Ten years’ clinical experience with biosimilar human growth hormone: a review of efficacy data

Abstract: In 2006, the European Medicines Agency (EMA) approved Omnitrope® as a biosimilar recombinant human growth hormone (rhGH), on the basis of comparable quality, safety, and efficacy to the reference medicine (Genotropin®, Pfizer). Data continue to be collected on the long-term efficacy of biosimilar rhGH from several on-going postapproval studies. Particular topics of interest include efficacy in indications granted on the basis of extrapolation, and whether efficacy of growth hormone treatment is affected when patients are changed to biosimilar rhGH from other rhGH products. Data from clinical development studies and 10 years of postapproval experience affirm the clinical efficacy and effectiveness of biosimilar rhGH across all approved indications. In addition, the decade of experience with biosimilar rhGH since it was approved in Europe confirms the scientific validity of the biosimilar pathway and the approval process. Concerns about clinical effect in extrapolated indications, and also about the impact of changing from other rhGH preparations, have been alleviated. Biosimilar rhGH is an effective treatment option for children who require therapy with rhGH.

Keywords: recombinant human growth hormone, Omnitrope®, biosimilar

Introduction

Growth hormone (GH, somatropin) is a potent metabolic hormone that is important for the metabolism of lipids, carbohydrates, and proteins. In children who have a deficiency of endogenous GH, use of GH replacement therapy stimulates linear growth and increases growth rate.1 GH therapy is also approved for pediatric use in other indications, such as children with Turner syndrome (TS) and Prader–Willi syndrome (PWS), short children born small for gestational age (SGA), and children with chronic renal insufficiency.1 In all pediatric indications, early diagnosis and initiation of GH treatment is important for optimizing the effects of treatment. In adults and children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth and by mobilizing body fat.1,2

GH replacement therapy with recombinant human growth hormone (rhGH) has been available since 1985.3 In 2006, the European Medicines Agency (EMA) approved Omnitrope® (biosimilar rhGH; Sandoz, Kundl, Austria) on the basis of comparable quality, safety, and efficacy to the reference medicine (Genotropin®, Pfizer). Data continue to be collected on the long-term efficacy of biosimilar rhGH from several ongoing postapproval studies. Particular topics of interest include efficacy in indications granted on the basis of extrapolation, and whether the efficacy of GH treatment is affected when patients are changed to biosimilar rhGH from other rhGH products. This paper reviews the efficacy of biosimilar rhGH during its clinical development program and the subsequent 10 years of postmarketing clinical use.
Efficacy in Phase III studies

A summary of the clinical studies in the Omnitrope development program is provided in Table 1. The objectives of the Phase III clinical development program for biosimilar rhGH were to demonstrate its therapeutic efficacy and clinical comparability with the reference medicine. The AQ study was a multicenter, randomized, controlled, open-label Phase III study of children (n=89) with growth hormone deficiency (GHD). This study was designed to compare the efficacy and safety of biosimilar rhGH with the reference medicine and also assessed the long-term (7 years of treatment) efficacy and safety of biosimilar rhGH and the reference medicine was demonstrated within 9 months of treatment.

For example, the baseline-adjusted difference between biosimilar rhGH and the reference medicine in mean HV was −0.20 cm/year (95% confidence interval [CI]: −1.34, 0.94) and in mean HVSDS was 0.76 (95% CI: −0.57, 2.10) after 9 months. Long-term efficacy (up to 7 years) of biosimilar rhGH and the reference medicine on radiograph of left hand and wrist

Table 1 Overview of Omnitrope® studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Key objectives</th>
<th>Main inclusion criteria</th>
<th>Treatment</th>
<th>Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQ study 13, 15</td>
<td>Compare the efficacy and safety of Omnitrope® with Genotropin® and assess the long-term efficacy and safety of Omnitrope® lyophilized formulation</td>
<td>• Idiopathic GHD, aged 2–14 years&lt;br&gt;• Prepubertal&lt;br&gt;• Treatment naive&lt;br&gt;• Height &lt;−2.0 SDS&lt;br&gt;• Height velocity &lt;−1.0 SDS&lt;br&gt;• Central radiograph of left hand and wrist</td>
<td>Omnitrope®&lt;br&gt;Primary: height, HSDS, HVSDS&lt;br&gt;Secondary: serum IGF-1 and IGFBP-3</td>
<td>Additional: BA</td>
</tr>
<tr>
<td>Lyo study 13, 15</td>
<td>Assess the long-term efficacy and safety of Omnitrope® lyophilized formulation</td>
<td>• Idiopathic GHD, aged &gt;2 years&lt;br&gt;• Prepubertal&lt;br&gt;• Treatment naive&lt;br&gt;• Height &lt;−2.0 SDS&lt;br&gt;• Height velocity &lt;−1.0 SDS&lt;br&gt;• BA ≥9 years (girls), ≥10 years (boys)&lt;br&gt;• BA over chronological age delay of at least 1 year</td>
<td>Omnitrope®&lt;br&gt;Primary: height, HSDS, HVSDS&lt;br&gt;Secondary: serum IGF-1 and IGFBP-3</td>
<td>Additional: BA</td>
</tr>
<tr>
<td>Spanish study 7, 8</td>
<td>Assess the long-term efficacy and safety of Omnitrope® liquid</td>
<td>• GHD, aged 4–12 years&lt;br&gt;• Prepubertal&lt;br&gt;• Height &lt;−2.0 SDS&lt;br&gt;• Height velocity &lt;−1.0 SDS&lt;br&gt;• Centrally read BA retardation on radiograph of left hand and wrist</td>
<td>Omnitrope®&lt;br&gt;Primary: height, HSDS, HVSDS&lt;br&gt;Secondary: serum IGF-1 and IGFBP-3</td>
<td>Additional: BA</td>
</tr>
<tr>
<td>PATRO Children (ongoing)</td>
<td>Assess the long-term efficacy and safety of Omnitrope®</td>
<td>• Infants, children, and adolescents&lt;br&gt;• Currently or previously receiving Omnitrope® treatment</td>
<td>Omnitrope®&lt;br&gt;Primary: HbA1c, HVSDS&lt;br&gt;Additional: IGF-1, IGFBP-3, body composition, and BMI</td>
<td>Additional: BMI</td>
</tr>
<tr>
<td>SGA study 11, 12 (ongoing)</td>
<td>Assess the efficacy and safety of Omnitrope®, and the long-term effect of Omnitrope® on the development of diabetes in SGA patients</td>
<td>• Prepubertal children born SGA&lt;br&gt;• Height &lt;−2.5 SDS and parental adjusted SDS &lt;−1.0&lt;br&gt;• Birth weight and/or length &lt;−2 SDS&lt;br&gt;• Height velocity SDS &lt;0 during the last year by 4 years of age or later</td>
<td>Omnitrope®&lt;br&gt;Efficacy: height, HSDS, HVSDS&lt;br&gt;Additional: IGF-1, IGFBP-3, fasting plasma glucose, insulin levels, and glyced hemoglobin (HbA1c)</td>
<td>Additional: GI</td>
</tr>
</tbody>
</table>

Notes: ¹Sample size in July 2016; ²sample size in 2015.

Abbreviations: BA, bone age; BMI, body mass index; GHD, growth hormone deficiency; HSDS, height standard deviation score; HV, height velocity; HVSDS, height velocity standard deviation score; SDS, standard deviation score; SGA, small for gestational age.
rhGH was also shown, with significant improvements observed in all four parameters between baseline and end of treatment.\(^5\)

A second study (Lyo study) was a noncomparative study of biosimilar rhGH 5 mg/mL lyophilized formulation in children (n=51) with GHD.\(^4,6\) The primary efficacy parameters assessed were height, HSDS, HV, and HVSDS. Efficacy was demonstrated by statistically significant increases in the efficacy parameters from baseline. For each, the mean differences were statistically significant between baseline and all subsequent visits (up to 48 months; Table 2).

A third study assessed the efficacy and safety of long-term (up to 5 years) treatment with biosimilar rhGH 3.3 mg/mL liquid formulation in children with GHD (n=70).\(^7\) After 4 years, significant increases (compared with baseline) were recorded in mean height (31.1 cm [95% CI: 29.6, 32.6]), HSDS (1.42 [95% CI: 1.13, 1.70]), HV (2.4 cm [95% CI: 1.7, 3.1]), and HVSDS (3.5 [95% CI: 2.7, 4.3]) values. After 5 years, those patients still growing were offered to remain on treatment (as in usual clinical practice) and continued to be monitored to determine adult height (n=39).\(^8\) The results for all auxological parameters evaluated (height, HSDS, and HV) indicate that rhGH therapy elicited a positive growth response and led to normalization of height parameters. In the initial Phase III trial, the projected final height values were an average height gain of 12–18 cm, leading to final adult height of 157.7 cm for females and 167.5 cm for males.\(^7\) At the end of the extension period, the average height gain was 11.6 cm for females and 18.9 cm for males, and the mean adult height achieved was 157.6 cm in females and 165.5 cm in males.

### Efficacy in postapproval studies and extrapolated indications

Several postapproval studies of biosimilar rhGH are ongoing and continue to provide data for biosimilar rhGH in pediatric GHD and also in indications granted on the basis of extrapolation. The PATient TREated with Omnitrope® (PATRO) Children study began in 2006 and is an ongoing, long-term, postmarketing surveillance (PMS) program; the long-term efficacy of biosimilar rhGH is a secondary objective.\(^9\) As of July 2016, 5,007 patients were enrolled in the PATRO Children study; mean (standard deviation [SD]) duration of treatment with biosimilar rhGH was 32.4 (22.8) months.\(^10\) The majority of patients included have GHD (n=2,854, 57%); there are also a relatively large number of patients included with a diagnosis of SGA (n=1,280, 26%), TS (n=228, 5%), and PWS (n=154, 3%). Up to 4 years of treatment with biosimilar rhGH resulted in significant improvements in growth parameters across all indications; height gains were, as expected, greater in naïve patients than in pretreated patients (see Figure 1 for examples – GHD and SGA).\(^10\) Results in different indications are also positive. For example, among TS patients who were GH treatment-naïve on study entry, HSDS improved from –3.05 at baseline to –1.77 at 4 years. Among treatment-naïve PWS patients, HSDS improved from –1.60 to –0.39.

Another ongoing study with biosimilar rhGH is the largest prospective clinical study of rhGH yet conducted in SGA patients.\(^11\) This Phase IV study began in 2007 and has enrolled 278 children, with 249 children completing 2 years of treatment.\(^12\) Treatment with biosimilar rhGH was effective; mean HSDS was –3.39 at baseline, –2.57 at 1 year, and –2.15 at 2 years of treatment. Mean HVSDS (peak-centered) also improved from –2.13 at baseline to +4.16 at 1 year and +2.23 at 2 years.

### Analyses of pooled data from Phase III, Phase IV, and PMS in children

Data from three Phase III studies (interventional), the Phase IV study in SGA children (interventional), and the PATRO Children PMS (observational) were pooled for various analyses of efficacy. This pooled efficacy population consisted of all patients diagnosed with GHD and SGA who had an evaluable height assessment after 6 months of treatment; for PATRO Children, only subjects who

### Table 2 Development of efficacy parameters in the Lyo study\(^4,6\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
<th>No of patients</th>
<th>Mean (SD) height (cm)</th>
<th>Mean (SD) HSDS(^a)</th>
<th>Mean (SD) HV (cm/year)</th>
<th>Mean (SD) HVSDS(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnitrope®</td>
<td>0</td>
<td>51</td>
<td>111.9 (15.5)</td>
<td>–2.97 (0.87)</td>
<td>3.72 (1.40)</td>
<td>–2.52 (1.68)</td>
</tr>
<tr>
<td>5 mg/mL lyophilized formulation</td>
<td>9</td>
<td>51</td>
<td>120.3 (14.4)</td>
<td>–2.25 (0.74)</td>
<td>11.13 (2.81)</td>
<td>6.05 (3.37)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>51</td>
<td>122.3 (14.3)</td>
<td>–2.15 (0.74)</td>
<td>10.39 (2.50)</td>
<td>5.22 (2.96)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>50</td>
<td>123.9 (13.9)</td>
<td>–2.02 (0.73)</td>
<td>9.27 (2.36)</td>
<td>4.01 (2.81)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>50</td>
<td>129.4 (13.9)</td>
<td>–1.76 (0.75)</td>
<td>7.58 (1.63)</td>
<td>2.09 (2.25)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>46</td>
<td>142.8 (14.0)</td>
<td>–1.11 (1.0)</td>
<td>6.3 (1.9)</td>
<td>1.4 (2.5)</td>
</tr>
</tbody>
</table>

Notes: \(^a\)Data based on local growth charts; \(^b\)Tanner peak-centered data.  
Abbreviations: HSDS, height standard deviation score; HV, height velocity; HVSDS, height velocity standard deviation score; SD, standard deviation.
Figure 1 Height SDS (A) and HVSDS (B) for pretreated and growth hormone–naive GHD and SGA patients following 4 years of Omnitrope® treatment.

Abbreviations: GHD, growth hormone deficiency; HVSDS, height velocity standard deviation score; PC, peak-centered; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age.
were GH treatment-naïve on study entry were included. Growth parameters were used as calculated in each original study (local growth references used where possible). Projected height and target height were also calculated. Growth parameters were also separately analyzed for subjects in the Phase III studies (pooled), the SGA Phase IV study, and PATRO Children. The pooled efficacy population comprised 3,582 subjects (3,103 from PATRO Children, 273 from the SGA Phase IV study, and 206 from Phase III studies). Figure 2 shows projected height minus target height for the whole pooled efficacy population, demonstrating clearly the benefit of treatment with rhGH. At the start of the treatment, the difference between projected height and target height was −12.6 cm; after 7 years’ treatment, the difference was only −0.4 cm.

A comparison of growth parameters between subjects in the interventional and observational (PMS) studies is shown in Figures 3 (GHD) and 4 (SGA). The examples shown are

Figure 2 Difference in projected height compared with target height (PH–TH) by visit (whole pooled efficacy population).

Figure 3 HSDS (A) and HVSDS (B) by visit for GHD subjects: comparison of clinical (interventional) and observational (PATRO Children) studies of Omnitrope® (unpublished data, June 2016).

Abbreviations: GHD, growth hormone deficiency; HSDS, height standard deviation score; HVSDS, height velocity standard deviation score.
for patients aged 7–9 years (prepubertal) at baseline. The
efficacy of biosimilar rhGH reported from interventional
studies is confirmed by the data from the PATRO Children
observational study.

**Changing to Omnitrope® from other rhGH treatments**

An analysis of Phase III clinical data assessed the impact
on efficacy and safety of changing from the reference
rhGH medicine to biosimilar rhGH. Changing from the
reference medicine to biosimilar rhGH had no negative
impact on efficacy; growth outcomes and effects on IGF-I
and IGFBP-3 continued as expected and showed no appreciable
difference to children treated continuously with
biosimilar rhGH.

A retrospective study, conducted using an integrated
database, examined the effectiveness of biosimilar rhGH in
children (n=103) with GHD, idiopathic short stature (ISS), and
TS who changed from a non-biosimilar rhGH rhGH
preparation during routine clinical care. The growth trajectory
of rhGH-treated patients were not negatively impacted
by changing to biosimilar rhGH, and growth rates remained
as expected prior to the switch.

**Summary**

Data from clinical development studies and 10 years of
postapproval experience confirm the clinical efficacy and
effectiveness of biosimilar rhGH across all approved indica-
tions. The decade of experience with biosimilar rhGH since it
was approved in Europe affirms the scientific validity of the
biosimilar pathway and the approval process. Concerns about
clinical effect in extrapolated indications, and also about the
impact of changing from other rhGH preparations, have been
alleviated. Biosimilar rhGH is an effective treatment option
for children who require therapy with rhGH.

**Acknowledgments**

Medical writing assistance was provided by Tony Reardon
of Spirit Medical Communications Ltd, funded by Sandoz
GmbH.

**Disclosure**

NH and MZ are employees of Sandoz International GmbH/
Hexal AG. PC has received unrestricted research and edu-
cational grants from Ipsen, Novartis, Novo-Nordisk, and
Pfizer as Head of the Department of Endocrinology and
Reproductive Diseases, Hôpitaux Universitaires Paris-Sud.
PC has served as investigator (principal or coordinator)
for clinical trials funded by Novartis, Pfizer, Ipsen, Ital-
harmaco, Antisense, Prolor Biotech, and Chiasma. PC is
a member of Advisory Boards from Ipsen, Novartis, and
Viropharma. PC has been a member of the Advisory Board
of HypoCCS sponsored by Eli Lilly. PC gave lectures for
Ipsen, Novartis, and Pfizer. All the fees and honoraria are
paid to his institution. The authors report no other conflicts
of interest in this work.

**References**

1. Omnitrope® Summary of Product Characteristics. Available from:
2. Consensus guidelines for the diagnosis and treatment of adults with
growth hormone deficiency: summary statement of the Growth Hormone
Research Society Workshop on Adult Growth Hormone Deficiency.
*J Clin Endocrinol Metab.* 1998;83(2):379–381.
6. Peter F, Romer T, Koehter B, et al. 4 years of treatment with the rhGH Omnitrope® 5 mg/mL lyophilized formulation in growth hormone deficient children: efficacy and safety results. Poster presented at the LWPES/ESPE 8th Joint Meeting; September 9–12; 2009; New York, NY.