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Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa

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ABSTRACT

Objective: Late-onset Pompe disease is a progressive, debilitating, and often fatal neuromuscular disorder resulting from the deficiency of a lysosomal enzyme, acid α-glucosidase. This extension study was conducted to determine the durability of the efficacy and safety of alglucosidase alfa observed over a period of 78 weeks in the Late-Onset Treatment Study (LOTS).

Methods: Patients who completed the LOTS study were eligible for this open-label extension study and received alglucosidase alfa 20 mg/kg biweekly for an additional 26 weeks. The primary efficacy assessments were the distance walked during a 6-minute walk test and the percentage of predicted forced vital capacity in the upright position. Data are reported as change from patient's original LOTS baseline for each measure.

Results: The benefit of alglucosidase alfa treatment observed in LOTS at Week 78 was, in general, maintained at Week 104. The mean increase in distance walked measured 28.2 ± 66.5 m from LOTS baseline to Week 78 and 21.3 ± 78.0 m from LOTS baseline to Week 104. The mean change from baseline in percentage of predicted forced vital capacity was 1.3% ± 5.7% from LOTS baseline to Week 78 and 0.8% ± 6.7% from LOTS baseline to Week 104. Treatment-related adverse events were mainly infusion-associated reactions observed in 35% of patients. No deaths or anaphylactic reactions were observed during the extension study.

Conclusions: The LOTS Extension study showed that patients treated with alglucosidase alfa for up to 104 weeks maintained the improved walking distance and stabilization in pulmonary function observed in the first 78 weeks of alglucosidase alfa therapy.

1. Introduction

Pompe disease is a progressive, debilitating, and often fatal neuromuscular disorder resulting from the deficiency of a lysosomal enzyme, acid α-glucosidase. Patients with late-onset Pompe disease present with progressive myopathy, predominantly of the proximal muscles in the pelvic and shoulder girdles, and a variable progression of respiratory involvement [1–4]. Eventually, most patients with late-onset Pompe

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disease become wheelchair-bound, require ventilator support, and ultimately succumb to respiratory failure [1,3,5].

Alglucosidase alfa (Myozyme®/Lumizyme®, Genzyme) is the first approved treatment for Pompe disease; it replaces the deficient acid α-glucosidase enzyme, thereby targeting the underlying cause of the disease. The therapy markedly extended survival and prevented or delayed time to invasive-ventilator dependence as compared to an untreated historical cohort in patients with infantile-onset disease [6].

The Late-Onset Treatment Study (LOTS) was the randomized, double-blind, placebo-controlled, multicenter study that demonstrated the safety and efficacy of alglucosidase alfa in 90 children and adults with late-onset Pompe disease [7]. The major findings of the LOTS study were that alglucosidase alfa treatment improved walking distance and stabilized pulmonary function over the 78-week study period, both of which were statistically significant compared to placebo. Treatment with alglucosidase alfa was well tolerated, with an acceptable risk-benefit profile.

All active and placebo patients who completed LOTS transitioned into an open-label extension study (LOTS Extension) and received treatment for a minimum of 26 weeks (104 weeks cumulatively). The objective of LOTS Extension was to determine the durability of the efficacy and safety of alglucosidase alfa treatment initially observed in LOTS.

2. Material and methods

Patients who completed 78 weeks of either alglucosidase alfa treatment or placebo in LOTS were eligible to continue to receive 20 mg/kg IV infusions of alglucosidase alfa biweekly for up to an additional 26 weeks (to Week 104) (Fig. 1). Patients at the US sites were eligible to continue treatment for another 26 weeks (to Week 130). Patients were included in the study if they were 8 years of age or older, ambulatory, and free of invasive ventilation. The study protocol and amendments were approved by the Investigational Review Boards at individual sites, and safety was periodically reviewed by an independent Data Safety Monitoring Board. Written informed consent was received from the participants. The clinical trial identifier number is NCT00455195.

The primary efficacy assessments were the 6-minute walk test (6MWT), to measure functional endurance, and the percentage of predicted forced vital capacity (FVC) in the upright position, to measure respiratory muscle strength. The secondary efficacy assessments included quantitative muscle testing (QMT), to measure proximal muscle strength in the arms and legs, and maximal inspiratory/expiratory pressures (MIP/MEP) to measure respiratory muscle strength. Adverse events, as well as their severity and relationship to treatment, were recorded. IgG antibody binding to alglucosidase alfa and *in vitro* inhibitory antibody assays were performed. Detailed descriptions of the safety and efficacy evaluations have been reported previously [7].

The long-term efficacy and safety profiles of alglucosidase alfa were assessed based on the cumulative data from both studies for the patients who were randomized to receive alglucosidase alfa in LOTS. Descriptive statistics were used to summarize the change from the onset of alglucosidase alfa treatment at follow-up visits, as well as from the start of the extension study (Week 78) to follow-up visits; 95% confidence intervals (CI) are also presented. For the patients who were randomized to receive alglucosidase alfa in LOTS at first infusion (denoted as "LOTS baseline"), long-term data at Week 78 (beginning of LOTS Extension) and Week 104 (end of LOTS Extension) are presented. The efficacy data (change from baseline to Week 78) reported are slightly different from those reported in the LOTS article because of the different statistical methods used [7]. While the present study uses a simple average of the observed differences from baseline to Week 78, the biostatisticians for LOTS adjusted the mean differences for several baseline variables using an analysis of covariance in order to appropriately compare the treatment effect of alglucosidase alfa to placebo. Additionally, for the patients who crossed over from placebo to active treatment in LOTS Extension, the primary efficacy endpoints after 26 weeks of open-label alglucosidase alfa treatment are reported.

3. Results

At LOTS baseline, 60 patients were randomized to receive alglucosidase alfa (Table 1). These patients were mainly male (57%) and Caucasian (95%), with a mean age of 45 years (range, 16–70 years). At the time of enrollment in LOTS, 38% of patients used a walking device and 33% of patients required respiratory support.

Efficacy results are reported on the 55 out of 60 patients from the alglucosidase alfa arm who completed LOTS and LOTS Extension through Week 104 (Fig. 1). Safety results are provided for all 60 randomized patients for the group that received alglucosidase alfa treatment during LOTS and LOTS Extension, whether or not they completed all study assessments. The median time of exposure from the first infusion at LOTS baseline until study completion was 113 weeks ± 29 weeks.

A crossover group, consisting of 26 patients in the placebo arm of LOTS who completed Week 78, enrolled in LOTS Extension and completed 26 weeks of treatment to Week 104; the results for this crossover

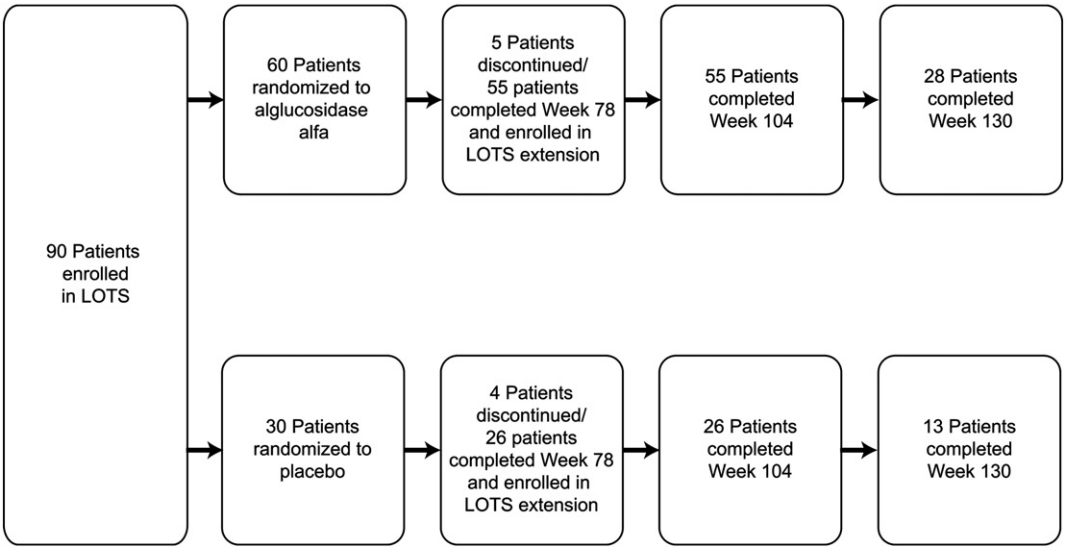

Fig. 1. Patient disposition for the LOTS and LOTS Extension studies. Note: Patients at the US sites were eligible to continue treatment from Week 104 to Week 130.

Table 1
Demographic and LOTS baseline characteristics for patients treated with alglucosidase alfa during the LOTS and LOTS Extension studies.

Demographic/baseline characteristics	Patients treated with alglucosidase alfa
Number enrolled and treated, n (%)	60 (100.0)
Gender	
Male, n (%)	34 (56.7)
Female, n (%)	26 (43.3)
Ethnicity	
Caucasian, n (%)	57 (95.0)
Black, n (%)	0
Hispanic, n (%)	1 (1.7)
Asian, n (%)	1 (1.7)
Other, n (%)	1 (1.7)
Geographic region of patient Enrollment	
United States, n (%)	39 (65.0)
Non-United States, n (%)	21 (35.0)
Weight (kg)	
N	60
Mean (SD)	73.7 (17.42)
Median	74.8
Min., max.	39.2, 118.8
Age at first symptoms (years)	
N	60
Mean (SD)	30.3 (12.29)
Median	33.6
Min., max.	5.3, 58.6
Age at first diagnosis (years)	
N	60
Mean (SD)	36.2 (13.34)
Median	37.5
Min., max.	5.8, 63.7
Use of walking device at LOTS baseline	23 (38.3)
Use of respiratory support at LOTS baseline	20 (33.3)
Age at first infusion of alglucosidase Alfa (years)	
N	60
Mean (SD)	45.3 (12.37)
Median	45.0
Min., max.	15.9, 70.0

group will be discussed separately. In addition, a smaller number of patients from both groups, 28 patients and 13 patients, respectively, continued in the extension study until the Week 130 visit.

3.1. Efficacy results

The benefit of alglucosidase alfa treatment observed at the end of LOTS at Week 78 was in general maintained at Week 104. Efficacy results from LOTS baseline to Week 78, from LOTS baseline to Week 104, and from Week 78 to Week 104 are presented in Table 2.

LOTS baseline 6MWT for the alglucosidase alfa arm was 332.2 ± 126.7 m. The mean (±SD) increase in distance walked measured 28.2 ± 66.5 m from LOTS baseline to Week 78 and 21.3 ± 78.0 m from LOTS baseline to Week 104 (95% CI = −0.2, 42.8; Fig. 2). LOTS baseline percentage of predicted FVC in the upright position for the alglucosidase alfa treatment arm was 55.4% ± 14.4%. The mean change in percentage of predicted FVC was 1.3% ± 5.7% from LOTS baseline to Week 78 and 0.8% ± 6.7% from LOTS baseline to Week 104 (95% CI = −1.1, 2.6; Fig. 3).

Improvements in the percentage of predicted QMT Leg score, percentage of predicted QMT Arm score, MIP, and MEP observed during the LOTS study were maintained during the extension study (Table 2).

Data at Week 130 were available from a subset of patients (n = 27), and the results were consistent with the results observed at Week 104. LOTS baseline 6MWT for the alglucosidase alfa arm was 365.0 ± 94.1 m. The mean (±SD) increase in distance walked measured 22.9 ± 50.0 m from LOTS baseline to Week 130 (95% CI = 2.3, 43.5). LOTS baseline percentage of predicted FVC in the upright position for the alglucosidase alfa treatment arm was 54.0% ± 15.7%. The mean change in percentage of predicted FVC was 0.2% ± 6.9% from LOTS baseline to Week 130 (95% CI = −2.6, 2.9).

For the placebo-to-active treatment crossover group, the mean distance walked in 6MWT prior to treatment initiation at LOTS Extension baseline was 312.7 ± 147.2 m. The mean increase in distance walked measured 4.2 ± 23.8 m after 26 weeks of treatment (95% CI = −6.1, 14.5; n = 23). LOTS Extension baseline percentage of predicted FVC in the upright position for the placebo arm was 51.1% ± 15.8%. The mean change in percentage of predicted FVC was −1.0% ± 5.4% after 26 weeks of treatment (95% CI = −3.4, 1.4).

3.2. Safety results

The most frequently reported AEs by percentage of patients affected were falls (65%), headache (52%), and nasopharyngitis (48%); every patient reported at least one AE. Thirty-five percent of patients (21 out of 60 patients) had IARs, which were generally mild to moderate in severity. The most frequent IARs occurring in at least 10% of patients were nausea, headache, and urticaria. Twenty-five percent of the patients (15 out of 60 patients) reported SAEs; the majority was unrelated to study drug. During LOTS, patients experienced related SAEs, including 3 patients who experienced anaphylactic reactions; 2 of these reactions were IgE-mediated and both were successfully rechallenged with alglucosidase alfa using desensitization regimens under close clinical supervision [8]. During LOTS Extension, there were no anaphylactic reactions and no deaths. In the placebo-to-active crossover group, no new safety concerns were observed.

All patients who received alglucosidase alfa for the entire study, and for whom post-exposure IgG antibody data were available (59 out of 60 patients), tested positive for IgG antibody titers to alglucosidase alfa by Week 12; the median time to seroconversion was 4 weeks (range, 4–12 weeks). Median peak IgG titer was 6400 (range, 200–819,200), and median time to peak titer was 20 weeks from the time of seroconversion. The median last titer was 1600 (range, 0–409,600). Sixty-one percent of patients showed trends toward decreasing titers (two dilutions less than the peak titer) at last assessment. There was no consistent relationship between time to seroconversion and onset of IARs, or between higher IgG titers and IAR occurrence. Eighteen patients developed inhibitory antibodies by *in vitro* enzyme uptake assay; however, only 6 patients were positive at the last 2 time points.

4. Discussion

The LOTS Extension study provides evidence that the positive effects of alglucosidase alfa treatment observed at 78 weeks of therapy are maintained over 104 weeks of therapy in patients with late-onset Pompe disease. This is consistent with the evidence of 1-year and 3-year effectiveness data reported recently [9,10]. In LOTS, in the total group of 90 patients (60 received alglucosidase alfa and 30 received placebo), the estimated mean changes from baseline to Week 78 in the primary endpoints significantly favored alglucosidase alfa compared to placebo. The difference between the treatment group and the placebo group was 28.1 ± 13.1 m for the 6MWT and 3.4% ± 1.2% in predicted percentage of FVC; p = 0.03 and p = 0.006, respectively.[7] For the 60 patients receiving alglucosidase alfa from LOTS baseline to Week 78, as reported in LOTS Extension, there was an increase in the 6MWT of 28.2 ± 66.5 m (25.13 [95% CI: 10.07, 40.19], as reported in LOTS) and in predicted FVC of 1.3% ± 5.7% (1.20% [95% CI: −0.16, 2.57], as reported in LOTS). These results obtained at 78 weeks compare well with the results obtained after 104 weeks for the patients who continued to be treated with alglucosidase alfa. These findings indicate that the average patient treated with alglucosidase alfa for up to 104 weeks maintained the improved walking distance and stabilization in pulmonary function observed in the first 78 weeks of alglucosidase alfa therapy.

While the onset and progression of late-onset Pompe disease is heterogeneous, patients entering the study had significant

Table 2
Results of analyses for changes from LOTS baseline to Week 78, LOTS baseline to Week 104, and LOTS Extension baseline (Week 78) to Week 104 for efficacy endpoints.

End point	N	Observed, mean ± SD	N	Change from LOTS baseline to Week 78, mean ± SD[a]	N	Change from LOTS baseline to Week 104, mean ± SD (95% confidence interval)	N	Change from LOTS Extension baseline (Week 78) to Week 104, mean ± SD (95% confidence interval)
Distance walked on a 6-minute walk test, m								
LOTS baseline	60	332.2 ± 126.7	–	–	–	–	–	–
LOTS Extension baseline (Week 78)	54[b]	362.7 ± 145.3	54	28.2 ± 66.5	–	–	–	–
LOTS Extension Week 104	53[b]	358.3 ± 150.1	–	–	53	21.3 ± 78.0 (−0.2, 42.8)	52	−6.9 ± 32.8 (−16.1, 2.2)
Forced vital capacity (upright), % of predicted								
LOTS baseline	60	55.4 ± 14.4	–	–	–	–	–	–
LOTS Extension baseline (Week 78)	54[a]	56.7 ± 16.4	54	1.3 ± 5.7	–	–	–	–
LOTS Extension Week 104	53[a]	57.2 ± 16.2	–	–	53	0.8 ± 6.7 (−1.1, 2.6)	52	−0.7 ± 3.7 (−1.7, 0.4)
QMT-Leg score, % of predicted								
LOTS baseline, mean (SD)	60	37.7 ± 18.9	–	–	–	–	–	–
LOTS Extension baseline (Week 78)	54[b]	39.2 ± 21.5	54	0.9 ± 10.1	–	–	–	–
LOTS Extension Week 104	53[b]	40.7 ± 23	–	–	53	2.1 ± 11.1 (−0.9, 5.2)	52	1.1 ± 4.8 (−0.2, 2.5)
QMT-Arm score, % of predicted								
LOTS baseline	60	55.9 ± 20.4	–	–	–	–	–	–
LOTS Extension baseline (Week 78)	53[c]	61.6 ± 20.7	53	4.9 ± 11.9	–	–	–	–
LOTS Extension Week 104	52[c]	61.1 ± 21.4	–	–	52	4.3 ± 14.2 (0.3, 8.2)	51	−0.5 ± 8.4 (−2.8, 1.9)
MIP, % of predicted								
LOTS baseline	60	40 ± 19.7	–	–	–	–	–	–
LOTS Extension baseline (Week 78)	54[b]	43.8 ± 21.8	54	3.6 ± 10.3	–	–	–	–
LOTS Extension Week 104	53[b]	45.8 ± 24	–	–	53	5.1 ± 10.7 (2.2, 8.1)	52	1.4 ± 7 (−0.6, 3.3)
MEP, % of predicted								
LOTS baseline	60	32 ± 12.1	–	–	–	–	–	–
LOTS Extension baseline (Week 78)	54[b]	35.1 ± 13.5	54	3.2 ± 8.3	–	–	–	–
LOTS Extension Week 104	53[b]	36.2 ± 13.7	–	–	53	4.0 ± 7.4 (2.0, 6.1)	52	1.0 ± 5.1 (−0.4, 2.4)

CI, confidence interval; LOTS, Late-Onset Treatment Study; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; QMT, quantitative muscle testing; SD, standard deviation.

[a] The observed mean values in this column differ to a small extent from those in Table 2 of van der Ploeg (2010, NEJM), which are adjusted estimates from an analysis of covariance model.

[b] A total of 55 alglucosidase alfa-treated patients enrolled in the LOTS Extension study; however, only 54 had baseline assessments and 53 had Week 104 data available.

[c] A total of 55 alglucosidase alfa-treated patients enrolled in the LOTS Extension study; however, only 53 had baseline assessments and 52 had Week 104 data available.

muscular and respiratory functional loss compared to the general population. The mean 6MWT distance at LOTS baseline was 332.2 m compared with a mean 6MWT distance of 630 m observed in healthy older adults [11]. Similarly, the mean percentage of predicted FVC at baseline was 55.4%, well below what is considered normal (80% to 120%). Therefore, stabilization of motor and respiratory function is considered an important therapeutic goal to prevent further functional loss in this compromised patient population.

The positive results on FVC of 1.3% and 0.8% at 78 weeks and 104 weeks, respectively, contrast with the 2.2% decline in predicted FVC observed for the placebo arm over the 78-week period in LOTS [7]. Decline in percentage of predicted FVC in untreated late-onset patients was also demonstrated in a 1-year prospective study showing a decline in FVC of 4.6% [4]. The rate of FVC deterioration in a 16-year retrospective study of 13 patients was shown to be on average 1.6% per year (range, 0.3% to −7.0%) [5]. The data stress that, if left untreated, patients with Pompe disease deteriorate. In a cross-sectional study in 255 patients with late-onset Pompe disease, Hagemans et al. found that 5 to 10 years after diagnosis, approximately 30% of patients required a wheelchair and approximately 40% of patients required a ventilator, while after 10 to 15 years, approximately 50% of patients used a wheelchair and/or ventilator [12]. At the start of our study, the median disease duration of patients receiving alglucosidase alfa was 9 years. At that time, 38% of patients needed walking devices and 33% of patients needed noninvasive ventilatory support. Longer follow-up is required to show whether timely treatment with alglucosidase alfa has the potential to prevent the need of supportive measures.

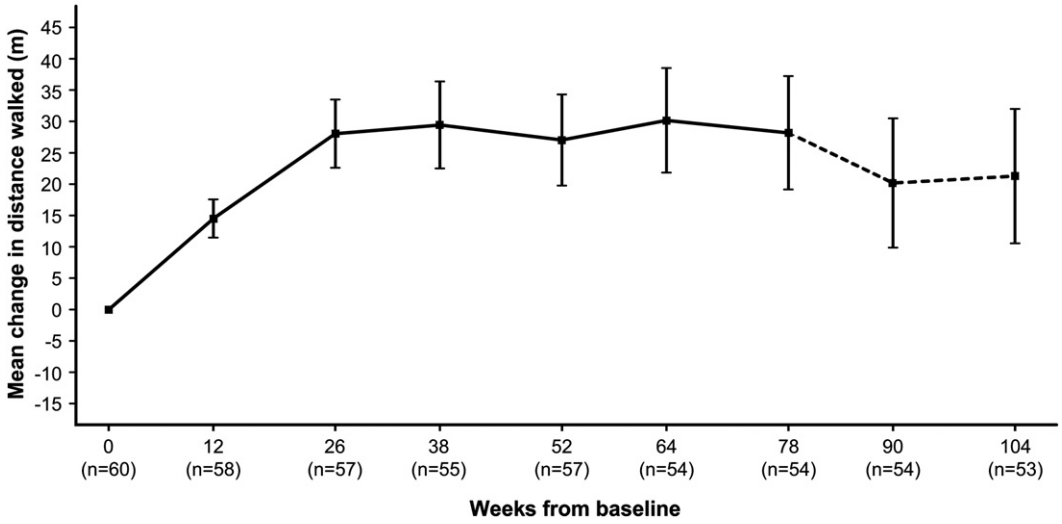

Fig. 2. Mean change from baseline in distance walked during a 6-minute walk test.

Additional efficacy measurements in LOTS Extension corroborated the efficacy results observed with 6MWT and FVC (Table 2). The QMT Leg scores suggest durability of the stabilizing effect of alglucosidase alfa on the continuing decline in muscle strength in the lower extremities, while the QMT Arm scores point to maintenance of a general positive effect on the upper extremities. Similar to the mean change for the percentage of predicted FVC in the upright position, the MIP and MEP changes were maintained above the baseline scores over the course of treatment. This improvement appears to be achieved primarily through stabilization of existing respiratory function, preventing or delaying the progressive decline that is commonly seen in untreated patients with late-onset Pompe disease.

When the patients in the placebo arm of LOTS were switched to alglucosidase alfa in LOTS Extension, 6MWT and FVC showed no further deterioration but did not show improvement after 6 months of active treatment. We cannot fully explain these results. The extension study was not designed to evaluate the treatment effect of alglucosidase alfa in the small number of patients who crossed over from the placebo group to active therapy for a relatively short period of time. In particular, the absence of a control group makes these findings difficult to interpret. For example, the 6MWT is a motivation-driven test. Patients may have been discouraged upon learning that their treatment assignment was placebo, with the consequence of delayed treatment for 18 months, negatively influencing their performance on the 6MWT. Finally, it is unknown whether the delay in initiating alglucosidase alfa therapy in the LOTS placebo patients diminished their subsequent response upon crossover to active therapy given the incremental progression of their untreated disease.

Long-term exposure to alglucosidase alfa was well tolerated. Treatment-related AEs were mainly IARs, which were reported in 35% of patients, and there were no reports of anaphylaxis or death in LOTS Extension. All patients who received alglucosidase alfa for the entire study tested positive for IgG antibodies to alglucosidase alfa by Week 12; there was no clear effect of IgG antibodies or inhibitory antibodies on safety or efficacy endpoints. Additional studies are needed to better understand the impact of antibodies on the safety and efficacy in alglucosidase alfa in patients with late-onset Pompe disease.

A limitation of LOTS Extension was that the study period was only an additional 6 to 12 months following the completion of LOTS. Conclusions regarding long-term effectiveness of alglucosidase alfa are therefore limited. Continuation of data gathering (via patient registries) is warranted (and may help to substantiate these findings over longer periods of time). In addition, while stabilization of the motor and respiratory findings observed in LOTS was maintained during the extension period, no further improvement in these clinical measures were noted. It is possible that muscle pathology (*i.e.*, degree of fibrosis, irregularities due to abnormal autophagy) in patients with Pompe disease may reach a state where reversibility

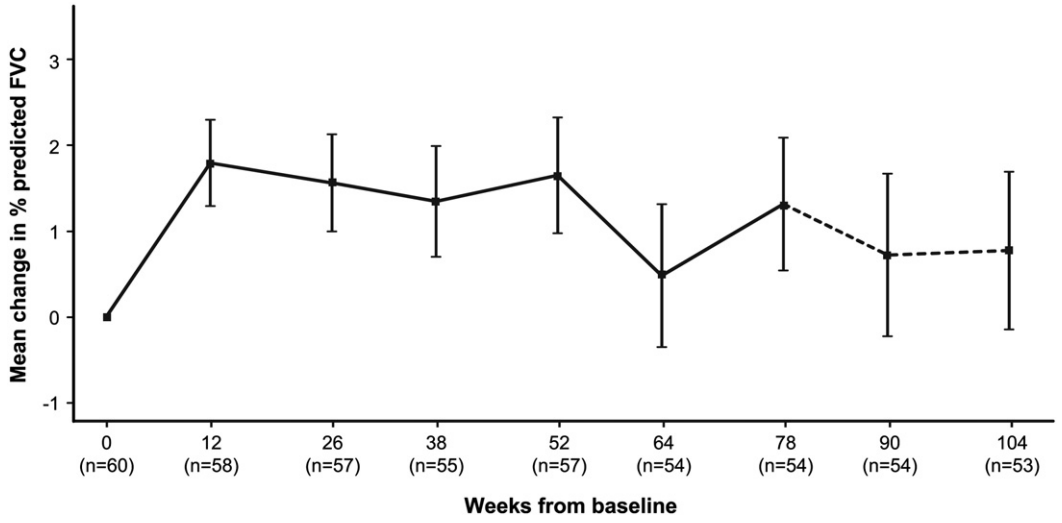

Fig. 3. Mean change from baseline in percentage of predicted forced vital capacity.

and subsequent improvement in function is not possible, despite continued therapy.

For a relentlessly progressive disease such as Pompe, maintenance of the initial treatment effect noted in LOTS may allow patients to retain ambulatory and respiratory independence and thereby modify a disease course that can lead to significant disability, respiratory failure, and early death. LOTS Extension showed that patients with late-onset Pompe disease continue to benefit from treatment with alglucosidase alfa with no increased risk. We await reports of additional experience in patients treated with alglucosidase alfa from the international Pompe Registry and other sources to help more fully understand the long-term clinical implications of these encouraging results.

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Appendix A

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