Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study

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Abstract
Objective: Initial GH-induced catch up growth is highly variable in short children born small for gestational age (SGA) and mainly influenced by age at start of therapy and GH dose. This study compared the first year growth-promoting effect of an individually adjusted GH dose (IAD) versus a fixed high GH dose (FHD) in pre-pubertal children born SGA with severe short stature.

Design: This was a randomized, open-label, multi-center study.

Methods: The FHD group received 0.067 mg/kg per day GH throughout the 12-month study. The IAD group initially received 0.035 mg/kg per day GH; at 3 months the Cologne growth-prediction model for first year change in height SDS was applied; if predicted change was <0.75, GH was increased to 0.067 mg/kg per day for the remaining 9 months, otherwise the initial dose was continued.

Results: In the IAD group, 38 out of the 80 patients required the higher GH dose from month 3. From an ANCOVA for non-inferiority, mean difference in change in height SDS between IAD and FHD groups was −0.24 (95% confidence interval (CI) −0.35: −0.12). the CI for height SDS being above the pre-defined non-inferiority margin of −0.5. GH dose reductions due to IGF-I SDS <0.5 and IGFBP-3 SDS >−0.5 were performed in 4/99 FHD patients, but none of the IAD group patients. Safety data were similar between groups.

Conclusion: With a mean treatment group difference of 1 cm in 12-month growth response, although statistically significant, the IAD group was considered non-inferior compared with the FHD group. Early growth prediction can be used to tailor the dose to the individual patient’s needs, resulting in lower overall GH dose.

Introduction
Current criteria and modalities for GH intervention in short children born small for gestational age (SGA) have been based on a series of clinical studies (1–3). The initial GH-induced catch up growth in these children has been shown to be influenced by age at start of therapy, weight, and height SDS and mid-parental height, as well as GH dose (4). The GH dose has been found to significantly affect growth response during the first years of treatment, but its growth-promoting effects become less pronounced after 4–5 years (during the maintenance phase) (3).

A recently published consensus statement on the management of children born SGA recommends starting treatment with GH doses between 0.035 and 0.070 mg/kg per day (5), which is a relatively large range reflecting the different GH regimens used to date in Europe and the USA. The consensus proposed the higher dose for patients with more marked growth retardation; this dose is up to three times greater than the standard replacement doses used to treat children with GH deficiency. However, the variability of growth response to GH therapy for short children born SGA is considerable, but similar to other indications. Furthermore, a study carried out to final height with two different doses (0.035 and 0.067 mg/kg per day) suggested that there is no dose effect for this long-term treatment, although this needs confirmation in further trials (6).

For the individual patient, the ideal regimen would be based on a dosing algorithm that prospectively selects the appropriate GH dose to achieve a clinically meaningful growth response in relation to the responsiveness of that patient. This treatment strategy will not only optimize the risk/benefit ratio, but will also optimize the benefit/cost ratio of treatment. Such an approach is feasible using growth-prediction models that are suitable to forecast early growth response to GH treatment (7). The OPTIMA study was designed to
examine this approach and is the first study to compare
the effect of an individually adjusted GH dose (IAD)
versus a fixed GH dose in a population of very short
children born SGA. It was hypothesized that children
starting treatment with a low GH dose, which was then
individually adjusted according to the early growth
prediction (within the first 3 months), would show a
growth improvement equivalent to that of children
receiving a fixed high dose GH regimen from the start.
The primary aim of the study was to evaluate whether
the IAD is non-inferior to the fixed high dose regimen
(FHD), as measured by the change in height SDS after
1 year of treatment. The present report describes the
outcomes for growth and safety aspects during the first
year of the study.

Patients and methods

Patients

The patients recruited to the study had to be at least
3 years of age and pre-pubertal, with a bone age ≤9
years in girls and ≤10 years in boys, and a height
SDS ≤−3.0 according to the local country-specific
references. To be defined as born SGA required a birth
weight below the 10th percentile for gestational age
or a birth length more than 2 S.D. below the mean for
gestational age by either local references or pre-specified
references for birth weight and length if no national
standards were available (8–10).

Patients with GH deficiency, any significant signs of
disproportion or underlying non-toxic or genetic
syndromal disease were excluded from the study. The
study was performed according to the declaration of
Helsinki and informed consent for each child was given
by a legal representative or, if capable, the child may
have given documented assent, depending on local laws
and regulations.

Study design and patient groups

This was a randomized, open-label, multi-center study
of GH treatment in pre-pubertal children with short
stature born SGA. The study was designed to demon-
strate non-inferiority of an IAD regimen compared
with a FHD regimen. The study involved 40 investigator
centers in five European countries (Belgium, Germany,
Netherlands, Spain, and UK). The study design is
summarized in Fig. 1. A total of 194 children born
SGA were randomized at a 1:1 ratio to receive GH
(Humatrope®, Eli Lilly & Co.), given as a single daily s.c.
injection, either at a FHD of 0.067 mg/kg per day for
12 months, or at an individualized dose (IAD) regimen
of 0.035 mg/kg per day for 3 months followed by either
dose adjustment to 0.067 mg/kg per day if the predicted
1 year change in height SDS was <0.75 or as
continuation on the starting dose for the remaining 9
months in cases of a predicted gain in height SDS of
≥0.75 during the first year. Of patients randomized to
the FHD group, 96 completed the first 3 months of study
and 89 patients completed the 12-month study, with no
major protocol violations, and were included in the per
protocol population. Of patients randomized to the IAD
group, 88 completed the first 3 months, at which point
48 remained on the low dose and 40 increased GH to
the high dose. Overall, 42 patients completed the
12-month study on the low dose and 38 on the high
dose, with no protocol violations, and were included in
the per protocol population (N = 169).

The individual dose adjustment in the IAD group was
carried out at month 3 based on the ‘Cologne’ growth
prediction model (7). The variables included in this
model are relative bone age retardation, pre-treatment
serum insulin-like growth factor 1 (IGF-I) levels,
urinary deoxypyridinoline (uDPD) measured 1 month
after the start of GH treatment in a 24-hour urine
sample as an early growth response bone marker, and
annualized HV after the first 3 months of therapy.
Predicted HV in the first treatment year can thus be
calculated after 3 months of treatment, using the following equation:

Predicted first year HV (cm/year) = 3.543 + 0.100 × uDPD after 1 month of GH treatment + 0.299 × HV after 3 months of GH treatment − 0.010 × IGF-I at start of GH treatment + 2.377 × relative bone age retardation at start of GH treatment.

The predicted first year height velocity (cm/year) was converted to a predicted change in height SDS, from baseline to 1 year.

In any case, GH dose was to be reduced in both treatment arms to 75% of the last dose if serum IGF-I levels fell below −0.5 SDS, while serum IGFBP-3 levels fell below −0.5 SDS (11). If the IGF-I SDS/IGFBP-3 SDS ratio remained abnormal after a maximum of two dose reductions, the patient was to be discontinued from GH treatment.

**Auxological measurements**

Study participants attended clinic visits at baseline, 3, 6 and 12 months. At each visit, measurements were made of standing and sitting height using a wall-mounted stadiometer, weight by electronic scale, and arm span using a ruler. Height SDS was calculated using central reference data (12), while BMI SDS calculation was based on the formula of Cole (13). Pubertal development was scored at every visit by an experienced investigator using the Tanner criteria.

**Laboratory measurements**

At each study visit, blood samples were taken, serum removed and shipped to a central laboratory (University Children’s Hospital, Giessen, Germany) for determination of IGF-I and IGFBP-3. Concentrations of serum IGF-I and IGFBP-3 were determined by RIA and were converted to SDS according to normal population reference values using established methods (11). The 24-hour urine for assessment of uDPD was collected at home using standardized equipment. A sample was sent at ambient temperature, together with information on total volume, to the central osteologic laboratory (University Children’s Hospital Cologne, Germany), where samples were stored at −20 °C until analyzed. Concentration of uDPD was determined using a commercially available enzyme immunoassay according to the manufacturer’s instructions (IMMULITE Pyrilinks-D, Metra Biosystems Inc., Mountain View, CA, USA), and normalized for urinary creatinine. Fasting glucose and insulin concentrations were measured by local laboratories.

**Safety parameters**

Safety was assessed on all patients who received at least one dose of GH, from reporting of adverse events, glucose and IGF-I/IGFBP-3 concentrations, as well as pubertal and bone age development. Impaired fasting glucose was defined according to WHO criteria (≥ 6.1 but < 7.0 mmol/l for plasma and ≥ 5.6 but < 6.1 mmol/l for whole blood (14)). In addition to standard reporting of adverse events, data were proactively collected by the use of specific directed questions for the following potentially GH-related conditions (in alphabetical order): arthralgia, benign intracranial hypertension, edema, hirsutism, hyperglycemia, hypoglycemia, hypothyroidism, insulin resistance, increase in number or size of cutaneous nevi, neoplastic disease, precocious pubarche, scoliosis, and slipped capital femoral epiphysis.

**Radiological bone age evaluation**

A standard left-hand and wrist radiograph was obtained at baseline and at 1 year for the determination of bone maturation. Bone age was determined locally by the investigator according to the Greulich and Pyle method or Tanner and Whitehouse method. Tanner and Whitehouse values were converted to the equivalent Greulich and Pyle values according to the method described in Wit et al. (15). Absolute bone age delay was calculated as chronological age minus bone age while bone maturation was expressed as the ratio between the change in bone age and change in chronological age for a given visit.

**Statistical analysis**

The non-inferiority margin for the difference (IAD minus FHD) of change in height SDS was defined prior to the statistical analysis in the study protocol and was chosen based on literature data to be −0.5 SDS to reflect the lower limit of a clinically relevant difference. A sample size of 148 per protocol patients was calculated to detect with 80% power that the 95% confidence interval (95% CI) of the between-group difference in change in height SDS would not cross the non-inferiority margin of −0.5, assuming a treatment-group difference of −0.175 SDS, and a common s.d. of 0.7 in each group. The analysis was performed in both the per protocol (N = 169) and full analysis (N = 193) populations and no difference was observed that would affect interpretation. Therefore, efficacy data are presented for the per protocol population only. All safety aspects were analyzed in the safety population comprising all randomized patients receiving at least one GH dose according to the treatment design (N = 193).

The between-group differences in height SDS changes after 1 year were analyzed using an analysis of covariance (ANCOVA) model incorporating treatment group as fixed factor effect and the baseline height SDS as a covariate. The two-sided 95% CI for the mean treatment group difference (IAD minus FHD) in change in 1 year height SDS was calculated based on least
square (LS) means from the ANCOVA model. If the lower limit of this 95% CI was higher than \(-0.5\), IAD treatment was considered to be non-inferior to FHD treatment in terms of growth response. Similar analyses of covariance were performed on absolute height velocity and change in absolute height velocity at 1 year.

Results

One year growth response

Baseline demographic and auxological data of the patients in the two treatment groups are summarized in Table 1. The FHD and IAD treatment groups were very similar in terms of age distribution, with baseline age ranging between 3 and 12 years. Groups were also balanced in terms of gestational age, birth weight and length, and baseline auxological characteristics.

At 3 months of treatment, the mean predicted 1 year change in height SDS was \(0.99 \pm 0.42\) in the FHD group. Based on the growth prediction results at 3 months, 38 out of the 80 patients in the IAD group were changed to the higher dose (IA high dose).

The 1 year growth results for the FHD and IAD group are presented in Figs. 2 and 3, the treatment group comparisons are presented in Table 2. The mean gain in standing height SDS after 1 year of GH treatment was \(1.13\) SDS in the FHD group and \(0.89\) SDS in the IAD group, which was statistically significantly different from zero \((P < 0.001)\) in both treatment arms (Fig. 2). The treatment group difference in change in height SDS (IAD minus FHD, LS mean) was \(-0.24\) with a 95%CI from \(-0.35\) to \(-0.12\), which was above the predefined non-inferiority margin of \(-0.5\) SDS. The 95%CI was narrow and below zero, resulting in a statistically significant p value in favor of the FHD group \((P < 0.001)\). Baseline mean height velocity was \(5.2 \pm 1.5\) and \(5.4 \pm 1.9\) cm/year in the FHD and IAD treatment groups respectively. After 12 months of GH treatment, mean height velocity had increased to \(10.3 \pm 1.9\) cm/year in the FHD and \(9.3 \pm 1.5\) cm/year in the IAD group, corresponding to a gain in height velocity of 5 and 4 cm/year respectively (Fig. 3). From the analysis with the ANCOVA model (Table 2), the LS mean difference in height velocity between the IAD and FHD treatment group was \(-1.01\). This corresponded to a mean difference in height velocity of 1 cm/year for the first year in favor of the FHD group, which was statistically significant \((P < 0.001)\).

Within the IAD group, 38 patients were changed to the higher GH dose (IA high dose), their mean predicted change in 1-year height SDS being \(0.42 \pm 0.28\) at 3 months (Table 3). Nevertheless, the actual change in

<table>
<thead>
<tr>
<th>Table 1 Baseline clinical characteristics.</th>
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<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>Female/male (%)</strong> (%/%)</td>
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<tr>
<td>Female/male</td>
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<tr>
<td><strong>Gestational age (weeks)</strong></td>
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<tr>
<td>Birth weight SDS</td>
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<td>Birth length SDS</td>
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<td>Height (cm)</td>
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<td>Height SDS</td>
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<td>Height velocity (cm/year)</td>
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<tr>
<td>Birth weight SDS</td>
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<tr>
<td>Birth length SDS</td>
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<td>Height SDS–mid-parent height SDS</td>
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height SDS at the end of the first treatment year in this group was comparable with the change in height SDS of the 42 patients who remained on the low GH dose for the entire year (IA low dose; Table 3).

**Bone maturation and pubertal development**

Baseline mean bone age delay was $-2.1 \pm 1.1$ and $-1.9 \pm 1.2$ years in the FHD and IAD treatment groups respectively. After 12 months of GH treatment, mean bone age delay was $1.5 \pm 1.0$ years in the FHD and $1.5 \pm 1.1$ years in the IAD group, corresponding to a bone maturation of $+1.5 \pm 0.8$ and $+1.4 \pm 0.8$ years respectively. Although pubertal onset was not expected during the first year of GH treatment, pubertal signs (Tanner stage genital development in boys and breast development in girls $\geq 2$) were reported in ten patients (three boys and seven girls) in total (two boys and four girls in the FHD group and one boy and three girls in the IAD group).

**Safety**

The safety profile did not differ between treatment groups and reported treatment emergent adverse events were typical for a pediatric population, with nasopharyngitis (8%), pyrexia (4.7%), vomiting (4.7%), and headache (4.2%) reported most frequently. There was one patient (IA high dose) who discontinued treatment due to a local glomerulosclerosis, which was considered to be unrelated to treatment by the investigator, but the patient remained in the study off drug treatment for safety reasons. There were 19 adverse events in 15 patients (eight in the FHD and seven in the IAD group) that were classified by the investigator as possibly related to study drug. These included seven events of specific interest, pro-actively collected: in the FHD group an increase in size or number of melanocytic nevi for two patients, increased serum insulin concentration for one patient and arthralgia also for one patient. In the IAD group one patient with slipped capital femoral epiphysis, one patient with hyperinsulinemia and another patient with edema were reported, all belonging to the IA high dose subgroup.

Baseline IGF-I and IGFBP-3 were $-1.23 \pm 1.39$ and $-0.12 \pm 1.46$ SDS respectively in the FHD group, and $-1.10 \pm 1.31$ and $-0.12 \pm 1.45$ SDS respectively in the IAD group. At year 1, IGF-I and IGFBP-3 values had increased to $1.27 \pm 0.93$ and $1.41 \pm 0.93$ SDS in the FHD group and $0.74 \pm 1.16$ and $1.05 \pm 0.95$ SDS in the IAD group ($0.43 \pm 1.05$ and $0.79 \pm 0.94$ respectively in the IA low dose and $1.10 \pm 1.19$ and $1.36 \pm 0.89$ respectively in the IA high dose group). GH dose reductions due to an IGF-I value above $+0.5$ SDS and IGFBP-3 value below $-0.5$ SDS were performed in 4/99 FHD (4.0%) patients, but no patient in the IAD group had a dose reduction.

Three patients in the FHD and three in the IAD group had a fasting plasma or whole blood glucose value after baseline within the defined range for impaired fasting glucose, but none had two consecutive elevated values within this range. However, for two patients in the FHD and one patient in the IAD group the elevated value occurred at the end of the first year (visit 4) while it returned to normal at visit 4 for the others. Based on the investigators assessment on the local laboratory insulin results, 15 patients in the FHD and 7 patients in the IAD group (four in the IA high dose group) showed at least 0.012).

### Table 2 Comparison of adjusted 1 year change in height velocity and height SDS.

<table>
<thead>
<tr>
<th></th>
<th>FHD group (N= 88)</th>
<th>IAD group (N= 80)</th>
<th>Group difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in height SDS, LS mean(^a)</td>
<td>1.13</td>
<td>0.89</td>
<td>$-0.24$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.05 to 1.20)</td>
<td>(0.81 to 0.98)</td>
<td>$(-0.35$ to $-0.12)$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Absolute HV (cm/year), LS mean(^b)</td>
<td>11.15</td>
<td>10.14</td>
<td>$-1.01$</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(10.57 to 11.73)</td>
<td>(9.53 to 10.74)</td>
<td>$(-1.49$ to $-0.53)$</td>
<td></td>
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</tbody>
</table>

\(^a\) ANCOVA with baseline height SDS, age and sex as covariates.

\(^b\) ANCOVA with baseline height velocity, sex, baseline age, and pubertal development as covariates.

### Table 3 Comparison of growth response for the IA low- and high dose group.

<table>
<thead>
<tr>
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<th>IA low dose (N= 42)</th>
<th>IA high dose (N= 38)</th>
<th>Group difference</th>
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<tbody>
<tr>
<td>Baseline height SDS</td>
<td>$-3.93 \pm 0.59$</td>
<td>$-3.75 \pm 0.64$</td>
<td></td>
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<tr>
<td>Predicted 1 year change in height SDS (prediction at month 3)</td>
<td>$1.08 \pm 0.41$</td>
<td>$0.42 \pm 0.28$</td>
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<tr>
<td>Observed 1 year change in height SDS</td>
<td></td>
<td></td>
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<tr>
<td>Mean change</td>
<td>$0.91 \pm 0.35$</td>
<td>$0.87 \pm 0.34$</td>
<td>$0.03$</td>
</tr>
<tr>
<td>LS mean(^a)</td>
<td>0.90</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.80 to 1.01)</td>
<td>(0.76 to 0.99)</td>
<td>$(-0.13$ to $0.18)$</td>
</tr>
</tbody>
</table>

\(^a\) ANCOVA with baseline height SDS, age and sex as covariates (post-hoc analysis).
one elevated insulin level during the first year. Three out of the four IA high dose patients had only one single insulin measurement above normal (one patient prior to dose adjustment, one patient each at the first visit after dose adjustment and at the end of the first treatment year). The insulin level of the fourth patient was within the normal range at baseline and month 3, and was rated above normal on the two visits following dose adjustment. None of these insulin levels have been rated significantly above normal, except for the one patient whose insulin measurement was elevated prior to dose adjustment and normalized thereafter. Furthermore, the insulin level of one patient in the FHD group and two patients in the remainder of the IAD group were rated as significantly above normal by the investigator.

Discussion

To our knowledge, this is the first study that has applied a growth prediction model (the Cologne prediction model) as a tool for optimizing individual GH dosing in very short children born SGA. GH treatment in short children born SGA is an appropriate setting for individual GH dosing because a range, including relatively high GH doses, has been used to promote growth and a high variability in the growth response to GH has been reported. Any algorithm by which the dose can be reduced in the individual while maintaining a clinically meaningful growth response for a given patient would also reduce the potential risks related to over-stimulation of the IGF-I system and effects on glucose control. Such safety parameters are of particular importance in this population (16).

The study showed that an IAD regimen in short children born SGA is non-inferior to a FHD and the use of high dose GH administration is not required in about half of the patients born SGA, at least for the first year.

The 1 year growth-prediction threshold for dose change was set at a predicted gain in height SDS of \(<0.75\) SDS, which was set to reflect a growth response to GH above the limit considered to be a clinically meaningful response (17, 18). For the purpose of dose-change intervention, use of this threshold resulted in a comparable height response at the end of the first treatment year: the 95% CI of the mean between-group difference in height SDS increase was above the predefined non-inferiority limit of \(-0.5\). According to the Reinken and van Oost reference data, a difference of 0.5 in height SDS translates into \(\sim 2\) cm of absolute height in the age group relevant for this study (19). While Spagnoli and coworkers considered an increase in HV of more than 2.5 cm/year a clinically meaningful response to GH (17), the Lawson Wilkins Pediatric Endocrine Society (LWPES) set this margin to an increase in HV of \(\geq 3\) cm/year (18). Consensus guidelines for the diagnosis and treatment of GH deficiency in childhood and adolescence (20) recommended a decrease in height SDS of \(>0.5\) over 1 year as a criterion to initiate immediate investigation for GH deficiency, indicating that a height difference \(>0.5\) SDS is clinically meaningful. Based on these data, the non-inferiority margin for the height SDS difference between the IAD and FHD group was chosen to be \(-0.5\).

The mean height SDS difference (IAD-FHD) between the two groups of \(-0.24\) translates into an actual growth response in the IAD group that was on average only 1 cm below that of the FHD group at 12 months. The study cohort was not only larger than in other studies but was also more homogenous in terms of baseline height due to the more stringent inclusion criteria of a height SDS equal to or below \(-3\). Furthermore, the individually tailored dose regimen may have resulted in a more homogeneous outcome reflected by the low variability of height SDS in the IAD group. Therefore, the 95% CI for the height SDS difference between IAD and FHD groups was rather small and below zero, leading to a statistically significant test result. The observed low variability of change in height SDS with S.D. values of 0.40 and 0.34 in the FHD and IAD groups respectively was well below the assumed common S.D. of 0.7 for power calculation. Thus, the more pronounced variability in the response to GH treatment seen in other reported SGA populations (S.D. values between 0.44 and 0.7) (1, 21, 22) did not apply to the present study cohort, at least for the first year of treatment. Although statistically significant, the growth response difference of only 1.0 cm between the FHD and IAD group is considered not to be clinically relevant, given the overall good response to GH treatment in both groups.

Within the group assigned to individualized GH treatment, the patients requiring a dose increase at 3 months based on the growth prediction result showed a first year change in height SDS comparable with those patients continuing low dose treatment. Therefore, this GH dose individualization resulted in a non-inferior change in height SDS for the entire IAD group compared with the FHD group.

The dose-adjustment carried out in the present study applies to the first year of GH treatment. It is important to optimize the first year growth response because it has been shown in a clinical prediction model that the most important predictor of the second year response is the height velocity during the first year of GH therapy (4). Apart from a first year dose change, an additional dose adjustment may prove necessary to maintain an adequate growth rate, specifically in those IA low dose patients who did not achieve the predicted gain in height SDS at the end of the first year of treatment.

No difference in the change of bone age between the two dose groups could be detected after 1 year of treatment. Both GH dose regimens were well tolerated with no difference in safety between the treatment groups, specifically for the effects on glucose and insulin levels. The dose-reduction algorithm, according to the...
IGF-I/IGFBP-3 thresholds, was based on published data associating a combination of high IGF-I/low IGFBP-3 levels with a risk of cancer development (11). This was the first time that such an algorithm has been prospectively used in a GH intervention study to monitor dose effects. However, dose reductions were rare and only observed in the fixed high dose group.

In conclusion, the study showed that in short children born SGA an IAD regimen is non-inferior to a FHD regimen. This is the first evidence that early growth prediction can be used to tailor the dose to the individual needs of a given patient resulting in lower overall GH dose, at least during the first treatment year. Longer follow-up of the patient cohort will demonstrate whether this therapeutic approach results in an improved long-term safety profile.

Declaration of interest
H Jung, C Nicolay, and W F Blum are employed by Eli Lilly & Co. H Jung and W F Blum have additional equity interests in Eli Lilly & Co. C Land consults for and has received lecture fees from Eli Lilly & Co. E Schönau consults for and has received grant supports and lecture fees from Eli Lilly & Co. J De Schepper has received lecture fees from Eli Lilly & Co.

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