Pediatric Phase 2 Data Demonstrate That TransCon hGH Has An Anti-hGH Immunogenic Profile That is Comparable to Daily hGH

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Background

TransCon Growth Hormone is a sustained-release prodrug of recombinant human Growth Hormone (hGH) that releases fully active, unmodified hGH into the blood compartment (Figure 1).

![Image](image1.png)

Figure 1: The TransCon hGH prodrug consists of hGH transiently bound to a polyethylene glycol carrier via a TransCon linker. The released hGH is unmodified, and designed to maintain the same mode of action in the body as daily hGH.

Daily administered hGH replacement therapy:
- Well tolerated, without significant anti-hGH immunogenicity
- Lower titers, non-neutralizing anti-hGH antibodies detected in 8% (7 of 87) of pediatric Growth Hormone Deficient (GHD) subjects treated with Genotropin [1]
- Patients with neutralizing anti-hGH antibodies, may not respond to hGH therapy, and may require long-term IGF-I therapy to facilitate growth
- New sustained-release therapies should maintain a comparable safety profile

TransCon hGH has been shown in a Phase 2 study in GHD children, to be safe and well tolerated, demonstrating an anti-hGH immunogenicity profile comparable to that reported for daily administered hGH.

Objectives

While permanent conjugation of carrier molecules to protein therapeutics has the potential to reduce immunogenicity through epitope shielding [2], the protein-carrier interface can also elicit unwanted immunogenicity [3]. TransCon hGH is designed to leverage the inherent low immunogenicity of recombinant hGH:
- In the prodrug form, the carrier shields both the protein and the protein-carrier interface
- Following release of unmodified hGH, the potentially immunogenic protein-carrier interface is removed

Sensitive anti-hGH binding and neutralizing antibody assays have been developed, validated and assessed to anti-hGH immunogenicity in a Phase 2 clinical study of GHD children and consequently support the TransCon hGH product concept.

Clinical Study Design

Pre-pubertal, treatment-naive, children with GHD (53 treated patients) received:
- Weekly s.c. injections of TransCon hGH (0.14, 0.21 or 0.30 mg hGH/kg/week [n=12, 14 and 14, respectively]) or
- Daily s.c. injections of Genotropin® (0.21 mg hGH/kg/week [n=13])
- Six-month treatment period

Serum samples were collected and assessed for anti-hGH binding and, if appropriate, neutralizing antibodies at:
- Screening, pre-dose at Weeks 1, 5 and 13 and 1 week after the last dose (Week 27)

References:

Immunogenicity Assessment

The potential presence of anti-hGH antibodies was assessed in serum using assays developed and validated in accordance with appropriate regulatory and industry guidelines [4 – 8, inclusive]:

<table>
<thead>
<tr>
<th>Assay Parameter</th>
<th>Binding Assay</th>
<th>Neutralizing Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay Format</td>
<td>Bridging ELISA</td>
<td>Cell-based (N22:11)proliferation assay</td>
</tr>
<tr>
<td>Antibody Evaluation</td>
<td>Screening, confirmation and titration (as appropriate)</td>
<td>Screening and confirmation (as appropriate)</td>
</tr>
<tr>
<td>IsoType Detection</td>
<td>Any hGH-specific IgG based on bridging assay format</td>
<td>IgG, IgM and IgA</td>
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<tr>
<td>Assay Cut-point</td>
<td>Plate specific cut-point derived from normalization factors which assumed a 5% false positive rate (screening assay) based on assessment of 50 male and female children with GHD</td>
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<tr>
<td>Sensitivity</td>
<td>&lt; 500 ng/mL (based on a control antibody)</td>
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<tr>
<td>Interference</td>
<td>Hemolyzed and isometric serum assessed</td>
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</tbody>
</table>

Drug Tolerance

Assessed for TransCon hGH and hGH - confirmed acceptable at typical Cough concentrations in the presence of currently observed treatment-emergent responses

Results – Immunogenicity

One subject (0.14 mg hGH/kg/week; 2.5% of subjects administered TransCon hGH [n=40]) developed a treatment-emergent anti-hGH immune response:
- Detected initially at Week 13
- Titration at Week 27 indicated the presence of very low levels of anti-hGH binding antibodies
- Antibodies confirmed to be non-neutralizing
- Drug levels at Week 27 were confirmed to be below levels considered to significantly interfere with the antibody assays

The presence of anti-hGH antibodies did not appear to impact:
- Pharmacokinetic (TransCon hGH and hGH) or pharamodynamic (IGF-I) profiles compared to antibody negative subjects
- Annualized height velocity (19.0 cm, in the upper half of the treatment cohort)

Conclusion

TransCon hGH has demonstrated an immunogenicity profile in a pediatric population comparable to that observed with daily administered hGH:
- Confirms immunogenicity data for TransCon hGH in two Phase 1 clinical studies in healthy volunteers and a Phase 2 clinical study in adults with GHD (AGHD)
- Detection of anti-hGH binding antibodies at a frequency comparable to that observed for Genotropin® indicates that analytical methodology are fit for purpose to support future clinical development of TransCon hGH

Based on the promising clinical results, the global Phase 3 heGHI Trial in GHD children has been initiated in mid-2016.

Disclosure Statement (Conflicts of Interest): Authors marked 1 above are employees of Ascendis Pharma A/S. The author marked 2 above was the Coordinating Investigator for Ascendis Clinical Study ACP-001_CT-004.