52-week study was conducted at 11 centers (9 in the United States, 1 in Australia, and 1 in Canada) with experience in treating Pompe disease. The primary objectives were to evaluate the safety and efficacy of 2 alternate alglucosidase alfa regimens and to evaluate differences in efficacy between the 2 dosing arms. The study protocol and informed consent forms were approved by an Institutional Review Board or Independent Ethics Committee at each individual study site, and the study complied with the Declaration of Helsinki. Written informed consent was provided by all patients or parents/legal guardians.

2.2. Study participants

Eligible patients were clinically diagnosed with Pompe disease, defined by documented endogenous GAA deficiency in skin fibroblasts or blood; were compliant in receiving the standard regimen of alglucosidase alfa (20 mg/kg/2 weeks) for ≥6 months immediately prior to study entry; and experienced clinical decline or a lack of improvement in ≥1 of the following parameters compared with their condition prior to beginning alglucosidase alfa treatment:

- Motor skills
  - For patients ≤2 years of age at study entry, failure to acquire ≥2 new gross motor milestones (e.g. turning head side to side [supine], grasping small objects with hands, transferring objects from hand to hand, holding head upright with body supported, rolling [supine to prone or prone to supine], sitting [supported or unsupported], walking [with support, i.e. cruising or independently], and walking upstairs [with assistance or independently])
  - For patients previously ambulatory, progression to the use of an assistive device for ambulation because of worsening of proximal lower extremity muscle weakness.
- Respiratory
  - New development of respiratory failure requiring the use of ventilatory assistance (invasive or noninvasive) for ≥4 weeks prior to study enrollment

Among other potential inclusion criteria were cardiac left ventricular mass (LVM) Z-score of ≥6 or LVM index of ≥150 g/m^2; or for patients >2 years of age at study entry, worsening of proximal UE muscle weakness through the loss of functional use of the UEs; or for patients >8 years of age at study entry, worsening of proximal UE muscle weakness through longitudinal assessments of manual muscle testing (MMT).

Exclusion criteria were CRIM-negative status and patients who used any investigational product other than alglucosidase alfa ≤30 days prior to study enrollment.

2.3. Treatment

Eligible patients were randomized 1:1 to a high-frequency group (alglucosidase alfa 20 mg/kg/week) or a high-dose group (alglucosidase alfa 40 mg/kg/2 weeks). Alglucosidase alfa was supplied by Genzyme, a Sanofi company. Randomization to the 2 treatment groups was stratified by age (<18 years of age and ≥18 years of age), which for the patients enrolled corresponded with the patients being randomized by phenotype (infantile-onset and late-onset, respectively). Randomization by age was done to achieve an even distribution of pediatric and adult patients in each dosing arm.

2.4. Efficacy assessments

Efficacy was evaluated at scheduled visits and included gross motor function as measured by the Gross Motor Function Measure 66 (GMFM-66) [9]; functional status as measured by the Pompe Pediatric Evaluation of Disability Index (Pompe PEDI) [10]; proximal and distal muscle strength as measured by MMT [11] in patients ≥8 years of age; respiratory function as

measured by ventilator use diary; and health-related quality of life as measured by the Physical Component Summary (PCS) score of the Medical Outcomes Study Short Form 36 (MOS SF-36) [12] in patients ≥14 years of age.

Scoring of the GMFM-66 was completed in a number of ways because the GMFM-66 has not been validated in Pompe disease but is considered a measure of functional strength that can be used to measure change over time. Although originally designed for use with individuals who have cerebral palsy (CP), validity in the use of the GMFM has been expanded to additional diagnoses [13–15], including spinal muscular atrophy [16], which has clinical characteristics of weakness that are similar to those of Pompe disease. In fact, at the time of this study no other assessments had been validated in Pompe disease, except the Pompe PEDI, which is a measure of disability and not a measure of performance. Raw scores, change in raw scores, and percentile change were analyzed to examine change as thoroughly as possible. Such analyses allowed consideration of minimal clinically important differences established for various components of the GMFM. Calculation of the Gross Motor Ability Estimator (GMAE), the classic and recommended scoring method for the use of the GMFM-66, was also performed.

The GMFM-66 total scores percent score was obtained by adding the percentage scores for GMFM-66 items in each dimension and dividing the sum by the total number of dimensions (5 dimensions: Lying and Rolling; Sitting; Crawling and Kneeling; Standing; and Walking, Running, and Jumping). The total and individual dimension scores were summarized over time. Analysis of the GMAE was considered secondary because the GMAE was based on the normative data from children with cerebral palsy.

2.5. Safety assessments

Safety evaluations included adverse events (AEs), vital sign parameters, physical examinations, electrocardiograms (ECGs), and laboratory measurements (hematology, chemistry, urinalysis, and antibody monitoring). Additional safety evaluations included assessments of anti-rhGAA antibody formation and inhibitory antibody formation (activity and uptake) in patients with a positive test result for immunoglobulin G (IgG); immunoglobulin E (IgE), serum tryptase, complement activation, and skin testing, when clinically indicated following moderate, severe, or recurrent infusion-associated reactions (IARs) suggestive of hypersensitivity; and circulating immune complex detection when clinically indicated.

2.6. Statistical analysis

Patients were evaluated at Week 52 for change from baseline in the parameters in which they demonstrated a lack of improvement or decline. Descriptive summary statistics were calculated for continuous variables and shift tables and/or frequencies for categorical variables. Confidence intervals (CIs) were used to estimate the mean change in efficacy parameters within patients irrespective of treatment received. AEs were summarized by severity, seriousness, relationship to treatment, and whether they were infusion-related.

3. Results

3.1. Patient demographics, characteristics and disposition

Patient demographics, characteristics, and disposition are summarized in Table 1. Of the 13 patients enrolled and treated, 11 were Caucasian, 1 was Asian, and 1 was Hispanic. In the late-onset (≥18 years of age) cohort, 2 patients (both male) were enrolled in the high-frequency group (alglucosidase alfa 20 mg/kg/week) and were considerably older than the 2 patients (both female) in the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks). In the infantile-onset cohort (<18 years of age), 4 patients (2 male, 2 female) were enrolled in the high-frequency group (alglucosidase alfa 20 mg/kg/week) and 5 patients (4 male, 1 female) in the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks). Patients with infantile-onset disease in the high-frequency group (alglucosidase alfa 20 mg/kg/week) were slightly younger than those in the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks). One patient was determined to be CRIM-negative after study entry when noted to have high titers, was discontinued at Week 13, and data from this patient was not included in the analysis. The patient had disease-related treatment-emergent AEs (TEAEs) of mild ptosis and severe right ventricular hypertrophy at the time of discontinuation. There were no additional patients with high and sustained titers (≥1:51,200 on more than 2 occasions at or beyond 6 months on ERT. One patient in the late-onset cohort discontinued the study after 50 weeks of treatment due to a treatment-unrelated AE of pneumonia.

3.2. Efficacy

3.2.1. Overall findings

3.2.1.1. Functional change. A total of 11 patients (4 in the late-onset group and 7 in the infantile-onset group) were included because they met the criteria for motor decline. Over the 52-week study period, 6 of the 11 patients (55%; 2 late-onset [1 high frequency and 1 high dose] and 4 infantile-onset [1 high frequency and 3 high dose]) displayed motor skill improvements in raw scores on the GMFM-66 and/or Pompe PEDI; 3 patients (27%; 1 late-onset [high dose] and 2 infantile-onset [1 high dose and 1 high frequency]) showed no change and maintained baseline status; and 1 patient (9%, infantile-onset [high frequency]) showed continued motor loss. One patient in the late-onset group experienced a decline in respiratory status. This patient was invasively vented 13 hours per day at baseline, required 24-hour ventilation after he was hospitalized for pneumonia after Week 50 and was not evaluated at Week 52.

At Week 52, an increasing trend in GMFM-66 total percent scores was driven by improvements in the sitting dimension (Table 2). The only difference by treatment group was a trend in change from baseline to Week 52 in the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks) with an increase in GMFM-66 total raw score of 6.7 ± 6.12 (95% CI: 0.2, 13.1)

Table 1
Patient demographics and disease history.

Variable	Alglucosidase alfa 20 mg/kg/week (n = 6)[a]	Alglucosidase alfa 40 mg/kg/2 weeks (n = 7)	Total (N = 13)
Male, n	4	4	8
Female, n	2	3	5
Age, years			
Mean (SD)	23.3 (27.75)	16.8 (15.56)	19.8 (21.29)
Median (range)	8.8 (1.8–60.1)	14.5 (3.2–40.2)	12.5 (1.8–60.1)
Patients <18 years, n	4	5	9
≤8	3	3	6
9–17	1	2	3
Patients ≥18 years, n	2	2	4
18–44	0	2	2
≥45	2	0	2
Age at first symptom, years			
n	5	7	12
Mean (SD)	7.1 (15.36)	8.7 (14.59)	8.0 (14.23)
Median (range)	0.3 (0–34.6)	0.3 (0–32.1)	0.3 (0–34.6)
Age at diagnosis, years			
n	6	7	13
Mean (SD)	17.5 (26.25)	9.9 (16.49)	13.4 (20.94)
Median (range)	1.1 (0.1–55.4)	0.4 (0–37.8)	0.5 (0–55.4)
Time on alglucosidase alfa treatment, years			
n	6	7	13
Mean (SD)	2.5 (1.27)	2.8 (0.91)	2.7 (1.05)
Median (range)	2.2 (1.2–4.7)	2.9 (1.3–3.7)	2.9 (1.2–4.7)
Duration of disease since symptom onset, years			
n	5	7	12
Mean (SD)	9.3 (9.94)	8.0 (5.37)	8.5 (7.22)
Median (range)	4.9 (1.5–25.5)	7.8 (2.9–16.3)	6.4 (1.5–25.5)

SD = standard deviation, CRIM = cross-reactive immunologic material.
[a] One patient in the 20 mg/kg/week group was determined to be CRIM negative after study entry, was discontinued at week 13, and data were not included in data analysis.

compared with the high-frequency group (alglucosidase alfa 20 mg/kg/week) total raw score change of 6.0 ± 8.49 (95% CI: −7.5, 19.5).

On the Pompe PEDI, trends for change were noted for the overall population and select subgroups in social function raw and scaled scores, with and without caregiver assistance; self-care raw and scaled scores without caregiver assistance; and self-care raw scores with caregiver assistance (Table 3). No trends for change in Pompe PEDI Mobility scores were observed for the overall study population or any of the subgroups analyzed.

No patient met any of the other potential inclusion criteria, which included cardiac parameters, worsening of proximal upper extremity (UE) muscle weakness through the loss of functional use of the UEs; or for patients >8 years of age at study entry, worsening of proximal UE weakness through longitudinal assessments of MMT.

3.2.1.2. Manual muscle testing. For MMT, no trends were observed for change in upper or lower body muscle strength, or total muscle strength scores generally, or for the proximal muscle groups.

3.2.1.3. Respiratory parameters. For respiratory parameters, no patients were recorded as improved.

3.2.1.4. Health-related quality of life (SF-36 PCS). No trends were observed for change in either the physical or mental component summary of the health-related quality of life assessment.

3.2.2. Late-onset cohort

In the late-onset cohort, all 4 patients were included because they met the inclusion criteria for motor decline. Most (75%; 3 of 4) patients maintained their baseline GMFM-66 raw scores or Pompe PEDI status or showed gains at Week 52; 1 patient, who was hospitalized for pneumonia after Week 50 was not evaluated and subsequently died. Of the 2 (50%; 2 of 4) patients who showed improvement, 1 patient in the high-frequency group (alglucosidase alfa 20 mg/kg/week) acquired the ability to squat to pick up an item off the floor and the other patient in the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks) acquired the ability to walk for 5 blocks, walk on the curb and on inclines and ramps, ascend an entire flight of stairs with the use of a handrail, and descend several stairs without a handrail. For the remaining patient in the late-onset, high-dose group (alglucosidase alfa 40 mg/kg/2 weeks), no significant change in motor function was observed.

3.2.3. Infantile-onset cohort

In the infantile-onset cohort, 7 of 9 patients were included because they met the inclusion criteria for a decline in motor function and 2 patients were initially included because they met the criteria for a decline in respiratory function, with one of these 2 excluded at 13 weeks when CRIM-negative status was

Table 2
Gross Motor Function Measure 66 (GMFM-66) percent scores.

Visit	Alglucosidase alfa 20 mg/kg/week (baseline, n = 5; week 52, n = 4; change, n = 4)	Alglucosidase alfa 40 mg/kg/2 weeks (baseline, n = 6; week 52, n = 7; change, n = 6)	Total (baseline, n = 11; week 52, n = 11; change, n = 10)
Total score			
Baseline			
Mean (SD)	42.1 (32.91)	47.1 (42.34)	44.8 (36.56)
Median (range)	30.8 (0.0–83.9)	46.8 (5.0–90.0)	30.8 (0.0–90.0)
Week 52			
Mean (SD)	40.8 (34.81)	54.6 (42.57)	49.6 (38.73)
Median (range)	39.0 (0.0–85.1)	86.1 (6.7–91.9)	40.5 (0.0–91.9)
Change from baseline			
Mean (SD)	4.5 (4.68)	2.1 (3.41)	3.1 (3.92)
Median (range)	4.2 (0.0–9.7)	2.7 (−4.1 to 5.8)	2.7 (−4.1 to 9.7)
95% CI	−2.9, 12.0	−1.5, 5.7	0.3, 5.9
Sitting score			
Baseline			
Mean (SD)	49.3 (39.67)	47.8 (48.29)	48.5 (42.38)
Median (range)	62.2 (0.0–91.1)	45.6 (0.0–100.0)	62.2 (0.0–100.0)
Week 52			
Mean (SD)	46.7 (46.44)	62.2 (47.59)	56.6 (45.47)
Median (range)	44.4 (0.0–97.8)	97.8 (0.0–100.0)	73.3 (0.0–100.0)
95% CI			
Change from baseline			
Mean (SD)	4.4 (5.44)	8.1 (10.20)	6.7 (8.45)
Median (range)	3.3 (0.0–11.1)	3.3 (0.0–22.2)	3.3 (0.0–22.2)
95% CI	−4.2, 13.1	−2.6, 18.9	0.6, 12.7

SD = standard deviation, CI = confidence interval.
The GMFM-66 total scores percent score was obtained by adding the percentage scores for each dimension and dividing the sum by the total number of dimensions.

identified, and this patient's data were not included in the analysis.

Four of the 7 patients (57%) included because of motor decline displayed improved motor skills on the GMFM-66 or Pompe PEDI. In the high-frequency group (alglucosidase alfa 20 mg/kg/week), 1 patient acquired the ability to transition from the sitting to the quadruped position and to maintain the quadruped position for 10 seconds. In the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks), 1 patient improved the ability to run and jump and acquired the ability to maintain a half-kneel position hands-free; 1 patient acquired the ability to sit independently for 5 seconds and shift weight to reach objects in front and behind; and 1 patient acquired the ability to walk farther distances, walk on uneven terrain, walk backward 10 feet, pick up an object from the ground, and walk up a full flight of stairs. For the remaining 3 patients in the infantile-onset group, 2 patients showed no change from baseline (1 in the high-frequency group [alglucosidase alfa 20 mg/kg/week] and 1 in the high-dose group [alglucosidase alfa 40 mg/kg/2 weeks]) and 1 patient showed continued motor loss (high-frequency group).

Two patients in the infantile-onset group entered the study based on the development of respiratory failure. Both patients were invasively ventilated 24 hours per day at baseline; 1 patient in the high-frequency group (alglucosidase alfa 20 mg/kg/weeks) who was CRIM-negative discontinued at Week 13, was not evaluated at Week 52, and was not included in the data analysis. The other patient, in the high-dose group (alglucosidase alfa 40 mg/kg/2 weeks), showed no change in ventilator status at Week 52.

3.3. Safety

All patients in both treatment groups experienced treatment-emergent AEs (TEAEs), the majority of which (97%; 135 of 139) were assessed as mild or moderate in severity and unrelated to study drug. The most common TEAEs were upper respiratory infection, diarrhea, and pyrexia, experienced by 5, 4, and 4 patients, respectively (Table 4). A total of 8 serious adverse events (SAEs) occurred in 3 of 13 (23%) patients: 1 patient in the infantile-onset, high-frequency group (alglucosidase alfa 20 mg/kg/week) experienced pneumonia, and 1 patient in the infantile-onset, high-dose group (alglucosidase alfa 40 mg/kg/2 weeks) experienced 5 SAEs. These SAEs included 1 moderate and possibly treatment-related infusion-associated reaction (IAR) of supraventricular tachycardia (SVT) and 4 SAEs (SVT, weight decrease, device-related infection, and dysphagia) considered unrelated to study treatment. In addition, 1 patient in the late-onset, high-frequency group died of a cause unrelated to study treatment (respiratory failure secondary to pneumonia). Additionally, 2 of 13 (15%) patients in the high-dose group (1 in the late-onset group and 1 in the infantile-onset group) experienced 12 treatment-related IARs; however, only 1 IAR (SVT) was considered serious. Both patients had a history of IARs during treatment at the standard dose of 20 mg/kg/2 weeks and experienced recurrent IARs (erythematous rash in the patient in the infantile-onset group and headache and dyspnea in the patient in the late-onset group) at the first 3 infusions of the current study. None of the IARs were indicative of

Table 3
POMPE Pediatric Evaluation of Disability Inventory (POMPE PEDI) component scores.

Score description	Visit	<18 Years of age (baseline, n = 8; week 52, n = 8; change, n = 8)	≥18 Years of age (baseline, n = 4; week 52, n = 3; change, n = 3)
Caregiver assistance social function raw score	Baseline		
	Mean (SD)	15.8 (8.12)	25.0 (0.00)
	Median (range)	18.0 (1.0, 25.0)	25.0 (25.0–25.0)
	Week 52		
	Mean (SD)	18.4 (7.31)	25.0 (0.0)
	Median (range)	19.0 (2.0–25.0)	25.0 (25.0–25.0)
	Change from baseline		
	Mean (SD)	2.6 (3.16)	0 (0.0)
	Median (range)	1.0 (0.0–8.0)	0.0 (0.0–0.0)
	95% CI	0.0, 5.3	
Caregiver assistance social function scaled score	Baseline		
	Mean (SD)	63.2 (26.43)	100.0 (0.0)
	Median (range)	67.7 (11.3–100.0)	100.0 (100.0–100.0)
	Week 52		
	Mean (SD)	71.5 (24.94)	100.0 (0.0)
	Median (range)	70.1 (20.4–100.0)	100.0 (100.0–100.0)
	Change from baseline		
	Mean (SD)	8.3 (8.39)	0 (0.0)
	Median (range)	5.8 (0.0–21.4)	0.0 (0.0–0.0)
	95% CI	1.3, 15.3	
Caregiver assistance self-care raw score	Baseline		
	Mean (SD)	10.9 (13.53)	40.0 (0.0)
	Median (range)	6.0 (0.0, 38.0)	40.0 (40.0, 40.0)
	Week 52		
	Mean (SD)	14.1 (13.09)	40.0 (0.0)
	Median (range)	12.5 (0.0–38.0)	40.0 (40.0–40.0)
	Change from baseline		
	Mean (SD)	3.3 (3.85)	0 (0.0)
	Median (range)	2.5 (0.0–11.0)	0.0 (0.0–0.0)
	95% CI	0.0, 6.5	
Social function raw score	Baseline		
	Mean (SD)	41.8 (20.20)	64.8 (0.50)
	Median (range)	49.5 (11.0–65.0)	65.0 (64.0–65.0)
	Week 52		
	Mean (SD)	49.3 (15.38)	65.0 (0.0)
	Median (range)	53.0 (18.0–65.0)	65.0 (65.0–65.0)
	Change from baseline		
	Mean (SD)	7.5 (8.68)	0 (0.0)
	Median (range)	4.5 (0.0–22.0)	0.0 (0.0–0.0)
	95% CI	0.2, 14.8	
Score description	Visit	<18 Years of age (baseline, n = 9; week 52, n = 8; change, n = 8)	≥18 Years of age (baseline, n = 4; week 52, n = 3; change, n = 3)
Social function scaled score	Baseline		
	Mean (SD)	59.8 (20.34)	99.1 (1.85)
	Median (range)	60.6 (35.1–100.0)	100.0 (96.3–100.0)
	Week 52		
	Mean (SD)	67.0 (19.08)	100.0 (0.00)
	Median (range)	63.2 (41.1–100.0)	100.0 (100.0–100.0)
	Change from baseline		
	Mean (SD)	7.1 (7.62)	0 (0.0)
	Median (range)	5.1(−1.0 to 20.2)	0.0 (0.0–0.0)
	95% CI	0.8, 13.5	
Self-care raw score	Baseline		
	Mean (SD)	45.5 (30.42)	118.3 (4.35)
	Median (range)	48.5 (7.0–86.0)	118.5 (114.0–122.0)
	Week 52		
	Mean (SD)	56.0 (31.14)	
	Median (range)	53.0 (12.0–103.0)	120.3 (2.89)
	Change from baseline		122.0 (117.0–122.0)
	Mean (SD)	10.5 (11.53)	1.0 (1.73)
	Median (range)	7.5 (0.0–36.0)	0.0 (0.0–3.0)
	95% CI	0.9, 20.1	−3.3, 5.3
Self-care scaled score	Baseline		
	Mean (SD)	49.8 (16.57)	92.9 (8.22)
	Median (range)	54.1 (23.1–69.0)	93.2 (85.2–100.0)
	Week 52		
	Mean (SD)	55.8 (14.96)	96.4 (6.18)
	Median (range)	56.1 (31.8–76.5)	100.0 (89.3–100.0)
	Change from baseline		
	Mean (SD)	6.0 (6.37)	1.4 (2.37)
	Median (range)	3.8 (0.0–20.0)	0.0 (0.0–4.1)
	95% CI	0.6, 11.3	−4.5, 7.2

SD = standard deviation, CI = confidence interval.

Table 4
Summary of treatment-emergent adverse events occurring in ≥2 patients.

Adverse event	Alglucosidase alfa 20 mg/kg/week (n = 6)		Alglucosidase alfa 40 mg/kg/2 weeks (n = 7)		Total (N = 13)	
	Patients, n (%)	Adverse events, n	Patients, n (%)	Adverse events, n	Patients, n (%)	Adverse events, n
Any adverse event	6 (100)	72	7 (100)	67	13 (100)	139
Upper respiratory infection	2 (33)	3	3 (43)	4	5 (38)	7
Pyrexia	2 (33)	2	2 (29)	2	4 (31)	4
Diarrhea	2 (33)	2	2 (29)	2	4 (31)	4
Pneumonia	3 (50)	6	0 (0)	0	3 (23)	6
Dermatitis diaper	1 (17)	2	2 (29)	2	3 (23)	4
Gastroenteritis viral	1 (17)	1	1 (14)	1	2 (15)	2
Nasopharyngitis	2 (33)	2	0 (0)	0	2 (15)	2
Otitis media	0 (0)	0	2 (29)	3	2 (15)	3
Viral infection	2 (33)	2	0 (0)	0	2 (15)	3
Abdominal pain upper	2 (33)	2	0 (0)	0	2 (15)	2
Vomiting	2 (33)	2	0 (0)	0	2 (15)	2
Fall	1 (17)	2	1 (14)	2	2 (15)	4

anaphylactic/allergic reactions. Eleven of the 13 patients were IgG seropositive at Day 0 (first study drug infusion) of the dosing regimen change (10 CRIM-positive, range 400–3200; 1 CRIM-negative, 204,800); 1 patient in the late-onset, high frequency group was seronegative at Day 0 and remained seronegative during the study (20 mg/kg/week); and 1 patient in the infantile-onset, high-dose group was not tested at Day 0 and remained negative during the study.

The CRIM-negative patient had inhibition of enzyme uptake and activity at Day 0, exhibited high, sustained anti-rhGAA IgG antibody titers (204,800 at Day 0, 819,200 at Week 4, and 409,600 at Weeks 8 and 12), experienced 6 TEAEs and was withdrawn from the study at Week 13, and data from this patient was not included in the data analysis. The median peak titer for the remaining 10 seropositive patients was 1600 (range 800–3200) and the median last titer was 1200 (range 0–3200). The median anti-rhGAA IgG antibody titers for patients by treatment group over time are presented in Fig. 1.

4. Detailed review of 2 patients with infantile-onset Pompe disease and evidence of response to alternative alglucosidase alfa dosing

4.1. Common characteristics

Children versus adults were chosen for the case studies to utilize the Pompe PEDI normative data to describe overall function and quality of life, including self-care and socialization. Cases represent patients who had a clear and well-defined motor decline and different levels of functional ability. Our goal was to highlight an example of a child experiencing subtle decline as evident through ambulation and another child whose highest functional ability was play in an independent sitting. Overall, we present 2 patients as examples of when alternative alglucosidase alfa dosing was safe and beneficial. Both patients were enrolled in this study because they met the criteria for motor decline. Prior to the study, they demonstrated an initial beneficial treatment response when

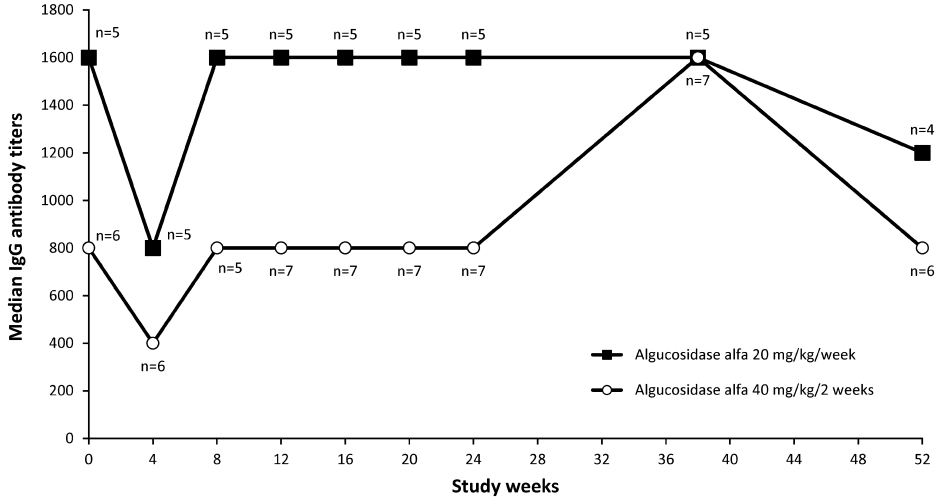

Fig. 1. IgG antibody titers over time by treatment group.

started on a standard ERT dose of 20 mg/kg/2 weeks. However, the clinical response reached a plateau and subsequently declined over time. These patients had low alglucosidase alfa antibody titers; thus, they had tolerized to ERT. These patients also received adequate nutrition (with good protein intake at ~3 g/kg/day) and regular physical and speech therapy.

4.2. Case 1: patient receiving alglucosidase alfa 20 mg/kg/week

4.2.1. Background

At the time of study initiation, this female patient was age 1 year 10 months and had been diagnosed with Pompe disease at age 6 months. Her medical history and test results are presented in Table 5. The patient met the inclusion criterion of failure to acquire ≥2 new gross motor milestones, and had shown a decline on the Alberta Infant Motor Scale (AIMS) compared to age-level peers. She had shown improvements as measured by the AIMS from 8 months to 20 months but remained below the 5th percentile on the AIMS and was falling further below age-level peers. On the GMFM-66 and the Pompe PEDI Functional Skills Mobility domain at baseline, the patient was able to initiate a head lift but could not sustain an upright head position in the prone position. She was also able to sit hands-free for 2 seconds and reach out of her base of support to touch a toy at shoulder level and return to sitting. She was able to move forward from a prone position <2 feet, and did not have any controlled transitions in or out of the sitting position. She was not credited for any items in the crawling, standing, or walking dimensions of the GMFM-66 test. The patient could bear minimal weight on her legs to participate in standing transfers.

4.2.2. Response to higher-frequency dosing (alglucosidase alfa 20 mg/kg/week)

Results of the patient's response to alglucosidase alfa 20 mg/kg/week are summarized in Table 5. AEs were mild and unrelated to alglucosidase alfa. No SAEs occurred. At Week 52, she showed a change rate of +5.41 on the GMAE, which would be considered a clinically important difference of moderate effect size [17], and would be considered statistically significant because of non-overlapping 95% CIs. In sub-analyses of individual dimensions of the GMFM-66, changes occurred in Dimension B (Sitting) and Dimension C (Crawling and Kneeling). On the Pompe PEDI Functional Skills Mobility domain, both raw and scaled scores increased.

Acquisition of additional motor skill acquisition was demonstrated on the GMFM-66 and Pompe PEDI, and included holding her head upright in prone position for 5 seconds, independent transition from sitting to quadruped positions and back, and maintenance of quadruped position for 10 seconds. She was able to take several steps in a walker.

The Pompe PEDI Social Skills domain showed an increase in both standard and scaled scores. Baseline Social domain standard score was >2 standard deviations below the mean, and

Table 5
Case 1: Higher-frequency (20 mg/kg/week) of alglucosidase alfa in a patient with infantile-onset Pompe disease.

Demographics							
Age	1.8 years						
Gender	Female						
Time of diagnosis	6 months after birth						
Medical history	Congestive heart failure, left ventricular hypertrophy, failure to thrive, gastroesophageal reflux, hepatomegaly, hypotonia, impaired swallowing, joint contractures, muscle weakness in the upper and lower extremities, pneumonia, reactive airway disease, and sleep apnea. She needs an orthopedic device and a feeding tube.						
Results							
GMFM-66 GMAE scores	Baseline (95% CI) 35.26 (32.16–38.05)			Week 52 (95% CI) 40.67 (38.38–42.96)			Change score +5.41[a]
GMFM-66 dimension scores	Dimension A (lying and rolling) raw score	Dimension B (sitting) raw score	Dimension C (crawling and kneeling) raw score	Dimension D (standing) raw score	Dimension E (walking, running,and jumping) raw score	Raw score total	Total % score
Baseline	11	28	0	0	0	39	30.78
Week 52	11	33	10	0	0	54	39.66
Change from baseline	0	5	10	0	0	15	8.88
Pompe PEDI functional skills	Self-care domain standard score	Mobility domain standard score	Social function domain standard score	Self-care domain scaled score	Mobility domain scaled score	Social function scaled score	Raw functional mobility score
Baseline	14.2	<10	26.7	35.25	31.28	38.8	22
Week 52	38.97	<10	41.1	55.23	35.57	52.6	30

CI = confidence interval, GMAE = Gross Motor Ability Estimator, PEDI = Pediatric Evaluation of Disability Index.

[a] Considered a clinically important difference of moderate effect size.

The Gross Motor Function Measure 66 (GMFM-66) total scores percent score was obtained by adding the percentage scores for each dimension and dividing the sum by the total number of dimensions.

Table 6
Case 2: higher dose of alglucosidase alfa (40 mg/kg/2 weeks) in a patient with infantile-onset Pompe disease.

Demographics							
Age	3.2 years						
Gender	Male						
Time of diagnosis	3 months after birth						
Medical history	Cardiac arrhythmia, left ventricular hypertrophy, chronic otitis media, failure to thrive, feeding difficulties, gastroesophageal reflux, hypotonia, joint contractures, delayed and regression of motor milestones, pneumonia, and reactive airway disease. He needs a feeding tube for nutritional support, although he can eat by mouth.						
Results							
GMFM-66 GMAE scores	Baseline (95% CI) 58.80 (56.39–61.21)			Week 52 (95% CI) 66.69 (63.81–69.57)			Change Score +7.89[a]
GMFM-66 dimension scores	Dimension A (lying and rolling) raw score	Dimension B (sitting) raw score	Dimension C (crawling and kneeling) raw Score	Dimension D (standing) raw score (%)	Dimension E (walking, running, and jumping) raw score (%)	Raw score total	Total % score
Baseline	12	35	30	26 (66%)	41(56.94%)	144	80.28
Week 52	12	45	27	31 (79%)	44 (61.11%)	159	86.12
Change from baseline	0	+10	−3	+5 (+12.82%)[a]	+3 (+4.17%)[a]	15	5.84
Pompe PEDI functional skills	Self-care domain standard score	Mobility domain standard score	Social function domain standard score	Self-care domain scaled Score	Mobility domain scaled score	Social function scaled score	Raw functional mobility score
Baseline	27.06	18.42	36.8	52.04	51.57	49.7	75
Week 52	12.42	13.95	37.9	56.08	57.27	62.3	94

CI = confidence interval, GMAE = Gross Motor Ability Estimator, PEDI = Pediatric Evaluation of Disability Index.
[a] Considered a clinically important difference of moderate effect size.
The Gross Motor Function Measure 66 (GMFM-66) total scores percent score was obtained by adding the percentage scores for each dimension and dividing the sum by the total number of dimensions.

Week 52 standard score fell within 1 standard deviation of the mean. Skills acquired during this period included increased communication with the ability to name things and to use 2 words together. More advanced peer interactions and play skills emerged, including the ability to manipulate and put toys together, and she was able to play at home without constant supervision.

The Pompe PEDI Self-Care domain scaled and standard scores both increased, and significant improvements in feeding were documented. At baseline, she was not taking any food or drinks orally. At Week 52, she was drinking liquids from a sippy cup, using a straw, and eating all textures of food except hard food – reflecting improved oral motor function, including strength needed for chewing and swallowing. Her level of participation increased in all activities of daily living, including dressing; bathing; and care of hair, teeth, and nose. Acquisition of new skills included the ability to scribble with a marker and to access a computer icon using a mouse, potentially reflecting increased distal strength.

4.3. Case 2: patient receiving alglucosidase alfa 40 mg/kg/2 weeks

4.3.1. Background

This male patient was diagnosed with Pompe disease at age 3 months and was enrolled in this study at age 3 years 2 months. His medical history and test results are presented in Table 6. The patient met the inclusion criterion of use of an assistive device for ambulation due to worsening of proximal lower extremity muscle weakness. He had shown a decreased rate of change on the GMAE prior to the study compared with previously higher rates of change (+20.66 in first year on ERT with alglucosidase alfa and +13.65 in the first half of the second year on ERT with alglucosidase alfa), with a decline in status over the subsequent 4 months in the second year (change rate of −1), and had begun to show increased falls in all settings. He initially achieved walking with a walker and began walking independently without a walker at 2 years 2 months, but began to show increased falls at 2 years 10 months. In addition, he showed deteriorating gait kinematics, including decreased ankle dorsiflexion, increased foot drop, and decreased hip extension (with increased use of compensatory patterns, including steppage gait), and increasing lumbar lordosis. On baseline GMFM-66 and PEDI Functional Skill Mobility domain testing, he was able to walk independently but was only able to climb stairs if holding onto 2 railings, 1 on each side, could not pick up an object off the floor without hand support, and could only stand on 1 foot if holding on with 2 hands.

4.3.2. Response to higher dosing (alglucosidase alfa 40 mg/kg/2 weeks)

Results of the patient's response to alglucosidase alfa 40 mg/kg/2 weeks are presented in Table 6. AEs were mild and unrelated to alglucosidase alfa. No SAEs occurred. At Week 52, there was a change score of +7.89 on the GMAE, which would

be considered a clinically important difference of moderate effect size [17], and would be considered statistically significant because of non-overlapping 95% CIs. In sub-analyses of change on individual dimensions of the GMFM-66, the patient demonstrated improvement in Dimension B (Sitting), Dimension D (Standing), and Dimension E (Walking, Running, and Jumping). In Dimensions D and E, for which individual GMFM Dimension change scores and minimal clinically important differences (MCIDs) are available, he showed a change score of +12.82 and +4.17, respectively, both of which would be considered clinically important differences of moderate effect size [18]. He could walk farther and on uneven terrain, stand on 1 foot while holding on with only 1 hand, pick up an object from the ground and return to standing position without hand support, and walk up stairs holding onto only 1 railing, reflecting improved functional lower extremity strength. His respiratory status remained unchanged (ventilator-free).

The patient's Pompe PEDI Social Skills domain scaled score increased. He acquired increased communication (put 4 to 5 words together), more complex fine-motor skills, and was able to play at home and in the community without constant supervision.

The Pompe PEDI Self-Care Skills domain scaled score increased, demonstrating increased independence, although a decrease in the standard score showed that his rate of skill acquisition was not the same as his normative peer sample. New skill items present at 52 weeks included drinking from a straw, managing a water faucet independently, and increased independence in brushing his teeth and wiping his nose.

5. Discussion

Before the approval of alglucosidase alfa for the treatment of Pompe disease in 2006, the prognosis for affected infants was poor and life expectancy was short. Since then, the natural history of infantile Pompe disease on ERT has changed significantly, in particular with regard to survival. The clinical experience among infantile survivors has shown residual weakness in some in spite of overall benefit and increased survival [7,8], with some patients eventually starting to exhibit progression of weakness and decline in function, prompting questions about long-term pathophysiology and dosing optimization. Factors such as ongoing glycogen storage, autophagic cellular abnormalities, and mitochondrial dysfunction may promote ongoing muscle damage or compromise effective enzyme delivery [19], perhaps contributing to a phenotype characterized by progression of weakness, and functional decline in some patients over time despite standard initial treatment [7,8]. Additionally, the initial dosing may not sufficiently keep up with increasing muscle mass and metabolic demands associated with physical maturation. Other potential factors include mounting an immune response to ERT, poor nutrition, a lack of adequate therapies (occupational, physical, and speech therapy), and not receiving a multidisciplinary approach to care. Increased dosage has been shown to improve the clinical outcome in ptosis and may be needed in additional situations [20]. The current study evaluated the safety and exploratory efficacy of alternative, more intensive alglucosidase alfa regimens (high frequency at 20 mg/kg/week or high dose at 40 mg/kg/2 weeks) in initially responsive patients with declining function during standard ERT with alglucosidase alfa at 20 mg/kg/2 weeks.

No systematic studies have examined the use of higher doses of ERT in patients with Pompe disease experiencing motor deterioration with standard dosing. In a case report, a higher ERT dose at 40 mg/kg/2 weeks yielded well-tolerated motor improvement and partial reversal of ptosis after 6 months in a 13-year-old patient who experienced diminished muscle strength after standard ERT with alglucosidase alfa for 2 years [20]. None of the patients in the current study had high and sustained anti-rhGAA titers (except one individual whose CRIM-negative status was diagnosed after study inclusion and was withdrawn from the study at week 13 with data not included in data analysis). Given these limitations, it is still important to recognize that this is the largest study looking at dose effect in a group of individuals with Pompe disease showing a clinical decline over time on ERT with alglucosidase alfa dosing based on the package insert [4]. Although improvement in motor function suggests a benefit of increased dose, stabilization can also suggest an improvement in patients who were in decline because continued decline could have been expected if treatment were continued with the standard dose of alglucosidase alfa at 20 mg/kg/2 weeks. In the current study, GMFM-66 total percent scores demonstrated an overall trend for motor improvement from baseline after 52 weeks of more intensive ERT with alglucosidase alfa. In addition, 6 of 11 (55%) patients who entered the study because of a decline or clinical plateau in motor skills showed functional improvement with increased dose of ERT. No trends for differences in efficacy emerged between the 2 dosing arms, although this may be attributed to the small sample size (N = 13), heterogeneity in age distribution (range, 1.8–60.1 years), and functional presentation (infantile-onset group and late-onset group) at baseline. Additionally, patients were enrolled based on either motor decline (n = 11) or respiratory decline (n = 2). The large variability in the level of disability and functional status in this study prevented a meaningful and conclusive analysis of mean functional change from baseline and between treatment arms.

The detailed review of 2 infantile patients may provide more informative clinical insights into the effects of higher or more frequent alglucosidase alfa dosing in selected patients who experience motor decline while receiving standard ERT with alglucosidase alfa. After the 52-week study period, these 2 patients demonstrated improvement in motor skills, with gains on the GMFM-66 raw scores and Pompe PEDI Functional Mobility, Self-Care, and Social Function domains. These data suggest that the improvements in functional mobility and quality of movement observed during treatment with higher doses of ERT with alglucosidase alfa may provide a basis for meaningful enhancements in self-care and socialization skills. Moreover, the improvements in fine motor skills seen in these patients may translate into increased levels of functional independence in the home and school

environments, with less reliance on adult caregivers for daily home and academic needs.

The overall safety profile in this study is consistent with the overall safety experience with alglucosidase alfa. Most TEAEs were of mild or moderate severity and unrelated to the use of alglucosidase alfa. No new safety concerns emerged for either dose regimen. None of the patients, other than the one CRIM-negative patient, had an increase in titers since the increase in dose on ERT; in fact, all had low antibody titers (IgG titers ≤3200 at Day 0, peak, and last titers).

This study was limited by the small sample size, although small clinical studies are not uncommon in the investigation of rare diseases [21]. Also, the study did not include direct assessment of muscle pathology which may or may not have identified potential causes of resistance to ERT. However, this is the largest study of increased dosing in individuals on ERT with alglucosidase alfa who had been showing clinical decline. The interpretation of the study results was also limited by the heterogeneity of the sample and the absence of a control group that continued to receive ERT with alglucosidase alfa at doses based on the package insert.

The results of this study, although statistically inconclusive, and the case studies presented, suggest that an increase in ERT alglucosidase alfa dose may be beneficial in patients with Pompe disease who are experiencing plateau or decline in motor function over time while receiving a standard regimen. The clinical improvements or stabilization observed in individual patients can be considered improvement in patients who are otherwise in clinical decline. Thinking about dose-adjustment experiences in the setting of clinical plateau and decline is important because rapid progression of the disease is well-documented. However, controlled studies in a more homogeneous patient cohort – i.e. in patients with infantile-onset disease experiencing motor decline – are clearly needed to elucidate the benefits and risks of this alternative regimen because the current recommend dose of ERT is alglucosidase alfa 20 mg/kg/2 weeks [4] and is insufficient in many cases [3].

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