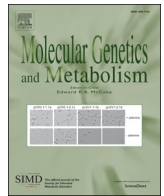




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## The effect of galsulfase enzyme replacement therapy on the growth of patients with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)

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## ABSTRACT

Mucopolysaccharidosis (MPS) VI is an autosomal recessive lysosomal storage disorder arising from deficient activity of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B) and subsequent intracellular accumulation of the glycosaminoglycans (GAGs) dermatan sulfate and chondroitin-4-sulfate. Manifestations are multi-systemic and include skeletal abnormalities such as dysostosis multiplex and short stature. Reference height-for-age growth charts for treatment-naïve MPS VI patients have been published for both the slowly and rapidly progressing populations. Categorization of disease progression for these charts was based on urinary GAG (uGAG) level; high (>200 µg/mg creatinine) levels identified subjects as rapidly progressing. Height data for 141 patients who began galsulfase treatment by the age of 18 years were collected and stratified by baseline uGAG level and age at ERT initiation in 3-year increments. The reference MPS VI growth charts were used to calculate change in Z-score from pre-treatment baseline to last follow-up. Among patients with high baseline uGAG levels, galsulfase ERT was associated with an increase in Z-score for those beginning treatment at 0–3, >3–6, >6–9, >9–12, and >12–15 years of age ( $p < 0.05$ ). Increases in Z-score were not detected for patients who began treatment between 15 and 18 years of age, nor for patients with low ( $\leq 200$  µg/mg creatinine) baseline uGAG levels, regardless of age at treatment initiation. The largest positive deviation from untreated reference populations was seen in the high uGAG excretion groups who began treatment by 6 years of age, suggesting an age- and severity-dependent impact of galsulfase ERT on growth.

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## 1. Introduction

Mucopolysaccharidosis VI (MPS VI, or Maroteaux-Lamy syndrome; OMIM 253200) is a rare autosomal recessive genetic disorder caused by a deficiency in *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B (ASB); E.C.3.1.6.1), which results in intracellular accumulation of the enzyme substrate, the glycosaminoglycans (GAGs) dermatan sulfate and chondroitin 4-sulfate. This progressive accumulation manifests as

clinically progressive disease with multi-systemic involvement [1]. Most patients with a rapidly progressing course show classical MPS VI symptoms by age 2 to 3 years, including short stature, joint and skeletal abnormalities, and spinal cord compression. Other manifestations include corneal opacification, respiratory insufficiency and impaired endurance, and cardiac valve stenosis and/or regurgitation [1]. Patients with a slower progression may not necessarily present with short stature and can sometimes reach adult heights that are comparable to unaffected (non-MPS VI) peers; however, these patients also experience significant morbidity by their teenage years or later, including skeletal complications, cardiac valve abnormalities, and reduced endurance [2].

Growth in height in MPS VI patients starts to falter by age 2 to 3 years. The degree of deceleration is greater in patients with high (>200 µg/mg creatinine) urinary GAG (uGAG) levels compared to

Abbreviations: ASB, Arylsulfatase B; CDC, Centers for Disease Control and Prevention; ERT, Enzyme replacement therapy; GAG, Glycosaminoglycans; MPS VI, Mucopolysaccharidosis VI; uGAG, Urinary glycosaminoglycans.

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those with low ( $\leq 200$   $\mu\text{g}/\text{mg}$  creatinine) levels [3]. MPS VI-specific height percentile growth charts up to 18 years of age were developed for both rapidly and slowly progressing populations [4]. Due to limited differences in growth between male and female MPS VI patients, these charts are not gender-specific [4]. Growth stops around 12 years of age for patients with high uGAG levels; mean adult height is approximately 110 cm. Conversely, patients with low uGAG levels continue growing into their teenage years with a mean adult height of 145 cm. Growth charts for these two patient populations provide a useful tool for monitoring height attainment in MPS VI children and allow tracking of the effect of therapeutic interventions on growth.

MPS VI clinical trials have shown that enzyme replacement therapy (ERT) with galsulfase (recombinant human (rh) ASB; Naglazyme®, BioMarin Pharmaceutical Inc., Novato, CA) is effective in improving endurance and pulmonary function, reducing intracellular GAG accumulation, and stabilizing cardiac manifestations [5,6,7]. In a cohort of patients, some of whom were included in the current study, a 10-year follow-up study [8] and longitudinal modeling of pooled data from clinical trials [9] indicated a long-term beneficial effect of galsulfase ERT on endurance, respiratory function, and growth rates. Reference growth charts for MPS VI were not available at the time for comparison of treated and treatment-naïve populations, but have since been developed [4]. The objective of the current study was to evaluate the impact of galsulfase ERT on growth using the recently developed height-for-age reference charts for untreated MPS VI patients.

## 2. Methods

### 2.1. Patient population and data collection

Serial height-for-age data for MPS VI patients were obtained from assessments collected during patient participation in the galsulfase clinical trials (NCT00299000, NCT00048620, NCT00048711, NCT00067470, NCT00104234), a cross-sectional survey study [3], a 10-year follow-up resurvey study (NCT01387854) [8], and the MPS VI clinical surveillance program (NCT00214773). Each patient was assigned a unique identification number and data were pooled from all studies at a per patient level to avoid redundancies for patients who had enrolled in more than one study. Patients who had baseline uGAG and height data available, began ERT by 18 years of age, and reported at least one post-ERT height measurement were included in the analysis. Height measurements had to be obtained before or within one month after galsulfase ERT initiation to be considered baseline values. None of the evaluated patients had undergone a hematopoietic stem cell transplant. For assessments performed under 2 years of age, reported height measurements likely represent length, the accepted method for assessment in this age group. The MPS VI standard growth curves do not extend below 2 years of age because of insufficient data [4]; however, patients under 2 years of age appear to differ very little in growth in length from the unaffected population (unpublished data). Therefore, U.S. Centers for Disease Control and Prevention (CDC) <2 years length-for-age data were used as a reference [10] for length and Z-score calculations for MPS VI patients under 2 years of age. Because the MPS VI growth charts are not sex-specific, CDC male and female length values were averaged.

### 2.2. Patient classification

Pre-treatment uGAG levels were quantified from the first voided morning sample by spectrophotometric detection of metachromatic change in the 1,9-dimethyl-methylene blue dye upon GAG binding

[11]. Urine GAG analysis was performed by either Cambridge Biomedical Inc. (Boston, MA) or BioMarin Pharmaceutical Inc. (Novato, CA). Values from each laboratory were in general alignment with each other; however, it was not possible to generate a direct correlation or conversion factor to equate results from one lab exactly with that of another, as has been reported as typical for this method of measuring uGAG [12]. If more than one pre-treatment uGAG value was available, the average was used. Patients with high uGAG levels were classified as rapidly progressing; patients with low uGAG levels were classified as slowly progressing.

### 2.3. Galsulfase treatment

All but five patients received galsulfase (Naglazyme®, BioMarin Pharmaceutical Inc., Novato, CA) infusions at 1 mg/kg weekly according to the prescribing information [13] and recommended standard of care [14]. Of the remaining five patients, three received 0.2 mg/kg during the Phase 1/2 clinical trial (NCT00048620) [15] and two received 2 mg/kg in a Phase 4 study (NCT00299000) [7,16]. All five patients subsequently received the 1 mg/kg/week dose.

### 2.4. Statistical methods

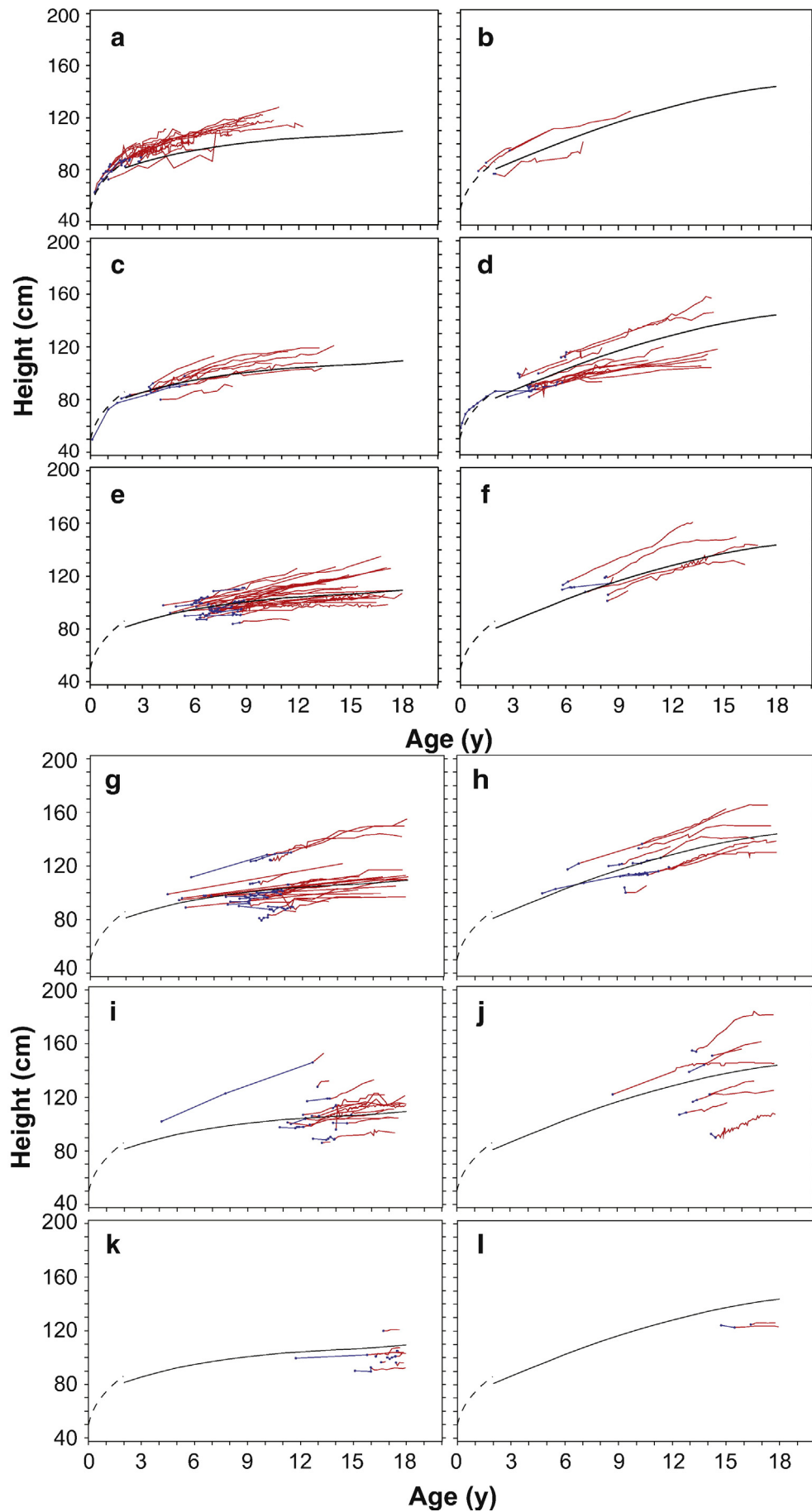
Height-for-age measurements were plotted together with the published 50th percentile reference curve for untreated rapidly or slowly progressing MPS VI patients [4]. Height Z-scores were generated separately for the group of patients with high uGAG levels and those with low uGAG and were based on the corresponding MPS VI reference population growth chart. Mean Z-score change from first available pre-treatment assessment to last follow-up was calculated with and without stratification by age at treatment initiation (0–3, >3–6, >6–9, >9–12, >12–15, and >15–18 years). P-values for the change in Z-score were derived from paired 2-sided *t*-tests. A Pearson correlation coefficient was calculated to assess the relationship between age at treatment initiation and change in Z-score.

## 3. Results

As of February 2016, 141 patients who began treatment by 18 years of age had the necessary height and uGAG data available to be included in this analysis. The majority (68%) were classified as rapidly progressing based on the 200  $\mu\text{g}/\text{mg}$  creatinine uGAG cut off level. Mean years of galsulfase exposure were 5.5, 6.3, 6.9, 5.4, 3.2, and 1.2 for those who started treatment at ages 0–3, >3–6, >6–9, >9–12, >12–15, and >15–18 years, respectively. The gender ratio was 72 males to 69 females.

Patient height-for-age data, grouped by baseline uGAG level and age at treatment initiation, are shown in Fig. 1. Table 1 lists results of the Z-score analysis. Among patients with high baseline uGAG levels, galsulfase ERT was associated with an increase in Z-score. A moderate negative correlation ( $r = -0.41$ ) between improvements in height Z-score and age at treatment initiation was detected (Supplemental Fig. 1). When patients were stratified by age at treatment initiation, a significant increase in Z-score was seen for those beginning treatment at 0–3, >3–6, >6–9, >9–12, and >12–15 years of age (Fig. 2). Significant increases in Z-score were not seen for patients who began treatment between 15 and 18 years of age, nor for patients with low baseline uGAG levels, regardless of age at treatment initiation.

**Fig. 1.** Height-for-age plots of galsulfase-treated MPS VI patients. Height measurements of MPS VI patients, stratified by age at treatment initiation and baseline uGAG level, are shown in blue (pre-galsulfase ERT) and red (post-galsulfase ERT initiation). Pre-galsulfase ERT uGAG values of  $\leq 200$  or  $> 200$   $\mu\text{g}/\text{mg}$  creatinine defined patients as slowly or rapidly progressing, respectively. Rapidly (a, c, e, g, i, k) and slowly (b, d, f, h, j, l) progressing patient data are shown in separate panels for those who started galsulfase ERT from ages 0–3 (a, b), >3–6 (c, d), >6–9 (e, f), >9–12 (g, h), >12–15 (i, j), and >15–18 years (k, l). Reference curves (black) are the 50th percentiles of the MPS VI height growth charts (age 2–18 years, solid line) and the average of US CDC male and female length charts (age 0–2 years, dotted line).



**Table 1**  
Mean (SD) height Z-scores (relative to slowly-progressing or rapidly-progressing MPS VI growth charts) of galsulfase ERT-treated patients.

Age at treatment initiation (years)	Baseline Z-score	Change in Z-score at last follow-up	P-value
0–18			
High uGAG (n = 96)	0.01 (0.9)	0.53 (0.6)	<0.0001
Low uGAG (n = 45)	0.06 (1.1)	−0.19 (0.7)	0.08
0–3			
High <sup>a</sup> uGAG (n = 15)	0.61 (0.8)	1.00 (0.8)	0.0002
Low <sup>b</sup> uGAG (n = 4)	0.55 (1.8)	0.26 (1.2)	0.7
>3–6			
High uGAG (n = 9)	−0.45 (1.0)	1.09 (0.8)	0.004
Low uGAG (n = 16)	0.10 (1.1)	−0.61 (0.8)	0.006
>6–9			
High uGAG (n = 25)	−0.11 (0.7)	0.49 (0.5)	<0.0001
Low uGAG (n = 6)	0.18 (0.9)	0.07 (0.4)	0.7
>9–12			
High uGAG (n = 23)	0.10 (1.1)	0.23 (0.4)	0.01
Low uGAG (n = 9)	0.25 (0.9)	−0.17 (0.4)	0.2
>12–15			
High uGAG (n = 16)	0.01 (1.0)	0.52 (0.6)	0.003
Low uGAG (n = 8)	−0.32 (1.4)	0.24 (0.4)	0.2
>15–18			
High uGAG (n = 8)	−0.47 (0.6)	0.06 (0.2)	0.4
Low uGAG (n = 2)	−0.86 (0.2)	−0.29 (0.3)	0.4

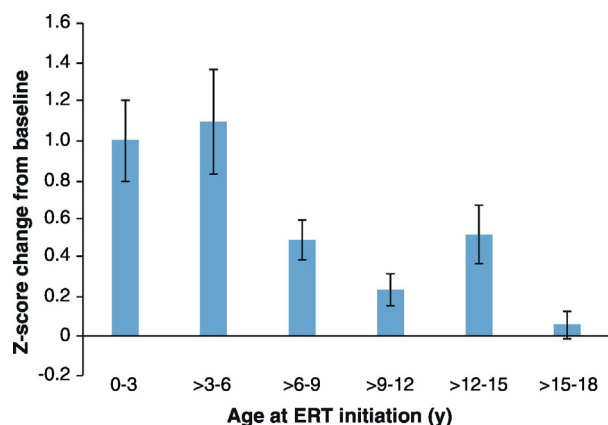
<sup>a</sup> >200 µg/mg creatinine.

<sup>b</sup> ≤200 µg/mg creatinine.

#### 4. Discussion

The availability of reference growth charts for the MPS VI population [4] allowed us to study the effect of galsulfase ERT and age at treatment initiation on growth in this patient group relative to expected growth for untreated patients. We found that the effect of galsulfase ERT on growth was dependent upon baseline uGAG levels and the magnitude of the effect was dependent upon age at treatment initiation. The largest positive deviation from untreated reference populations was seen in the high uGAG excretion groups who began treatment by 6 years of age, suggesting an age- and severity-dependent impact of galsulfase ERT on growth.

Our findings suggest that early initiation of galsulfase ERT is important to maximize growth potential. The finding of an age-dependent benefit of galsulfase ERT is consistent with previous studies [8,9,17,18]. In particular, sibling studies in which one sibling begins therapy at a much younger age than the other provide compelling evidence of benefits of early galsulfase ERT initiation [17,18]. Additionally, a 2-year Brazilian study of MPS VI children undergoing galsulfase ERT starting



**Fig. 2.** Mean Z-score change by age group at ERT initiation for patients ≤ 18 years of age with pre-ERT uGAG values > 200 µg/mg creatinine. Calculations are based on first baseline and last follow-up height measurements. Z-scores are relative to the 50th percentile of the published reference growth chart for the rapidly progressing MPS VI population [4]. Error bars represent standard error.

at 3 years of age showed that 15 of 32 (47%) patients maintained or increased their pre-treatment growth percentile (per World Health Organization reference charts) relative to unaffected individuals [19]. Whether the greater height gain also results in reduced morbidity and increased survival [3,8] is an important topic for future investigation.

We found no positive effect on height gain in patients with low uGAG levels and, for one group (those who began treatment at >3–6 years of age), a statistically significant decrease in Z-score was inexplicably observed. Patients with low uGAG levels are typically classified as having a more slowly progressing form of the disease and, in the absence of treatment, tend to be significantly taller than patients with high uGAG levels, though still exhibiting reduced stature relative to the unaffected population. Our findings indicate that the positive impact of galsulfase on height outcomes may be dependent upon pre-treatment uGAG level, with more rapidly progressing individuals experiencing greater benefit.

Typically, patients with rapidly progressing disease experience growth delay around 2 to 3 years of age [1], and the difference in height between slowly and rapidly progressing patients increases after age 4 to 5 years [4]. Although the mechanism of growth failure in patients experiencing a rapid disease progression is poorly understood, accumulation of GAGs in the growth plates and joints that leads to chondrocyte dysfunction, growth plate disorganization, and cytokine and inflammatory responses may contribute [20,21,22]. Because the effect of galsulfase ERT on height in this study was more substantial in patients who started treatment by 6 years of age, prevention of GAG accumulation in the growth plates may be a potential mechanism for improving growth in rapidly progressing patients.

The role of the endocrine system in the growth failure of MPS VI is not known, and investigations into these factors are limited [9]; however, MPS VI is characterized by delayed puberty and the absence of a pubertal growth spurt [9]. The MPS VI reference growth charts also showed no evidence of a pubertal growth spurt during the teen years, either by gender or by disease progression [4]. Based on the current data, galsulfase ERT treatment does not seem to induce a growth spurt coincident with the resolution of delayed puberty reported previously [9]; however, more longitudinal data are required. Growth during the pubertal period was not addressed directly in this or the previous growth chart study [4]. This gap suggests an avenue for further research, particularly considering that in clinical trials, 42% (10/24) of patients were identified as having delayed puberty onset or progression of puberty [9] and that galsulfase ERT treatment led to completion of puberty in six of these patients while the rest showed progression.

Based on the findings from the current study as well as the previously mentioned evidence of age-dependent impacts of ERT from the literature, early diagnosis and prompt initiation of galsulfase ERT seem to be of critical importance. However, diagnosis of MPS VI during the first year of life is currently challenging. In most patients, growth is normal up to 2 years of age; accelerated growth during infancy has also been reported [18,23,24]. In addition, uGAG levels are naturally high and creatinine levels low during infancy and the upper limit of normal for the ratio is not well defined [25,26,27]. Hence the use of uGAG as a screening biomarker during infancy is limited to experienced laboratories [28]. Mild dysmorphic features, frequent airway infections, umbilical hernias, and orthopedic abnormalities including hip displacement and kyphosis are frequently present and often play a critical role in developing clinical suspicion of MPS VI. Demonstration of low ASB activity in leukocytes or fibroblasts or identification of two pathogenic genetic mutations in the *ARSB* gene is necessary to confirm the diagnosis. Currently, newborn screening for lysosomal storage diseases, including MPS VI, is in the pilot stage, and comparatively simple dried blood spot-based assays are under development [29,30,31,32].

The main limitation of this study is the small sample size in some of the age groups, particularly for patients with low uGAG levels. Although no impact of ERT on height was found for these slowly progressing patients, further study of a larger patient population over a longer period is

needed to better understand this phenomenon. Additionally, the length of exposure to galsulfase was substantially shorter for patients over 15 years of age at treatment initiation relative to the rest of the patients studied. More time may be required to detect the effect of treatment for these patients. When interpreting the results of this study, the limitations of the reference growth charts used as the basis for the analysis must also be taken into consideration. The reference growth charts were developed with data from a relatively small number of patients (207). However, as these patients were from multiple countries and regions, and represented approximately 19% of the estimated worldwide MPS VI population [4], they likely provided a reasonable representation of the overall natural history of the disease. Both the development of the original reference growth charts and the current study exemplify that sufficient data on an ultra-rare disease like MPS VI can only be obtained through the joint efforts of many clinicians. On a country-by-country basis these cumulative data could not have been collected. At the same time, it demonstrates that continuous efforts remain needed to obtain further supportive evidence in larger numbers of MPS VI patients over longer periods of time.

In conclusion, we observed that the effect of galsulfase ERT on the growth of MPS VI patients relative to MPS VI reference growth charts depends on age of treatment initiation and pre-treatment uGAG levels. Patients with high baseline uGAG levels who started treatment by 15 years of age demonstrated a significant increase in height Z-score relative to the untreated population. Overall, our findings indicate that early diagnosis of MPS VI enabling early initiation of galsulfase ERT is essential for maximizing growth potential in children with MPS VI.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ymgme.2017.03.008>.

### Conflict of interest

P. Harmatz, C.J. Hendriks, C. Lampe, J.J. McGill, R. Parini, and V. Valayannopoulos provided consulting services, received research grants, and participated in advisory board meetings and received speaker honoraria and travel support from BioMarin. E. Leão-Teles provided consulting services and participated in advisory board meetings for BioMarin. T. Cole reports no conflicts of interest related to this study. N. Guffon has participated in and received research grants for clinical trials sponsored by BioMarin and participated in advisory board meetings. R. Matousek, S. Graham, and A. Quartel are employees and stockholders of BioMarin.

### Author contributions

P. Harmatz contributed to the conception and research design, acquisition of data, writing of the manuscript, and revising the manuscript critically for important intellectual content. C.J. Hendriks, C. Lampe, J.J. McGill, R. Parini, E. Leão-Teles, V. Valayannopoulos, and N. Guffon contributed to the conception and research design, acquisition of data, and revising the manuscript critically for important intellectual content. T. Cole contributed to the statistical research design and revising the manuscript critically for important intellectual content. S. Graham contributed to the conception and research design, and revising the manuscript critically for important intellectual content. R. Matousek contributed to the development of the statistical methodologies, performed statistical analyses and interpretations, and revised the manuscript critically for important intellectual content. A. Quartel contributed to the conception and research design, performed data analysis, and contributed to the writing of the manuscript.

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