Background: Recombinant human insulin-like growth factor-1 (rhIGF-1) is approved in Europe and the US for the treatment of growth failure in children with severe primary IGF-1 deficiency (IGF-1 deficiency in severe growth failure).

The European Incrlex® Growth Forum Database (EU-IGFD) registry was established to monitor the safety and effectiveness of rhIGF-1 (measuring arm) (Novo Nordisk) for height stimulation in children with IGF-1 deficiency.

Subgroups of interest identified from the EU-IGFD registry: patients with and without Laron syndrome (LS) and patients considered as responders or non-responders have previously been described based on effectiveness and safety data.

Here, these subgroups are combined to describe clinically relevant effectiveness and safety data from the EU-IGFD registry.

Objective: To describe clinically relevant subgroups of patients likely to achieve an increase in height in response to rhIGF-1 therapy, together with safety.

Methods
Study design: Data were compiled from this ongoing open-label, multicentre, observational study (EUCTHD20030312, 30 May 2007-31 May 2017). The study was initiated in December 2008 and children from 13 countries in Europe have been enrolled.

Patients: Patients were divided into 5 clinically relevant subgroups.

3 treatment naïve-patients (NPP) subgroups:
- NPP LS (treatment-naïve and prepubertal).
- NPP Non-LS with treatment response (NPP non-LS-responder; responder = year 1 height SDS change ≥ 0.3).

2 subgroups of patients who were not treatment naïve or who were pubertal:
- Non-NPP LS.
- Non-NPP Non-LS.

Assessments at the cut-off date of 10 May 2017:
- Data collected at baseline and during treatment included:

  - Baseline characteristics (demographic and growth parameters).
  - Changes in growth parameters.
  - Safety data collected included:

    - Targeted adverse events (AEs) related to rhIGF-1 and all serious AEs, up to completion in the EU-IGFD registry.

Statistical analyses:
- Height standard deviation score (SDS) was calculated:
  - In France and southern European countries using Semip reference values.
  - In the UK, Belgium, Sweden, and Poland, using UK reference values.

- Annualized height velocity (HV1) (cm/year) was calculated using height values measured at the first point of interest and at 3 years before this time point, divided by the time interval between the 2 measurements (6 months and 3 years).

This analysis was mainly descriptive.

Logistic regression analysis was used to identify baseline predictive factors together with safety.

Results:
Patients: Of 249 patients enrolled, 213 were included in this analysis.

NPP in 30: 2: 2: 1: 0: 1
- NPP-Non-LS: 38: 38: 15: 0: 70

Of 33 patients who were excluded 29 patients had missing treatment response status and 4 patients had missing pubertal status and/or missing data.

Effectiveness (year 2)
- NPP LS and NPP Non-LS responders:
- In addition to NPP non-LS responders, in whom by definition a higher height SDS change was expected, there was a higher change in mean height SDS in patients with NPP LS (Figure 5).

Safety
- Safety is summarised in Figure 2.

- The targeted AE reported in the greatest proportion of patients was hypoglycaemia, except in patients who were NPP non-LS poor-responders. Headache.

Conclusions:
- Patients who were NPP responder better to rhIGF-1 treatment than those who were NPP responders in terms of height SDS and HV improvements at year 1.

- Patients who were NPP with LS were younger and shorter than those who were NPP non-LS at first rhIGF-1 intake, and showed a slightly better response at year 1.

- Compared with other subgroups, patients in the NPP LS and NPP non-LS responders subgroups had:
  - Lower mean age at first rhIGF-1 intake.
  - Higher mean height SDS changes from baseline at year 1.

- Safety is consistent with the known profile of rhIGF-1 in all 5 subgroups.

Table 1: Patient characteristics at baseline (enrolled population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NPP</th>
<th>NPP Non-LS</th>
<th>Non-NPP LS</th>
<th>Non-NPP Non-LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>16</td>
<td>5</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Age (years) at 1/2 intake (mean SD)</td>
<td>11.4</td>
<td>12.5</td>
<td>13.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td>SPIGFD</td>
<td>SPIGFD</td>
<td>LS</td>
<td>NPP LS</td>
</tr>
<tr>
<td>Height velocity (first measurement)</td>
<td>8.3</td>
<td>6.7</td>
<td>9.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Height velocity (year 1)</td>
<td>3.5</td>
<td>3.6</td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Log. of rhIGF-1 (mg/kg body mass)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>TLC (Quick Response) code</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

References:
1. EMA. Increlex - Summary of Product Characteristics 2017

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