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## Effect of Recombinant Human Growth Hormone on Changes in Height, Bone Mineral Density, and Body Composition Over 1-2 Years in Children with Hurler or Hunter Syndrome

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### Abstract

Patients with Hurler or Hunter syndrome typically have moderate to severe growth deficiencies despite therapy with allogeneic hematopoietic stem cell transplantation and/or enzyme replacement therapy. It is unknown whether treatment with recombinant human growth hormone (hGH) can improve growth in these children. The objectives of this study were to determine the effects of hGH on growth, bone mineral density (BMD), and body composition in children with Hurler or Hunter syndrome enrolled in a longitudinal observational study. The difference in annual change in outcomes between hGH treated and untreated subjects was estimated by longitudinal regression models that adjusted for age, Tanner stage, and sex where appropriate. We report on 23 participants who completed at least 2 annual study visits (10 [43%] treated with hGH): Hurler syndrome (n=13) average age of 9.8±3.1 years (range 5.3-13.6 years; 54% female) and Hunter syndrome (n=10) average age of 12.0±2.7 years (range 7.0-17.0 years; 0% female). As a group, children with Hurler or Hunter syndrome treated with hGH had no difference in annual change in height (growth velocity) compared to those untreated with hGH. Growth velocity in hGH treated individuals ranged from -0.4 to 8.1 cm/yr and from 0.3 to 6.6 cm/yr in the untreated individuals. Among children with Hunter syndrome, 100% (N=4) of those treated but only 50% of those untreated with hGH had an annual increase in height standard deviation score (SDS). Of the individuals treated with hGH, those with GHD had a trend towards higher annualized growth velocity compared to those without GHD (6.5±1.9 vs. 3.5±2.1; p=.050). Children treated with hGH had greater annual gains in BMD and lean body mass. In conclusion, although as a group we found no significant difference in growth between individuals treated versus not treated with hGH,

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**Conflicts of interest:** WT and PO have no conflicts of interest.

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individual response was highly variable and we are unable to predict who will respond to treatment. Thus, a trial of hGH may be appropriate in children with Hurler or Hunter syndrome, severe short stature, and growth failure. However, efficacy of hGH therapy should be evaluated after 1 year and discontinued if no increase in growth velocity or height SDS. Finally, the long-term benefits of changes in body composition with hGH treatment in this population are unknown.

## Keywords

Mucopolysaccharidosis; Hurler syndrome; Hunter syndrome; growth; growth hormone; body composition

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## 1. Introduction

Hurler syndrome (MPS IH) and Hunter syndrome (MPS II) are lysosomal storage diseases due to deficiency of alpha-L-iduronidase and iduronate-2-sulfatase respectively; each of these enzymes is required for normal degradation of glycosaminoglycan (GAG). Without these enzymes, GAG accumulates throughout the body, resulting in multi-system disease affecting bone, skeletal muscle, heart, lungs, liver and frequently cognitive development [1,2]. Despite treatment with hematopoietic cell transplantation (HCT) for Hurler syndrome or enzyme replacement therapy (ERT) for Hunter syndrome, a moderate to severe short state is characteristic of both Hurler and Hunter syndromes [3–5].

Some children with Hurler or Hunter syndrome and short stature receive treatment with recombinant human growth hormone (hGH) in clinical practice, despite the paucity of data supporting this practice. These treatment decisions rely on a large body of literature showing that hGH has been used safely and successfully to improve growth and increase adult height in children with short stature; including those who are growth hormone deficient [6,7] and those who are not (i.e. Turner syndrome, small for gestational age [SGA], idiopathic short stature [ISS]) [8–11]. Besides the augmentation of growth, treatment with hGH in children with Prader-Willi Syndrome, Turner syndrome, born SGA, and with growth hormone deficiency (GHD) has been shown to increase lean body mass (LBM), bone mineral density (BMD) and exercise performance, and decrease percent body fat [12–17]. However, we are aware of no studies of hGH treatment in Hunter syndrome, and only one retrospective study of hGH treatment in Hurler syndrome, showing a modest improvement in growth velocity over the first year of treatment [18].

There has been concern that treating children with MPS with hGH will worsen skeletal disproportionality based on a report in achondroplasia [19], however another study of hGH treatment in achondroplasia did not find worsening skeletal disproportionality [20]. In addition, it is possible that the hip dysplasia in MPS increases the risk of a known rare complication of hGH treatment – slipped capital femoral epiphysis (SCFE) – as we have previously reported in a small group of children with Hurler syndrome treated with hGH after HCT [18].

Therefore, the objectives of this prospective observational study were to 1) determine if children with MPS treated with hGH have significantly higher annual growth velocity vs.

those not treated, 2) evaluate the safety of hGH treatment in MPS, and 3) determine if children with MPS treated with hGH have greater annual gains in LBM, BMD and less gains in body fat % vs. those not treated.

## 2. Material and methods

### 2.1. Participants

Potential participants were recruited locally, through advertisements in patient advocacy newsletters, [clinicaltrials.gov](http://clinicaltrials.gov), and from patients with Hurler syndrome treated with HCT at our institution. Eligibility requirements were age 5 years and 16 years of age, a confirmed diagnosis of Hurler or Hunter syndrome, and ability to travel to the study center for annual evaluations. Exclusion criteria were pregnancy or participation in a therapeutic clinical trial. All participants with Hurler syndrome had previously been treated with HCT. All participants with Hunter syndrome started on ERT prior to study enrollment. Pubertal Tanner stage (20) was assessed by a trained study physician. GH deficiency was defined as a peak GH level less than 10 ng/ml during arginine and clonidine GH stimulation testing [21]. The University of Minnesota Institutional Review Board approved the study protocol.

### 2.2. Anthropometrics

Sitting and standing heights were measured by wall-mounted stadiometer (without shoes) to the nearest 0.1 cm and the average of three measurements taken. Upper to lower body ratio was calculated as sitting height/(standing height-sitting height). Weight was measured by electronic scale to the nearest 0.1 kg. Body mass index (BMI) was calculated by weight (kg) divided by height (m) squared. Height, weight, and BMI percentiles and standard deviation scores (SDS, also called height-for-age Z scores) were calculated using the SAS program from the Centers for Disease Control [<http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm>, accessed Dec 2012].

### 2.3. Bone density and body composition measurements

Dual-energy x-ray absorptiometry (DXA) total body and lumbar spine scans were performed using a Lunar Prodigy scanner (pediatric software version 9.3; General Electric Medical Systems, Madison, WI). BMD ( $\text{g}/\text{cm}^2$ ) was measured for the total body excluding head and the lumbar spine. Whole body and lumbar spine BMD Z-scores (adjusted for age, gender and ethnicity) were calculated from the GE Lunar Prodigy database. Lumbar spine region of interest was L1-L4; vertebrae were excluded if BMD Z-score for an individual vertebra was 1 SD greater than any other vertebrae and 2 or more vertebrae were required for inclusion in analyses. Body fat (%) and LBM (kg) were determined from whole body scans.

### 2.4. Statistical analysis

Children were included in the analysis only if they had at least 2 annual study visits, so that annual changes in study outcomes could be estimated. During the observational period, individuals treated with hGH for at least 6 months were included in the hGH treated group; those treated for less than 6 months were excluded (N=2). Descriptive statistics are presented as means  $\pm$  standard deviation for continuous variables and as numbers and percents for nominal variables. Student's t-test and Fisher tests were used to analyze cross-

sectional differences between groups at last evaluation (Table 1). LBM, body fat %, total body BMD, and lumbar spine BMD were compared between groups by multivariable linear regression adjusted for age, sex, height and Tanner stage [Table 1]. Mixed-effects longitudinal regression was used to compare average annual change in growth velocity, height SDS, sitting height, and upper to lower body ratio in hGH treated vs. untreated subjects adjusted for age, sex (Hurler syndrome analysis only), and Tanner stage (Table 2); a random intercept for each patient was used to model the correlation between repeated measurements of the same subject. The difference in annual change between hGH treated and untreated subjects was estimated by the difference in age-slope between hGH groups, which was given by the interaction term between age and hGH treatment status. A similar mixed-effects model was used to compare average annual change in LBM, body fat %, total body and lumbar spine BMD in hGH treated vs. untreated subjects adjusted for age, sex (Hurler syndrome analysis only), Tanner stage, and height for LBM, total body and lumbar spine BMD, and for age, sex (Hurler syndrome analysis only), and Tanner stage for body fat % (Tables 2 and 3). Fisher's exact test was used to analyze differences in adverse events between hGH treated vs. untreated subjects (Table 4). Height values were plotted relative to percentiles from the CDC 2000 growth charts [22].

### 3. Results

#### 3.1. Participants

33 participants with Hurler or Hunter syndrome were enrolled; 23 were included in the analysis, with mean follow-up of 1.7 years (range 1.0 – 2.3 years) (Table 1). There were 13 participants with Hurler syndrome, average age at study entry of  $9.8 \pm 3.1$  years (range 5.3-13.6 years; 54% female), and 10 participants with Hunter syndrome, average age  $12.0 \pm 2.7$  years (range 7.0-17.0 years; 0% female). Four (31%) participants with Hurler syndrome had received treatment with ERT peritransplant. Three (23%) participants with Hurler syndrome had been treated with total body irradiation (TBI) prior to HCT. All of the participants with Hunter syndrome were receiving treatment with ERT for the duration of the study and had begun ERT an average of 4.0 years (range 1.1-7.6 years) prior to study enrollment.

Of 23 participants, 10 (43%) were receiving treatment with hGH from their local physicians for at least 6 months (6 Hurler syndrome; 4 Hunter syndrome). Four of the participants receiving hGH treatment had been diagnosed with GHD (2 Hurler syndrome; 2 Hunter syndrome). hGH dose was  $0.34 \pm 0.10$  mg/kg/wk (range 0.18-0.49 mg/kg/wk) and duration  $3.6 \pm 1.4$  years (range 1.4-5.7 years).

#### 3.2. Growth

Participant growth data are shown superimposed on Center for Disease Control 2000 growth charts in Figure 1. Changes in annual growth outcomes between participants treated versus not treated with hGH are detailed in Table 2. Of note, there was no difference in growth velocity for participants with Hurler or Hunter syndrome treated versus not treated with hGH. Growth velocity was however quite variable; in hGH treated individuals growth velocity ranged from -0.4 to 8.1 cm/yr and from 0.3 to 6.6 cm/yr in the untreated

individuals. For individuals with Hurler syndrome, there was no effect of history of TBI, peritransplant ERT, or age at HCT on annual change in height (cm) or height SDS between those treated versus not treated with hGH. Of the individuals treated with hGH, those with GHD had a trend towards higher annualized growth velocity compared to those without GHD ( $6.5 \pm 1.9$  vs.  $3.5 \pm 2.1$ ;  $p = .050$ ).

For all participants, change in height SDS for those treated with hGH ranged from -0.7 to 0.8 SDS compared to -0.7 to 0.3 in those not treated with hGH. All 4 (100%) participants with Hunter syndrome treated with hGH compared to 3 (50%) participants with Hunter syndrome not treated with hGH had an annual increase in height SDS. No participant with Hurler syndrome had an annual increase in height SDS. There was no difference in age, duration of hGH treatment, or hGH dose between those with an annual increase in height SDS and those without an annual increase in height SDS.

### 3.3. Bone density and body composition

Detailed comparison of annual changes in bone density and body composition between participants treated with hGH versus those not treated with hGH divided by diagnosis is shown in Table 3. Participants with Hunter syndrome treated with hGH had a significantly greater annual change in lumbar spine BMD ( $p = .03$ ) and a trend towards increased annual change in total body BMD ( $p = .07$ ) compared to untreated participants. Changes in LBM in participants with Hurler syndrome treated vs. not treated with hGH were significantly higher ( $p = .03$ ); the remaining changes in body composition were no different between groups (Table 3).

### 3.4. Safety concerns

There was no difference in annual change in upper to lower body ratio (Table 2) and no significant difference in adverse events described in Table 4 between treatment groups. However, one individual with Hunter syndrome treated with hGH developed worsening intracranial hypertension (IH) requiring intraventricular shunt placement 4.7 years after starting hGH. The IH was diagnosed by headache that did not resolve with discontinuation of hGH, enlarged ventricles with evidence of transependymal flow on brain MRI, and a central spinal fluid (CSF) opening pressure 3 days after discontinuation of hGH of 35 cm. Opening pressure prior to start of hGH was 24 cm and 1 year after starting hGH treatment was 24.8 cm. Estimated difference in annual change in bone age in hGH treated vs. not treated participants with Hurler and Hunter syndromes was  $0.1 \pm 0.2$  ( $p = .755$ ) and  $-0.6 \pm 0.3$  ( $p = .147$ ) respectively.

## 4. Discussion

In this prospective observational study we found no difference in mean annual growth velocity in the cohorts of children with Hurler or Hunter syndrome treated versus not treated with hGH. However, there was a higher proportion (100%) of children with Hunter syndrome treated with hGH compared to not treated (50%) with hGH that had an annual increase in height SDS. This is particularly significant in that previous studies have shown progressive growth failure (i.e., decreasing height SDS over time) in children with Hurler

and Hunter syndromes [3–5]. Finally, GH deficiency was common in our study population and we speculate related to HCT treatment and/or GAG deposition in the pituitary [23–25].

There are likely multiple factors contributing to the apparent lack of response in growth velocity for children with Hurler or Hunter syndrome treated with hGH. Abnormalities of the growth plate, such as chondrocyte and osteoblast abnormalities, including GAG accumulation, resulting in disorganized epiphyseal elongation and mineralization [26–30], may inhibit the efficacy of hGH treatment. In addition, we have previously shown that children with Hurler syndrome who received total body irradiation after HCT did not respond to treatment with hGH [18] likely due to radiation induced damage to the growth plate [31–33]; although we did not find that TBI was a significant confounder to response to hGH in the current study. Finally, the variability in growth measurements, hGH dosing and duration, combined with a relatively small sample size limited our ability to determine statistical significance.

HGH has been shown to have beneficial skeletal effects. Similar to our findings of increased annual change in BMD in MPS participants treated with hGH, treatment with hGH has been shown to increase bone mineral density and improve peak bone mass accrual in children with GH deficiency, cerebral palsy, and children born small-for-gestational-age [34–37]. This effect on bone is likely mediated through the increased production of insulin-like growth factor-1 (IGF-1) which has been shown in both humans and animal models to stimulate bone turnover in favor of bone formation resulting in increased bone mineral density [34,38–40].

We hypothesized an increased annual change in LBM would be observed in participants with MPS treated with hGH, based on previous reports in other pediatric populations treated with hGH. A positive effect of hGH on body composition is independent of whether a child is GH deficient; children with Turner syndrome, Prader-Willi syndrome, idiopathic short stature and born SGA who are not GH deficient have been shown to have improvements in LBM as well as decreased body fat [11–13,16,17]. In our study, participants treated with hGH had a higher average increase in LBM of 0.4-0.8 kg/year. Changes in body composition could have long-term benefits for bone and cardiovascular health.

Increased growth velocity, with or without treatment with hGH, is associated with progression or onset of scoliosis [41,42]. Thus, there has been concern that treatment of children with syndromes associated with scoliosis (e.g. Prader-Willi syndrome) will result in worsened abnormal spinal curvatures. However, a randomized, controlled clinical trial of hGH in children with Prader-Willi syndrome found no significant difference in progression of scoliosis by X-ray measurement in children treated vs. those not treated with hGH [43]. Although we did not have direct measurements of spinal curvature in our population (we relied on parental report), it is reassuring that we too did not find any difference in progression or new onset of scoliosis or kyphosis between individuals with MPS treated versus not treated with hGH.

One child with Hunter syndrome in our study developed worsening IH during treatment with hGH. IH is a known complication of Hunter syndrome [44–46]. IH is also a rare side effect of treatment with hGH in any population. One review of 57,968 children treated with hGH



in the KIGS (Pfizer International Growth Study database) found the overall incidence of IH to be 27.7 per 100,000 treatment years, with a slightly higher incidence found in children with Turner syndrome and Prader-Willi syndrome (56.4 and 68.3 respectively) and no cases reported in children with ISS [47]. The National Cooperative Growth Study (NCGS) found 61 cases of IH in 54,996 children treated with hGH [48]. The typical onset of IH in children treated with hGH is approximately 0.01 to 1.3 years from initiation of hGH treatment, however 22% of cases were reported more than 2 years after initiation of hGH treatment in the NCGS study [47,48]. The development of IH in our participant treated with hGH was thought most likely due to Hunter syndrome and not hGH treatment, given the presence of mild IH prior to initiation of hGH treatment, the late onset of progression of IH, and persistence after discontinuation of hGH. However, it is impossible to exclude hGH treatment as the stimulus for worsening IH.

This study is limited by being a retrospective observational study in design, and by reliance on the use of parental reports for adverse events. However, we do not think this is a significant limitation, given that all of the participants are followed at least annually for known complications of their disease, which typically includes x-rays for kyphoscoliosis and hip dysplasia, an echocardiogram for cardiac function and valvular disease, brain MRI for ventricular size, and sleep studies for obstructive sleep apnea. Thus, it seems unlikely that significant adverse events known to be associated with hGH treatment were not appreciated. In addition, we have no long-term data on the effect of hGH in this population.

## 5. Conclusions

In conclusion, we found no difference in annual growth velocity in children with Hurler or Hunter syndrome treated with hGH compared to those not treated with hGH in this prospective observational study; individuals with GHD responded better to treatment with hGH than those without GHD. hGH treatment in Hurler or Hunter syndrome may improve body composition and bone mineral density; however, the long-term implications of this are unknown. Finally, we found no safety concerns related to hGH treatment in children with Hurler or Hunter syndrome except for 1 patient with Hunter syndrome with worsening of IH 4.7 years after starting hGH treatment.

Based on our findings, and the variability in response to hGH treatment in these cohorts of children with Hunter or Hurler syndrome, we think a trial of hGH treatment for 1 year in children with Hurler or Hunter syndrome, short stature and growth failure, with or without GHD, with discontinuation of treatment after 1 year if no improvement in growth velocity or change in height SDS, is appropriate. Monitoring before and during treatment with hGH for IH is recommended. Finally, we found that GH deficiency was common in individuals with either Hurler or Hunter syndrome and therefore recommend that individuals should be screened for this annually and treated with hGH if found to be deficient.

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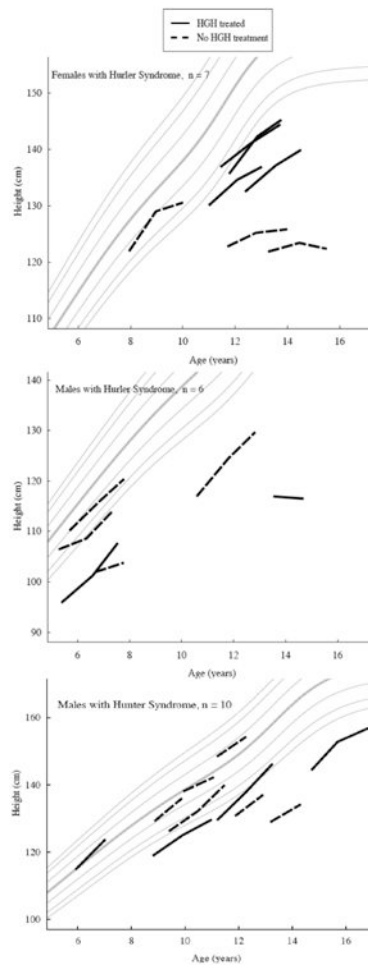
## Abbreviations

**MPS**            Mucopolysaccharidosis

<b>HCT</b>	hematopoietic stem cell transplantation
<b>ERT</b>	enzyme replacement therapy
<b>hGH</b>	recombinant human growth hormone
<b>BMD</b>	bone mineral density
<b>SDS</b>	standard deviation score
<b>GAG</b>	glycosaminoglycan
<b>SGA</b>	small for gestational age
<b>GHD</b>	growth hormone deficiency
<b>LBM</b>	lean body mass
<b>SCFE</b>	slipped capital femoral epiphysis
<b>BMI</b>	Body mass index
<b>TBI</b>	total body irradiation
<b>IH</b>	intracranial hypertension
<b>CSF</b>	central spinal fluid

### Highlights

- We examined safety and efficacy of growth hormone (hGH) treatment in MPS
- Growth velocity was not significantly different in hGH treated individuals
- All children with Hunter syndrome treated with hGH had an increase in height SDS
- Individuals treated with hGH had greater gains in bone density and lean body mass.
- No safety concerns were identified except one child with intracranial hypertension



**Fig. 1.** Change in height by gender for hGH treated (solid line) vs. not treated (dashed line) with Hurler syndrome and Hunter syndrome plotted on CDC 2000 growth charts.

**Table 1**

Population characteristics at study entry.

	hGH treatment (n=10)	No hGH treatment (n=13)	P value Treated vs. untreated
Diagnosis, n (%)			
Hurler syndrome	6 (60)	7 (54)	1.000
Hunter syndrome	4 (40)	6 (46)	
Age, yrs	11±3	10±3	0.436
Sex, %F	4 (40)	3 (23)	0.650
Race, % black	0 (0)	0 (0)	-
Tanner stage			
1	3 (30)	9 (69)	
2-3	2 (20)	1 (8)	0.262
4-5	5 (50)	3 (23)	
GH deficient, yes	4 (40)	0 (0)	0.024
Height, SDS*	-2.4±1.6	-2.0±1.8	0.575
BMI, %*	84±14	65±20	0.022
LBM, kg†	23±7	21±6	0.033
Body fat, %†	27±15	25±12	0.616
Total body BMD, gm/cm <sup>2</sup> †	0.73±0.08	0.73±0.07	0.798
Lumbar spine BMD, gm/cm <sup>2</sup> †	0.66±0.12	0.68±0.15	0.588

Mean ± SD or n(%) are presented. hGH=human growth hormone; GH=growth hormone; SDS=standard deviation score; BMI=body mass index; LBM=lean body mass; BMD=bone mineral density.

\* Relative to age and sex derived from CDC growth data.

† Adjusted for age, sex, height and Tanner stage.



**Table 2**

Annual change in height and height SDS in hGH vs. no hGH treatment groups.

	hGH treatment – no hGH treatment	P value
<b>Hurler syndrome (n=15) <sup>†</sup></b>		
Growth velocity, cm/year	-0.3 (0.4)	.436
Height SDS, SDS/year	-0.07 (0.05)	.168
Sitting height, cm/year	1.2 (1.7)	.466
Upper to lower body ratio	0.05 (0.13)	.694
<b>Hunter syndrome (n=10) <sup>††</sup></b>		
Growth velocity, cm/year	0.5 (1.0)	.642
Height SDS, SDS/year	0.3 (0.2)	.127
Sitting height, cm/year	1.5 (0.8)	.110
Upper to lower body ratio	0.01 (0.01)	.511

Difference between groups estimate (SE). hGH=human growth hormone.

<sup>†</sup> Adjusted for age, sex, and Tanner stage.<sup>††</sup> Adjusted for age and Tanner stage.

**Table 3**

Annual change in body composition in hGH vs. no hGH treatment groups.

	hGH treatment – no hGH treatment	P value
<b>Hurler syndrome (n=15)<sup>†</sup></b>		
LBM, kg/year	0.4 (0.2)	.034
Body fat, %/year*	0.3 (0.7)	.665
Total body BMD, gm/cm <sup>3</sup> /year	.005 (.005)	.371
Lumbar spine BMD, gm/cm <sup>3</sup> /year	.005 (.014)	.749
<b>Hunter syndrome (n=10)<sup>††</sup></b>		
LBM, kg/year	0.8 (0.5)	.155
Body fat, %/year*	-1.9 (1.9)	.333
Total body BMD, gm/cm <sup>2</sup> /year	.019 (.009)	.071
Lumbar spine BMD, gm/cm <sup>2</sup> /year	.036 (.014)	.033

Difference between groups estimate (SE). hGH=human growth hormone; LBM=lean body mass; BMD=bone mineral density.

<sup>†</sup> Hurler outcomes adjusted for age, height, Tanner stage and sex.

<sup>††</sup> Hunter outcomes adjusted for age, height, and Tanner stage.

\* Body fat not adjusted for height.

**Table 4**  
**Frequency of adverse events in hGH treated subjects**

	hGH treatment N =10	No hGH treatment N =13
Worsening ejection fraction?	0	2 (15)
Worsening/new obstructive sleep apnea?	1 (10)	1 (8)
Worsening/new intracranial hypertension?	1 (10)	0
Worsening/new kyphosis or scoliosis?	0	1 (8)
Slipped capital femoral epiphysis (SCFE)?	0	0
If taking GH – injection site reactions?	0	-
Development of diabetes?	0	0

N(%) with adverse event presented.

No significant differences by Fisher's exact test