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# Long-Term Galsulfase Treatment Associated With Improved Survival of Patients With Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome): 15-Year Follow-Up From the Survey Study

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## Abstract

Mucopolysaccharidosis VI (MPS VI) is a progressive lysosomal storage disorder with multiorgan and multisystemic pathology. Currently, galsulfase enzyme replacement therapy (ERT) is the only approved treatment for MPS VI. A cross-sectional survey study of 121 patients with MPS VI conducted in 2001 to 2002 and a 10-year follow-up study of the same patients (resurvey study; ClinicalTrials.gov NCT01387854) found that those receiving galsulfase at any time showed physical improvements and a lower mortality rate (16.5%) versus treatment-naive patients (50%). After ~15 years, galsulfase-treated patients (n = 104) continue to have a survival advantage over treatment-naive patients (n = 14), as demonstrated by a 24% versus 57% mortality rate. This survival advantage is further supported by data from the commercial use of galsulfase (2005-2016), which show a 5-year mortality rate for galsulfase-treated patients of 12.5%. Together, these findings suggest that galsulfase ERT can increase life expectancies for patients with MPS VI over a period of at least 15 years.

## Keywords

mucopolysaccharidosis VI, Maroteaux-Lamy syndrome, enzyme replacement therapy, arylsulfatase B, galsulfase, survey study

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## Introduction

Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome, MPS VI) is a metabolic disorder caused by a deficiency in the lysosomal enzyme *N*-acetyl-galactosamine-4-sulfatase (also called arylsulfatase B),[1–3] which breaks down the glycosaminoglycan (GAG) dermatan sulfate.[4] Defects in metabolism that result from this deficiency include excess lysosomal GAG storage and processing and excess urinary GAG excretion,[5] as well as abnormal autophagy, abnormal protein ubiquitination, inflammation, apoptosis, and disturbance of other aspects of cell signaling.[6]

First described in 1963,[7] common clinical manifestations of MPS VI include short stature, corneal clouding, coarse facial features, joint contractures, and claw hands.[8] Cardiac abnormalities may also be present, including electrocardiogram abnormalities and valvular disease.[8] Pulmonary complications, including pneumonia, restrictive lung disease, and pulmonary hypertension, are also noted.[8] Unlike some other types of mucopolysaccharidoses, physical and visual impairments are predominant issues, while central nervous system pathology is absent; mental development is usually normal.[4] The physical limitations of patients with MPS VI, however, can affect learning and development.[9] A cross-sectional survey study of 121 patients with MPS VI, conducted in 2001 to 2002, found heterogeneity in the clinical presentation, with patients presenting with short stature, lower body weights, reduced pulmonary function, impaired endurance, and reduced joint range of motion.[9] More severely affected patients appeared to have higher urinary GAG concentrations for their age than those with lesser clinical expression of the disease.[9] This association of urinary GAG and body stature with MPS VI severity has been suggested as a means of grouping patients into those with rapidly progressing disease (stature of 80-120 cm and urinary GAG concentrations >200 μg/mg creatinine) and slowly progressing disease (stature above 140 cm and urinary GAG concentrations <100 μg/mg creatinine).[9,10]

Enzyme replacement therapy (ERT) with the recombinant human enzyme galsulfase (Naglazyme; BioMarin Pharmaceutical Inc, Novato, California) was approved in 2005 to 2006 for the treatment of MPS VI in the USA, Europe, Brazil, Australia, and several other countries.[11,12] In multiple clinical studies, including a randomized, double-blind, placebo-controlled phase 3 trial, Harmatz et al demonstrated that galsulfase administration to patients with MPS VI improved endurance when compared to placebo, as measured by the 12-minute walk test (12MWT), by the average number of steps climbed per minute in the 3-minute step climb test (3MSC), and by decreased urinary GAG excretion.[13–16] The physical improvements and the reduction in urinary GAG concentration were also shown to be sustained following long-term administration of galsulfase for up to 5 years.[17] A case report series by Lin et al[18,19] have also shown the long-term benefit of chronic galsulfase administered over 6.2 to 11.2 years to 9 Taiwanese patients with MPS VI ranging in age from 1.4 to 21.1 years at study initiation. Urinary GAG concentration declined in all patients, and there was either no worsening or improvements on average in a wide range of clinical functional assessments, including endurance, mobility (assessed by 6MWT and 3MSC), joint function, pulmonary function, liver and spleen size, cardiac hypertrophy, and cardiac diastolic function.

A resurvey study of patients with MPS VI 10 years following the initial survey and initiation of treatment with galsulfase (mean [standard deviation, SD] of 6.8 [2.2] total years of treatment) showed that ERT patients <13 years old improved forced vital capacity (FVC) by 68% and forced expiratory volume in 1 second ($FEV_1$) by 55%.[12] Patients ≥13 years old increased FVC by 12.8% and maintained $FEV_1$.[12] Significantly, mortality in non-ERT patients was 50% (7/14 patients), while mortality in galsulfase-treated patients was 16.5% (17/103 patients, hazard ratio [HR]: 0.24; 95% confidence interval [CI]: 0.10-0.59).[12]

## Aim

In this report, we present the 15-year survival data for patients receiving galsulfase following the initial survey study and compare survival with nontreated patients, as well as survival data for patients receiving galsulfase obtained commercially.

## Methods

### *Patient Population*

The current study is a 15-year continuation of the resurvey study (ASB-00-03; ClinicalTrials.gov NCT01387854), which was a multicenter, multinational study to obtain repeat 10-year survival data on patients who took part in the survey study (ASB-00-02) in 2001 to 2002.[9] Only patients who had previously participated in the survey study ASB-00-02 and had met the criteria of an MPS VI diagnosis were eligible. Of the 121 patients who participated in the survey study, survival status was available for 117 participants as of October 24, 2013, for a total survival follow-up of up to 12 years. The remaining 4 patients were considered lost to follow-up, since no information was available after 3 attempts to reach them via study sites. By 2016, survival data were available for 111 of 121 of these patients, with 10 patients lost to follow-up between 2013 and 2016, 3 of whom were also lost to follow-up at the time of the resurvey study.

Additionally, adverse events (AEs), including death, in patients receiving galsulfase obtained commercially were collected through galsulfase pharmacovigilance monitoring. Survival data were compiled for patients between the time galsulfase was approved in 2005 through August 2016.

### *Statistical Methods*

Kaplan-Meier survival analyses were performed to compare the overall survival for galsulfase-treated versus ERT-naive patients. The difference in overall survival was compared using the log-rank and Wilcoxon tests. Any missing dates of death

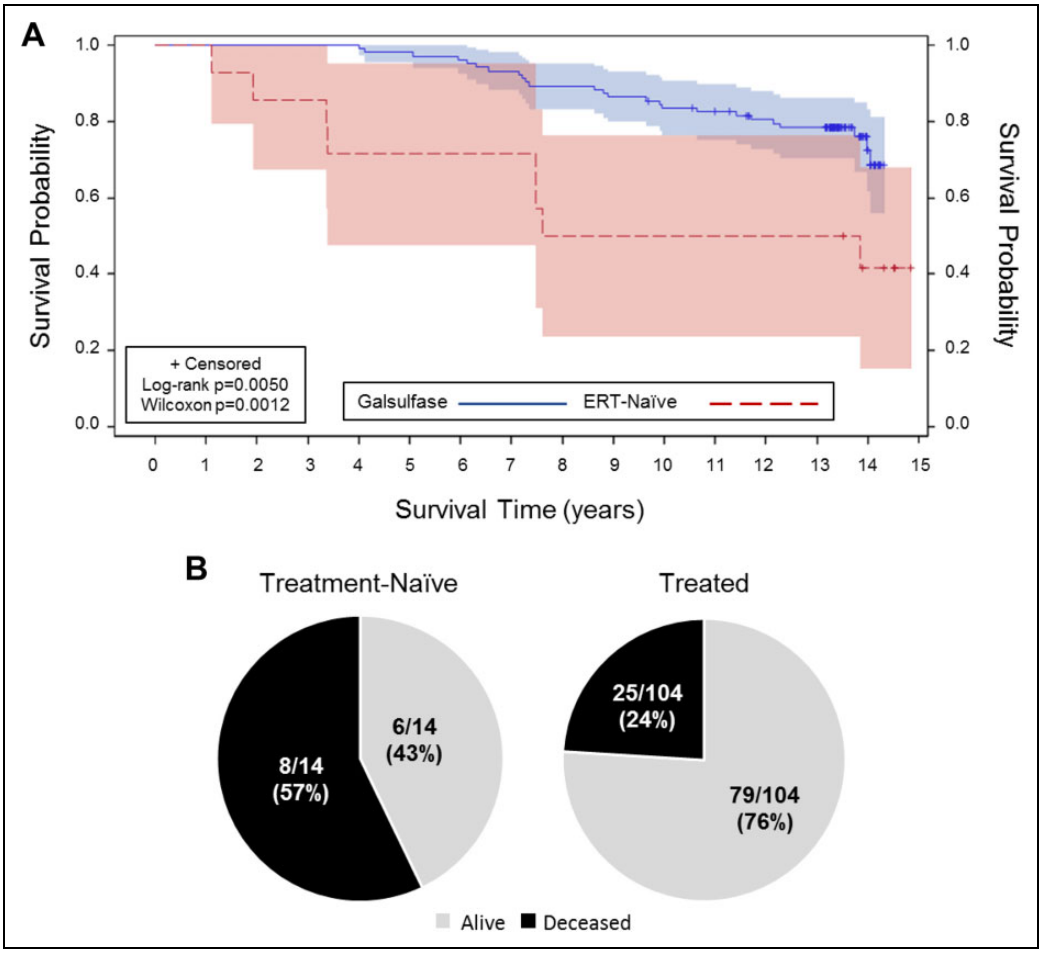


**Figure 1.** A, Kaplan-Meier survival estimates for galsulfase-treated (n = 104) and ERT-naive patients (n = 14). Shaded areas indicate 95% confidence limits. B, Proportional survival among galsulfase-treated and ERT-naive patients. ERT indicates enzyme replacement therapy.

were imputed using the most conservative method, whereby the latest HR was estimated by using Cox proportional hazards model (both for univariate as well as multivariate analyses); HRs are presented with 95% CIs. Survival data from the pharmacovigilance database are provided as percentage surviving.

## Results

### *Patient Demographics*

Detailed baseline demographic data for the patients in the survey have previously been reported.[9] Demographics of patients from the pharmacovigilance database were not available.

### *Survival—Survey Study Cohort*

Figure 1 provides the Kaplan-Meier current survival estimates for patients with MPS VI receiving galsulfase and naive patients while abbreviated demographic and mortality data are provided in Table 1. As of August of 2016, 118 patients with MPS VI contributed data to this survival analysis (111 patients contributed data in 2016 and 7 patients provided data in 2013 but were subsequently censored from the Kaplan-Meier analysis due to being lost to follow-up); 104 treated with galsulfase long term and 14 naive to ERT. Twenty-five (24%) of 104 galsulfase-treated patients have died since the survey study, whereas 8 (57%) of 14 ERT-naive patients have died.

**Table 1.** Mortality Data.[a]

| Parameter | Galsulfase | ERT-Naive |
|---|---|---|
| All patients with survival data, n | 104 | 14 |
| Mean baseline age, years | 13.7 (9.7) | 19.7 (12.9) |
| Mean baseline height, cm | 114.3 (25.6) | 125.8 (29.7) |
| Mean baseline urinary GAG, μg/mg creatinine | 326.8 (199.1) | 250.2 (206.0) |
| Deceased patients | | |
| Mortality, n (%) | 25/104 (24%) | 8/14 (57%) |
| Hazard ratio (95% CI) | 0.348 (0.156-0.776) | |
| Mean baseline age, years | 14.4 (10.7) | 15.2 (12.7) |
| Mean age at death, years | 23.3 (10.1) | 21.0 (14.9) |
| Mean survival time, years[b] | 8.9 (3.0) | 5.8 (4.2) |

Abbreviations: CI, confidence interval; ERT, enzyme replacement therapy; GAG, glycosaminoglycans; SD, standard deviation.
[a]Values given as mean (SD) unless otherwise indicated.
[b]From study initiation to death.

This represents a HR of 0.348 (95% CI: 0.156-0.776) favoring galsulfase. The mortality over time observed in these 2 patient groups showed significant separation of the Kaplan-Meier curves (log-rank $P = .0050$; Wilcoxon $P = .0012$). This result is consistent with the 10-year mortality in the galsulfase group of 16.5% previously reported by Giugliani et al.[12] Although baseline age was higher in the naive group, lower baseline urinary GAG concentration and greater height in these patients suggest that they were likely less severely affected by MPS VI than the treated patients, even though they were older.

Although the baseline age for patients in the galsulfase treatment group was somewhat younger than in the ERT-naive patients, the baseline ages for the patients who died were similar for both groups. Despite the similar baseline ages between deceased patient groups, the age at death tended to be older in the galsulfase group with patients living longer (8.9 years) compared with the ERT-naive group (5.8 years; Table 1).

Cause of death was available for 13 of the 25 galsulfase-treated patients who died. Five deaths were respiratory related (respiratory distress, obstructive airway disorder, bronchospasm, bronchopneumopathy, apnea), 6 were cardiopulmonary related (pulmonary hemorrhage, aortic stenosis, cardiopulmonary arrest, cardiac arrest, congestive cardiac failure, cardiorespiratory arrest), 1 was due to intestinal obstruction, and 1 was due to sepsis.

Cause of death was available for 3 of the ERT-naive patients. Death in these patients was found to be due to suspected atrial fibrillation, respiratory failure secondary to spinal cord compression, and bone marrow transplantation complications.

### *Survival—Pharmacovigilance*

The above findings are further supported by data from the pharmacovigilance monitoring of galsulfase. From the time of regulatory approval in 2005, through August 2016, 1193 patients with MPS VI have received $\geq$5 years of galsulfase ERT. Over this period, 149 deaths have been reported, corresponding to a 5-year mortality for treated patients of 12.5%. Where data were available in the pharmacovigilance database, the age at death of these patients was 16.0 (9.9) years (n = 116; mean [SD]), and the average time on treatment of the deceased patients was 3.5 (2.8) years (n = 108).

In 125 of the 149 patients, cause of death was identified and included respiratory dysfunction (30%), respiratory infection (22%), cardiac dysfunction (18%), cardiopulmonary dysfunction (13%), and infection (6%). Other causes of death (12%) included acute lymphocytic leukemia, anaphylactic shock, cerebrovascular accident, choking, encephalitis, intubation complication, gastrointestinal hemorrhage, hydrocephalus, intestinal obstruction, oliguria, perforated ulcer, spinal decompression, and tonsillectomy. Cause of death in the remaining 24 patients was not specifically identifiable based on the information provided. Thus, the majority of patients experienced a respiratory or cardiovascular death. Note that these causes of death are similar to the causes of death in the survey cohort reported above.

## Discussion

Improvement in survival has been shown to be a benefit of galsulfase treatment. The survey study was originally conducted to assess the natural history of MPS VI.[9] Subsequently, some patients from this cohort were treated with galsulfase, while some remained naive to ERT. A 10-year resurvey of this cohort demonstrated improved survival of patients receiving galsulfase for an average of 6.8 (2.2) years. Mortality in patients receiving galsulfase was 16.5% (17/103) compared with 50% (7/14) for ERT-naive patients.[12]

In the current 15-year follow-up study, galsulfase continues to provide a survival advantage. From the original patient cohort, of the 104 galsulfase-treated patients available for follow-up, 24% mortality was significantly better than the 57% mortality observed for ERT-naive patients, although the ERT-naive group was small (n = 14). The unadjusted HR of 0.348 indicates that galsulfase therapy reduced the odds of death by 65.2% compared to those not receiving galsulfase therapy. Since the majority of treated patients in this study did not receive galsulfase until they were teenagers, it is possible that earlier initiation of therapy may further reduce mortality from MPS VI. Improved survival may also be reflected by the somewhat older average age at death and the survival time from study initiation for those patients receiving galsulfase compared with ERT-naive patients. Improved growth may be a contributing factor to improved mortality because respiratory issues, commonly implicated in patient with MPS VI death, are likely to improve based on increasing lung volumes resulting from growth. A recent study has shown that patients receiving galsulfase treatment between the ages of birth and 15 years old with elevated urinary GAG (>200 μg/mg creatinine) showed significant growth improvement.[20] Additionally, a primary effect of galsulfase may be to improve pulmonary function. Harmatz et al have reported that FVC and $FEV_1$ improved over time in a combined cohort of patients with MPS VI from phases 1, 2, and 3 studies of galsulfase and that this improvement in pulmonary function occurred independent of age.[21] Although there was a significant difference in survival between the ERT and ERT-naive groups, we recognize that the small number for the ERT-naive group may diminish the general applicability of this observation.

Results from the data collected in the pharmacovigilance database on the commercial use of galsulfase also support the finding of reduced mortality with treatment. This cohort represents the majority of the estimated MPS VI population globally.[9] Mortality in this group, which received an average of 5 years of galsulfase therapy, was 12.5%. This low mortality rate is consistent with that observed in the survey study population[12] and suggests that these observations are applicable to the overall patient with MPS VI population. However, little is known regarding demographics and clinical characteristics of the pharmacovigilance-monitored patients. Patient heterogeneity may contribute to the mortality rate observed in this group, and without an ERT-naive group for comparison or additional details for this group, it is difficult to identify

the variables that may be impacting the mortality in these ERT-treated patients.

A substantial proportion of patients died from cardiorespiratory complications, especially respiratory infection. This observation confirms that cardiac and respiratory function should be carefully monitored and suggests that early and aggressive treatment of respiratory infections may be advisable. Further study is warranted.

Although only mortality data were assessed in the current study, several long-term studies demonstrate galsulfase safety and tolerability. Infusion-associated reactions have been shown to be manageable.[17–19,22] Galsulfase treatment–related serious AEs are rare: only 31 events were reported for 11 patients in a 5-year follow-up of patients in a clinical surveillance program designed to follow up ERT patients (n = 123).[22] Most patients developed immunoglobulin G antibodies to galsulfase,[13,23] but only in 1 (1/38) patient could impairment of enzyme uptake or activity be substantiated.[13] Lin et al reported skin rash, dyspnea, and pyrexia in approximately one-third of their patients (n = 9).[18,19] These AEs were easily controlled with oral antihistamines, steroids, and antipyretics. No patient discontinued treatment due to AEs. Thus, AEs in this patient cohort were tolerable and easily manageable.

## Conclusion

Patients with MPS VI receiving galsulfase treatment continue to demonstrate a survival advantage over patients who are ERT-naive. Further assessment at longer time points is warranted to determine whether this survival advantage continues to be observed.

### Authors' Note

Data are available from the corresponding author on request. Data from this report were presented at the 13th Annual WORLDSymposium (February 13-17, 2017, San Diego, California) and published in abstract form as Giugliani R, et al. *Molec Genet Metab*. 2017;120(1-2): S56. Abstract 113.

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