ORIGINAL ARTICLE

# A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease

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## ABSTRACT

### BACKGROUND

Pompe's disease is a metabolic myopathy caused by a deficiency of acid alpha glucosidase (GAA), an enzyme that degrades lysosomal glycogen. Late-onset Pompe's disease is characterized by progressive muscle weakness and loss of respiratory function, leading to early death. We conducted a randomized, placebo-controlled trial of alglucosidase alfa, a recombinant human GAA, for the treatment of late-onset Pompe's disease.

### METHODS

Ninety patients who were 8 years of age or older, ambulatory, and free of invasive ventilation were randomly assigned to receive biweekly intravenous alglucosidase alfa (20 mg per kilogram of body weight) or placebo for 78 weeks at eight centers in the United States and Europe. The two primary end points were distance walked during a 6-minute walk test and percentage of predicted forced vital capacity (FVC).

### RESULTS

At 78 weeks, the estimated mean changes from baseline in the primary end points favored alglucosidase alfa (an increase of 28.1±13.1 m on the 6-minute walk test and an absolute increase of 3.4±1.2 percentage points in FVC; $P=0.03$ and $P=0.006$, respectively). Similar proportions of patients in the two groups had adverse events, serious adverse events, and infusion-associated reactions; events that occurred only in patients who received the active study drug included anaphylactic reactions and infusion-associated reactions of urticaria, flushing, hyperhidrosis, chest discomfort, vomiting, and increased blood pressure (each of which occurred in 5 to 8% of the patients).

### CONCLUSIONS

In this study population, treatment with alglucosidase alfa was associated with improved walking distance and stabilization of pulmonary function over an 18-month period. (ClinicalTrials.gov number, NCT00158600.)

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Pompe's disease is a rare, autosomal recessive, progressive neuromuscular disease caused by a deficiency of acid α-glucosidase (GAA), which degrades lysosomal glycogen. In patients with the classic infantile form, the deposition of glycogen in the heart, skeletal, and respiratory muscles causes severe cardiomyopathy, hypotonia, and respiratory failure, typically leading to death within the first year of life.[1-5] Children and adults, in contrast, have variable rates of disease progression. Glycogen deposition is confined mainly to skeletal and respiratory muscles, causing progressive limb-girdle myopathy and respiratory insufficiency.[1,5-9] Respiratory failure is a major cause of death.[7,10,11]

No disease-specific treatment was available for Pompe's disease until 2006, when enzyme-replacement therapy with alglucosidase alfa (Myozyme, Genzyme) was approved for all patients with Pompe's disease in the United States and the European Union, on the basis of open-label studies of infantile-onset Pompe's disease.[12] Trials involving infants showed improvements in survival and motor outcomes as compared with untreated historical controls.[12-16] Preliminary studies showed positive effects in children and adults but were small and not controlled.[10,17-19] We report the results of a randomized, controlled trial of alglucosidase alfa in late-onset Pompe's disease.

## METHODS

### STUDY DESIGN

The protocol was designed by Genzyme, with input from the authors and an independent statistical center (Cytel). The protocol and all amendments were approved by local review boards, ethics committees, and health authorities. Genzyme employees analyzed the data in accordance with the statistical plan and with additional suggestions from the investigators. Study conduct was monitored by an independent data and safety monitoring board. Primary efficacy analyses were ratified by the independent statistical center. All the authors collected the data, had access to the data, and decided to submit the manuscript for publication. The first author and the coauthors wrote the manuscript, with the assistance of medical writers at Genzyme, and the first author determined the final content of the manuscript. All authors vouch for the completeness and veracity of the data and analyses.

This was a randomized, double-blind, placebo-controlled, multicenter study of the safety and efficacy of alglucosidase alfa in 90 patients with late-onset Pompe's disease. The study began in early September 2005 and was completed at the end of September 2007. Patients were screened and, after providing written informed consent (by patients 18 years of age or older and by guardians for younger patients), underwent a full baseline evaluation. Those who qualified were randomly assigned in a ratio of 2:1 to receive biweekly infusions of alglucosidase alfa (20 mg per kilogram of body weight) or placebo. The Pocock and Simon minimization algorithm[20] was used to balance the baseline distance walked on a 6-minute walk test (<300 or ≥300 m) and the baseline percentage of the predicted forced vital capacity (FVC) in an upright position (<55 or ≥55%) between study groups at each site.

### PATIENTS

All eligible patients had a confirmed diagnosis of Pompe's disease (GAA deficiency and two GAA gene mutations); were 8 years of age or older; were able to walk 40 m on the 6-minute walk test (with assistive devices permitted); had a percentage of the predicted FVC within the range of 30% to less than 80% in the upright position, with a postural drop in FVC (in liters) of 10% or more (from upright to supine); and had evidence of muscle weakness in the lower extremities, defined as bilateral knee extension less than 80% of predicted performance, as measured by quantitative muscle testing (QMT). Patients were excluded if they required any invasive ventilation or if they required noninvasive ventilation while awake and upright (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

### ASSESSMENTS OF CLINICAL EFFICACY

Coprimary efficacy end points were meters walked on the 6-minute walk test and percentage of the predicted FVC in the upright position. Secondary and tertiary efficacy end points included changes in the percentage of the predicted QMT leg score and QMT arm score, maximum inspiratory pressure, and maximum expiratory pressure. Changes in walking distance on the 6-minute walk test were evaluated according to American Thoracic Society guidelines.[21]

Spirometric and manometric assessments of pulmonary function and respiratory muscle

strength were performed according to American Thoracic Society and European Respiratory Society guidelines.[22-24]

The quantitative measurement system of the Cooperative International Neuromuscular Research Group was used to perform QMT to assess muscle force production during maximal voluntary isometric contraction of bilateral shoulder and hip adductors, elbow and knee flexors and extensors, and grip.[25,26] Data were reported as composite QMT leg and arm scores (i.e., the average of the percentage of predicted scores for bilateral knee flexors and extensors and bilateral elbow flexors and extensors).[25]

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was administered to patients 14 years of age or older. The scores for the Physical Component Summary are reported.[27]

### ANTIBODY MONITORING

Serum samples were obtained every 4 weeks for the first 52 weeks and again at weeks 64 and 78. IgG antibodies to alglucosidase alfa were assessed by means of the enzyme-linked immunosorbent assay (ELISA), and results were confirmed on radioimmunoprecipitation, as described previously.[28] Patients who tested positive for IgG antibodies were evaluated for antibodies that inhibit enzyme activity or uptake into cells.[29] Two-fold dilution series of serum samples were preincubated with a fixed amount of enzyme. These samples were then analyzed to determine whether the antibodies interfered with the enzyme–substrate interaction. Similarly diluted samples were also preincubated with fluorescence-labeled enzyme and analyzed by means of flow cytometry to determine their ability to interfere with enzyme internalization into fibroblasts (an easily grown cell type that expresses mannose-6-phosphate receptors, which mediate enzyme uptake). The last serum dilution that inhibited enzyme activity relative to the established assay cutoff point was recorded as the titer.

### SAFETY ASSESSMENTS

All adverse events, serious adverse events, and infusion-associated reactions were recorded. The site investigator and the study sponsor determined whether an adverse event was related to the study drug.

### STATISTICAL ANALYSIS

We calculated that a minimum sample of 63 patients would be required to detect a treatment difference of 0.75 SD with 80% power (on the basis of a two-sample t-test with a significance level of 5% and a 2:1 ratio for randomization). Enrollment of at least 72 patients was planned, assuming a 10 to 15% dropout rate. The planned model for the primary efficacy analysis was a linear mixed-effects model with random intercepts and slopes. The estimated treatment effect was the absolute difference in the linear slopes of change between the alglucosidase alfa and placebo groups.

An adaptive design was implemented (under a protocol amendment) in which the initial 52-week treatment period could be extended by 3 or 6 months on the basis of an interim estimate of the standard error of the treatment effect on the 6-minute walk test; the estimate was used to determine the length of follow-up required to ensure adequate power for assessment of this end point. Because only the interim estimate of the standard error was used, no adjustment of the type I error rate was needed (see the Supplementary Appendix).[30] An interim analysis of the data on the 6-minute walk test was performed by an independent statistical center after all patients had completed week 38. On the basis of this interim analysis, the data and safety monitoring board recommended that the study be extended to 78 weeks; there were no interruptions in the study regimens during the 78-week trial. Neither the study sponsor nor the investigators had access to the interim results until the conclusion of the study.

The efficacy analysis was performed for the intention-to-treat population, defined as all patients randomly assigned to either alglucosidase alfa or placebo. A fixed-sequence testing procedure was used to account for multiple testing and to preserve the overall significance level of 5% for both coprimary end points. Formal testing for a treatment effect on FVC in the upright position was performed only after the significance of the treatment effect on the 6-minute walk test had been shown by means of a two-sided test. Prespecified testing of the assumptions for the linear mixed-effects model indicated that use of this model was not warranted; therefore, the pri-

mary efficacy analysis was an analysis of covariance (ANCOVA) for the change from baseline to week 78. The last-observation-carried-forward method was used for the ANCOVA model, with adjustment for randomization strata and baseline scores. Treatment effects were also estimated in predefined subgroups, and a post hoc sensitivity analysis with the use of mixed models for repeated measures and nonparametric tests was conducted to assess the robustness of the efficacy findings (see the Supplementary Appendix). Secondary and tertiary end points were analyzed by means of ANCOVA. The reported P values are two-sided and were not adjusted for multiple testing.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

A total of 90 patients between 10 and 70 years of age were randomly assigned to either alglucosidase alfa (60 patients) or placebo (30 patients). Of this group, 81 completed the study; 5 in the alglucosidase alfa group and 4 in the placebo group dropped out (see Fig. 1 in the Supplementary Appendix). The demographic and baseline characteristics of the patients are summarized in Table 1. In the alglucosidase alfa group, there were more men, the patients were slightly older, and fewer patients used a walking device at baseline. The only significant difference between the groups in disease-related characteristics was age at symptom onset (P=0.02). In both groups, the mean SF-36 Physical Component Summary scores were more than 1.5 SD below the norm for the U.S. general population (50±10), indicating that baseline physical health status was substantially diminished.

### EFFICACY

By 78 weeks, treatment with alglucosidase alfa had significantly increased both the distance walked on the 6-minute walk test and the percentage of the predicted FVC (Table 2 and Fig. 1). The alglucosidase alfa group had a mean increase of 25.1 m on the 6-minute walk test (the average baseline was 332.2 m), whereas the placebo group had a decrease of 3.0 m (the average baseline was 317.9 m), for an estimated differential treatment effect of 28.1 m (P=0.03). The estimated change in FVC, expressed as a percentage of each patient's predicted value, was an increase of 1.2 percentage points for the patients who received alglucosidase alfa and a decrease of 2.2 percentage points for the patients who received placebo, for an estimated treatment effect of 3.4 percentage points (P=0.006).

For each subgroup evaluated, the patients who received alglucosidase alfa had numerically better results (Fig. 2 in the Supplementary Appendix). Subgroup analyses showed a greater difference between the study groups among patients with better baseline status — that is, patients whose baseline distance on the 6-minute walk test was 300 m or greater and whose baseline FVC was 55% or more of the predicted value. In addition, sensitivity analyses with the use of alternative statistical methods showed that the results were consistent and robust across analytic methods (Table 1 in the Supplementary Appendix).

The pattern of response with respect to QMT leg and arm scores and the percentage of the predicted maximum expiratory and inspiratory pressures support the findings for the two coprimary end points, although only the change in the percentage of the predicted maximum expiratory pressure differed significantly between the groups (Table 2 and Fig. 2).

### SAFETY

Patients in the two groups had similar frequencies of adverse events, serious adverse events, treatment-related adverse events, and infusion-associated reactions. Most adverse events were mild or moderate in severity and were not considered to be related to the study drug (Table 3, and Table 2 in the Supplementary Appendix). The most frequently reported events (falls, nasopharyngitis, and headache) were similar between groups. Infusion-associated reactions occurred in 28% of alglucosidase alfa recipients and 23% of placebo recipients. Most of the reactions were not serious or were mild to moderate in severity and resolved with no need to withdraw the study treatment (Table 3 in the Supplementary Appendix).

Anaphylactic, allergic, and infusion-associated reactions that involved urticaria, flushing, hyperhidrosis, chest discomfort, vomiting, and increased blood pressure occurred in 5 to 8% of the patients treated with alglucosidase alfa but were not reported in the placebo group. Of the

**Table 1. Demographic and Baseline Characteristics of the Study Population.***

| Characteristic | Alglucosidase Alfa Group (N=60) | Placebo Group (N=30) | P Value |
|---|---|---|---|
| Age at first infusion — yr | | | |
| Mean | 45.3±12.4 | 42.6±11.6 | 0.32 |
| Range | 15.9–70.0 | 10.1–68.4 | |
| Sex — no. (%) | | | |
| Male | 34 (57) | 11 (37) | 0.12 |
| Female | 26 (43) | 19 (63) | |
| Race — no. (%)† | | | |
| White | 57 (95) | 27 (90) | 0.40 |
| Other | 3 (5) | 3 (10) | |
| Age at onset of symptoms — yr | | | |
| Mean | 30.3±12.3 | 23.9±11.0 | 0.02 |
| Range | 5.3–58.6 | 2.7–42.6 | |
| Duration of disease — yr | | | |
| Mean | 9.0±6.3 | 10.1±8.4 | 0.48 |
| Range | 0.3–24.8 | 0.5–31.3 | |
| Normal GAA activity — % | | | |
| Mean | 10.8±8.2 | 10.1±7.8 | 0.71 |
| Range | 0–47.4 | 0–32.2 | |
| Use of walking device — no. (%) | 23 (38) | 16 (53) | 0.19 |
| Use of ventilatory support — no. (%) | 20 (33) | 11 (37) | 0.82 |
| Score on SF-36 Physical Component Summary | 34.33±8.93 | 34.91±7.26 | 0.23 |
| Performance on 6-min walk test | | | |
| Distance walked — m | | | |
| Mean | 332.2±126.7 | 317.9±132.3 | 0.62 |
| Range | 77.0–626.0 | 41.0–608.0 | |
| % of predicted value | | | |
| Mean | 52.5±19.0 | 50.3±20.5 | 0.61 |
| Range | 9.8–82.2 | 6.2–99.0 | |
| FVC — % of predicted value | | | |
| Mean | 55.4±14.4 | 53.0±15.7 | 0.47 |
| Range | 31.0–78.0 | 30.0–78.0 | |

* Plus–minus values are means ±SD. Fisher's exact test was used for comparisons of binary variables, and Student's t-test for comparisons of continuous variables. FVC denotes forced vital capacity, GAA acid $\alpha$ glucosidase, and SF-36 Medical Outcomes Study 36-Item Short-Form Health Survey.
† Race was reported by the patient.

60 patients in the alglucosidase alfa group, 3 (5%) had anaphylactic reactions, 2 of whom tested positive for IgE antibodies to alglucosidase alfa; 2 had respiratory and cutaneous reactions, and the third had severe tongue edema. Two of these three patients withdrew from the study. One patient in the placebo group withdrew owing to headaches. During the study, one patient in the alglucosidase alfa group who was receiving clinical care for two broad-based basilar-artery aneurysms died from brain-stem ischemia due to basilar-artery thrombosis.

**Table 2. Results of Analysis of Covariance for Changes from Baseline to Week 78 for Primary and Secondary End Points.***

| End Point | Alglucosidase Alfa Group (N=60) | Placebo Group (N=30) | Difference between Groups | P Value |
|---|---|---|---|---|
| Distance walked on 6-min walk test — m | | | | |
| Baseline | 332.2±126.7 | 317.9±132.3 | | |
| Week 78 | 357.9±141.3 | 313.1±144.7 | | |
| Change (95% CI) | 25.13 (10.07 to 40.19) | −2.99 (−24.16 to 18.18) | 28.12 (2.07 to 54.17) | 0.03 |
| Forced vital capacity — % of predicted | | | | |
| Baseline | 55.4±14.4 | 53.0±15.7 | | |
| Week 78 | 56.7±16.3 | 50.7±14.9 | | |
| Change (95% CI) | 1.20 (−0.16 to 2.57) | −2.20 (−4.12 to −0.28) | 3.40 (1.03 to 5.77) | 0.006 |
| Quantitative muscle testing, leg — % of predicted | | | | |
| Baseline | 37.7±18.9 | 32.5±18.2 | | |
| Week 78 | 39.1±21.8 | 30.4±20.5 | | |
| Change (95% CI) | 1.18 (−1.07 to 3.42) | −2.00 (−5.16 to 1.17) | 3.18 (−0.73 to 7.08) | 0.11 |
| Quantitative muscle testing, arm — % of predicted | | | | |
| Baseline | 55.9±20.4 | 56.9±18.2 | | |
| Week 78 | 60.9±21.7 | 58.3±20.9 | | |
| Change (95% CI) | 5.05 (1.91 to 8.18) | 1.47 (−2.92 to 5.87) | 3.57 (−1.83 to 8.97) | 0.19 |
| Maximum inspiratory pressure — % of predicted | | | | |
| Baseline | 40.0±19.7 | 42.6±21.0 | | |
| Week 78 | 43.7±21.0 | 41.7±19.3 | | |
| Change (95% CI) | 3.48 (0.91 to 6.04) | −0.35 (−3.95 to 3.25) | 3.83 (−0.60 to 8.26) | 0.09 |
| Maximum expiratory pressure — % of predicted | | | | |
| Baseline | 32.0±12.1 | 30.8±12.0 | | |
| Week 78 | 35.1±13.3 | 30.5±13.1 | | |
| Change (95% CI) | 3.24 (1.19 to 5.29) | −0.56 (−3.43 to 2.31) | 3.80 (0.27 to 7.33) | 0.04 |
| Score on SF-36 Physical Component Summary† | | | | |
| Baseline | 34.3±8.9 | 34.9±7.3 | | |
| Week 78 | 35.1±9.8 | 36.5±9.6 | | |
| Change (95% CI) | 0.80 (−1.22 to 2.82) | 1.16 (−1.64 to 3.97) | 0.37 (−3.83 to 3.09) | 0.83 |

* Plus–minus values are means ±SD. CI denotes confidence interval.
† The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) consists of an interview and self-administered questionnaire designed to assess generic health-related quality of life in healthy and ill adult populations.

Anti–alglucosidase alfa IgG antibodies developed in all 59 patients in the treatment group who underwent at least one post-treatment assessment, with a median time to seroconversion of 4 weeks (range, 3.6 to 12). After seroconversion, the median time to the peak titer was 12 weeks; the median peak titer was 6400, and the median final titer (last sample or sample at week 78) was 1600. The geometric mean titer of anti–alglucosidase alfa IgG antibodies on ELISA in-

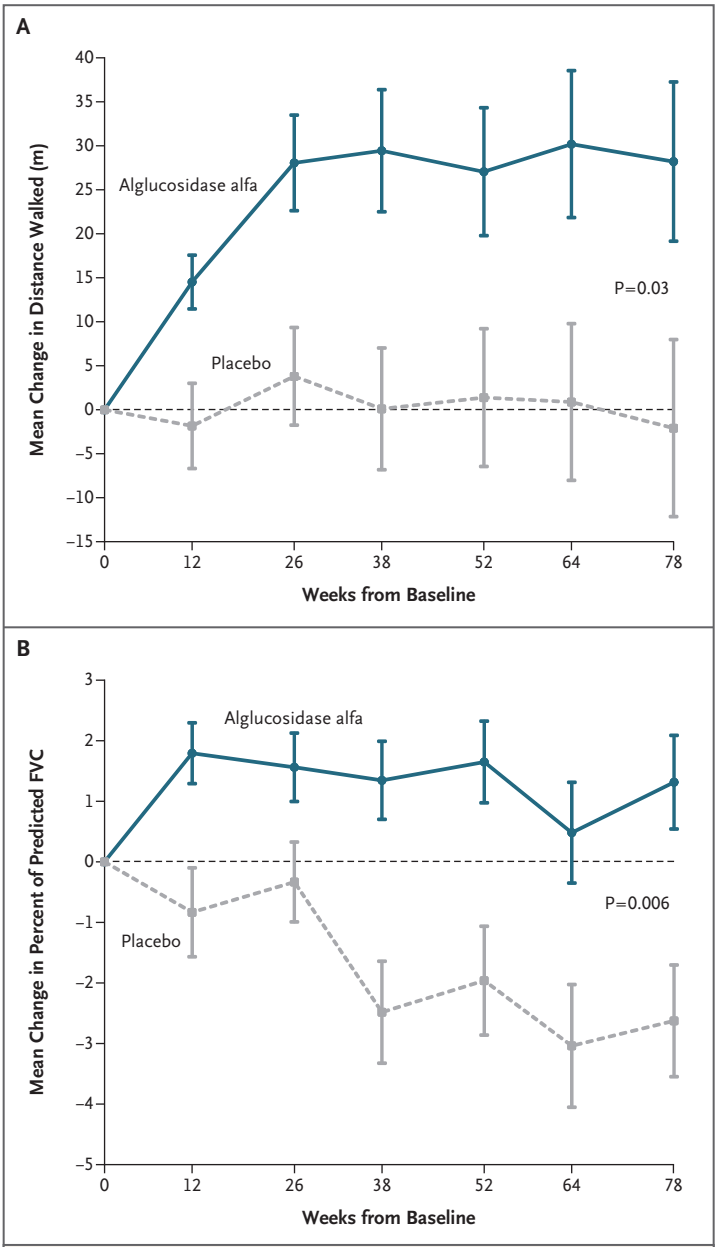


**Figure 1. Changes from Baseline in Distance Walked and in Forced Vital Capacity, According to Study Group.**

The graphs show the changes from baseline to week 78 for the two study groups. On the 6-minute walk test (Panel A), the alglucosidase alfa group had an increase of 25 m, whereas the placebo group had a decrease of 3 m — a difference of 28 m. The percentage of predicted forced vital capacity (FVC) (Panel B) increased by 1.2% in the alglucosidase alfa group but decreased by 2.2% in the placebo group — a difference of 3.4%. These values represent estimates of the mean on analysis of covariance.

creased from baseline through week 44 (2925) and declined slightly through week 78 (1607) (Fig. 3 in the Supplementary Appendix). In 36 of 59 patients (61%) with one or more post-treatment assessments, there was a trend toward decreasing titers by a factor of two or more, whereas titers in the remaining patients plateaued. No consistent association was found between the serum IgG antibody titer and the coprimary efficacy end points or the incidence of adverse events, serious adverse events, and infusion-associated reactions (Tables 4 and 5 in the Supplementary Appendix).

No patients tested positive for inhibition of enzyme activity. Of the 59 patients who were positive for anti–alglucosidase alfa IgG antibodies, 18 (31%) tested positive for inhibition of enzyme uptake. The mean time to the first detection of inhibitory antibodies was 36 weeks after the first infusion.

## DISCUSSION

In this randomized, controlled trial of alglucosidase alfa in patients with late-onset Pompe's disease, significant differences were observed at 78 weeks between the alglucosidase alfa and placebo groups in the distance walked on the 6-minute walk test and in the percentage of the predicted FVC. Alglucosidase alfa treatment was associated with improvements in walking distance and stabilization of pulmonary function; therefore, the coprimary end points of the study were met. Treatment effects were supported by the consistently favorable pattern of response in proximal and respiratory muscle strength among the patients who received alglucosidase alfa. Of these secondary and tertiary end points, the percentage of predicted maximum expiratory pressure (a surrogate marker of expiratory muscle strength) differed significantly between the study groups. These results indicate that alglucosidase alfa has a positive effect on the complex process that leads to impaired ambulation and respiratory failure in late-onset Pompe's disease. Whether alglucosidase alfa exerts a differential effect on the various respiratory muscles (diaphragm or intercostal muscles) requires further investigation.

Natural history studies of late-onset Pompe's disease indicate that it is defined by progressive deterioration in proximal arm, leg, and respiratory muscle strength and function.[5-7,9,31-33] Two recent natural history studies showed mean annual declines of 4.6% and 1.7% in the percentage of predicted FVC, measured in the upright posi-

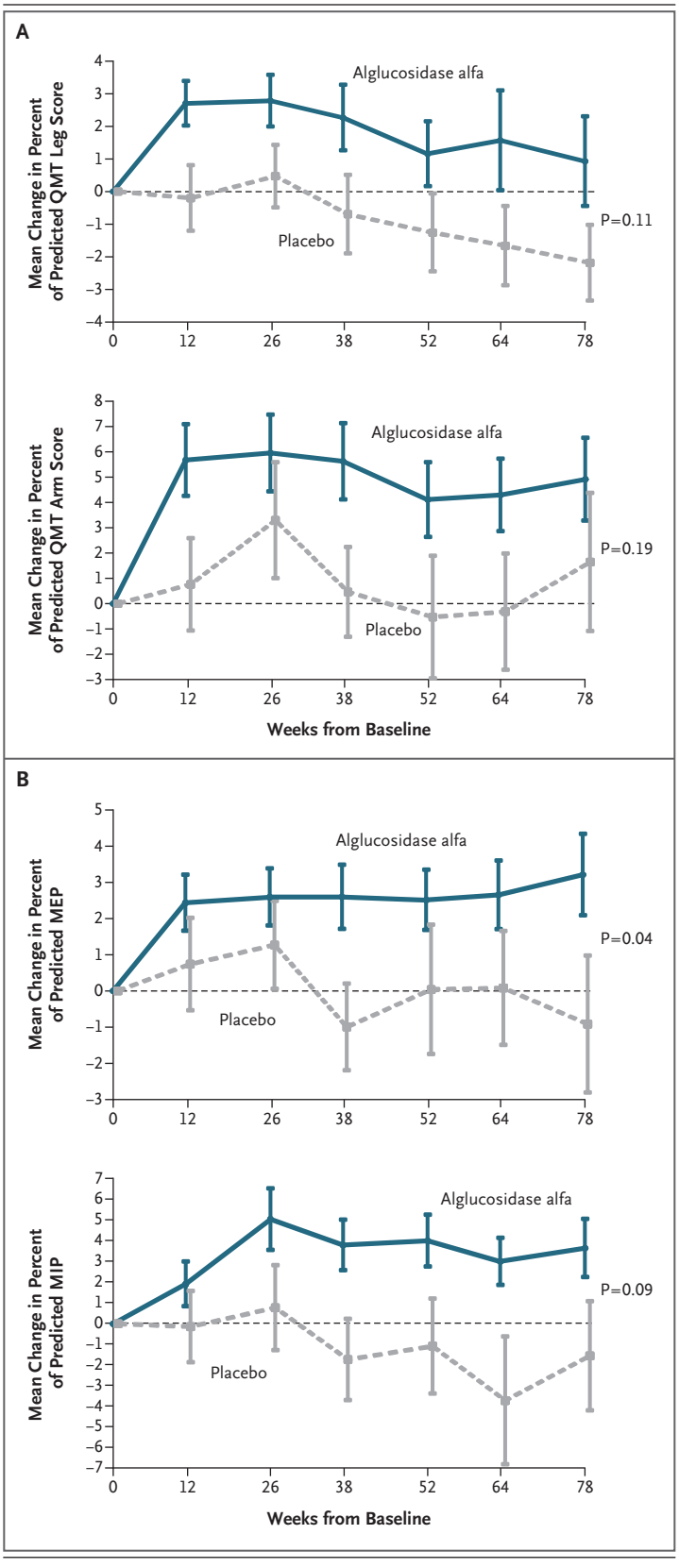


**Figure 2. Changes from Baseline in Quantitative Muscle Testing (QMT) Arm and Leg Scores and Maximum Expiratory and Inspiratory Pressures.**

The graphs show changes in the percentage of predicted values from baseline to week 78 for the alglucosidase alfa group and the placebo group. On QMT (Panel A), the changes in leg scores were 1.2% for the alglucosidase alfa group and –2.0% for the placebo group; the corresponding values for the arm scores were 5.1% and 1.5%. In Panel B, the changes in maximum expiratory pressure (MEP) were 3.2% for the alglucosidase alfa group and –0.6% for the placebo group; the corresponding changes in maximum inspiratory pressure (MIP) were 3.5% and –0.4%. These values represent estimates of the mean on analysis of covariance.

tion[9,33]; these findings are consistent with the 2.2% decline that occurred over a period of 18 months in the placebo group in our study. Important clinical benefits can be provided if further deterioration in pulmonary and motor function can be prevented, and the patient's independence can be maintained by preventing the need for a ventilator or a wheelchair.

The estimated treatment response to alglucosidase alfa as compared with placebo, although variable in its magnitude, was consistently positive for all subgroups. Hypotheses about the nature and progression of muscle damage in Pompe's disease led us to speculate that patients with less baseline impairment would benefit more from treatment. Subgroup analyses of the changes in the 6-minute walk test and the percentage of the predicted FVC suggest a more pronounced treatment effect in patients with better clinical status at baseline (all estimated treatment effects >0) (Fig. 2 in the Supplementary Appendix). However, individual patients' responses did not consistently show this effect, nor did the subgroup analyses identify any consistent predictor of a treatment response.

The effect of alglucosidase alfa treatment became apparent early; the greatest improvement in all end points in the treated group occurred during the first 26 weeks, with those gains then generally being maintained. This response pattern may be due to the limited capacity to repair muscle tissue that has sustained substantial damage. Functional recovery may then be explained by the uptake of exogenous alglucosidase alfa and subsequent lysosomal glycogen clearance from muscle tissue that has not yet sustained end-stage damage.[34] The overall clinical response

**Table 3. Serious Adverse Events during the Treatment Period.***

| Adverse Event | Alglucosidase Alfa Group (N = 60) | Placebo Group (N = 30) |
|---|---|---|
| | *no. of patients (%)* | |
| Any event | 13 (22) | 6 (20) |
| Infections | 2 (3) | 1 (3) |
| Diverticulitis | 0 | 1 (3) |
| Gastroenteritis | 1 (2) | 0 |
| Pneumonia | 1 (2) | 0 |
| Cardiac disorders | 2 (3) | 0 |
| Coronary artery disease | 1 (2) | 0 |
| Supraventricular tachycardia | 1 (2) | 0 |
| Immune system disorders | 2 (3) | 0 |
| Hypersensitivity | 2 (3) | 0 |
| General disorders and conditions at site of administration | 2 (3) | 0 |
| Chest discomfort | 1 (2) | 0 |
| Noncardiac chest pain | 1 (2) | 0 |
| Respiratory, thoracic, and mediastinal disorders | 2 (3) | 0 |
| Lung disorder | 1 (2) | 0 |
| Throat tightness | 1 (2) | 0 |
| Injury, poisoning, and complications of procedure | 1 (2) | 1 (3) |
| Fall | 1 (2) | 1 (3) |
| Fracture (humerus) | 1 (2) | 1 (3) |
| Musculoskeletal and connective-tissue disorders | 1 (2) | 1 (3) |
| Intervertebral disk protrusion | 1 (2) | 0 |
| Flank pain | 0 | 1 (3) |
| Gastrointestinal disorders | 1 (2) | 1 (3) |
| Generalized abdominal pain | 1 (2) | 0 |
| Upper abdominal pain | 0 | 1 (3) |
| Nervous system disorders | 1 (2) | 1 (3) |
| Brain-stem ischemia | 1 (2) | 0 |
| Headache | 0 | 1 (3) |
| Skin and subcutaneous-tissue disorders | 1 (2) | 1 (3) |
| Angioedema | 1 (2) | 0 |
| Septal panniculitis | 0 | 1 (3) |
| Metabolism and nutritional disorders | 1 (2) | 0 |
| Dehydration | 1 (2) | 0 |
| Vascular disorders | 1 (2) | 0 |
| Aneurysm | 1 (2) | 0 |

* Patients may have had more than one adverse event.

observed in our study may represent the balance between more mildly affected muscle fibers and those with potentially irreversible damage and might suggest that prevention of further loss of muscle tissue and function is an important treatment goal. Longer-term study of alglucosidase

alfa in children and adults with Pompe's disease would be needed to understand fully the potential of treatment.

Adverse events occurred in both groups of patients in our study. Anaphylactic reactions occurred in 3 of the 60 patients treated with alglucosidase alfa; 2 of these reactions were IgE-mediated. One patient who tested positive for IgE underwent a successful rechallenge with the use of a modified regimen and remained in the study. After discontinuing the study, the second IgE-positive patient was successfully rechallenged with alglucosidase alfa and was able to continue treatment. IgG antibodies to alglucosidase alfa were detected in all the patients who received alglucosidase alfa, with a trend toward decreasing levels with continued treatment. Although we found no consistent effect of these antibodies on clinical response or safety variables, such an effect may emerge over time. Anaphylactic reactions are a serious potential complication of treatment with any recombinant human protein and have previously been reported to occur with alglucosidase alfa.[12] Antibodies, particularly neutralizing antibodies, have a negative effect on clinical response in some diseases treated with infused proteins, but this effect has been inconsistent across patient populations.[29] Patients treated with alglucosidase alfa who have persistently high antibody titers should be followed closely until the effect of the antibodies is more fully understood.

Our study has several limitations. Although 90 patients is a large population for a clinical trial designed to study an orphan disease, the number is relatively small when the goal is to judge the progression of a clinically heterogeneous disease. Before the start of this trial, no longitudinal data were available on changes in the 6-minute walk test over time in patients with untreated Pompe's disease, and the mean decline in the distance walked was minimal in the patients in our study who received placebo. Longer follow-up will be needed to confirm our results, given the variable presentation and rate of deterioration among the patients in our study and the possible effect of the degree of muscle destruction at baseline on their response to treatment.

In summary, our data indicate that alglucosidase alfa treatment, as compared with placebo, has a positive, if modest, effect on walking distance and pulmonary function in patients with late-onset Pompe's disease and may stabilize proximal limb and respiratory muscle strength.

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## APPENDIX

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