**BACKGROUND**

With growth hormone (GH) receptors on virtually all cells, GH replacement therapy should achieve the same tissue distribution and effects as endogenous GH. Thus, the fundamental challenge of developing a long-acting growth hormone (LAGH) is to create a more convenient GH dosing profile while retaining the same excellent safety, efficacy, and tolerability of daily human growth hormone (HGH), including maintaining GH and resulting IGF-1 levels within the physiologic range.

To create a LAGH that extends the GH half-life thereby allowing less frequent dosing, two basic approaches have been followed: (a) combine unmodified GH with a prolongation technology (a depot, crystal, or prodrug) or (b) modify GH in such a way (protein enragiement or albumin binding) that the GH analogue has a longer half-life. TransCon GH, designed to release unmodified GH, is therefore expected to have the same tissue distribution and receptor activation as daily GH.

**METHODS**

We reviewed LAGHs that have reached various stages of clinical development, categorized them by development approach, and evaluated their status for the indication, pediatric growth hormone deficiency (GHD).

**RESULTS**

Four LAGHs have been developed in which GH half-life extension was achieved by combining unmodified GH with a prolongation technology. Ten LAGHs have been developed in which GH half-life extension was achieved by modifying GH such that its molecular size was increased (or modified with high affinity albumin).

**Approach**

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Design</th>
<th>Pediatric GHD Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GentaTech, Inc.</td>
<td>Nutropin Depot</td>
<td>GH encapsulated in polysaccharide-coglycogenic acid microparticles</td>
<td>Approved in the U.S.; later withdrawn</td>
</tr>
<tr>
<td>LG Life Sciences, Ltd.</td>
<td>LB30002</td>
<td>GH encapsulated in sodium hyaluronate microparticles</td>
<td>Approved but not marketed in Europe; available in South Korea</td>
</tr>
<tr>
<td>Ascendis Pharma A/S</td>
<td>TransCon GH</td>
<td>GH crystallization</td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

**Toranlong**

Permanently PEGylated GH

Available in China

**Novo Nordisk A/S**

Permanently PEGylated GH

Discontinued

**Ambo, Inc.**

Permanently PEGylated and mutated GH

Discontinued

**Teva Pharmaceutical Industries, Ltd.**

GH fused to albumin

Discontinued

**Versartis, Inc.**

GH fused to XTEN

Discontinued

**OPKO Health, Inc.**

GH fused to carboxyterminal peptides

Discontinued

**Novo Nordisk A/S**

Mutated GH attached to an albumin affinity tag

Phase 2

**Genexine, Inc., and Handok, Inc.**

GH fused to an Fc fragment

Phase 2

**Hamni Pharmaceutical Co., Ltd.**

GH fused to an Fc fragment

Phase 2

Of these 14 LAGHs, only 2 have been approved by either the Food and Drug Administration (FDA) or the European Medicines Agency (EMA); both released unmodified GH, thus presumably replicating distribution and pharmacological actions of daily GH.

In contrast to LAGHs that release unmodified GH, 5 of the 10 LAGHs that modify GH have been discontinued. Problems associated with modified GH configurations included lipolysis, inadequate IGF-1 profiles, supraphysiologic GH levels, neutralizing antibodies, inadequate HV, and failure to normalize body composition.

**REFERENCES:**


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**DISCUSSION**

TransCon GH is a LAGH produg in phase 3 development in which GH is transiently bound to an inert carrier. It was designed to sustainably release unmodified GH over 7 days to achieve the same safety, efficacy, and tolerability as daily GH but with more convenient weekly dosing.

In a phase 2 trial of children with growth hormone deficiency (GHD), a similar safety, efficacy and tolerability to daily GH was shown. IGF-1 standard deviation scores (SDS) increased into normal range. Annualized height velocity (HV) was not statistically different from daily GH. Anti-drug antibody formation (immunogenicity) was low and comparable to daily GH, with no neutralizing antibodies.

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**CONCLUSION**

The only LAGHs that have succeeded in replicating both accelerated HV as well as improvement of metabolic profiles observed with daily GH have been formulations that release unmodified GH. A viable LAGH would likely have to maintain the same tissue distribution as endogenous GH, ie, a candidate based on unmodified GH.

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**Appendix:**

<table>
<thead>
<tr>
<th>Dose (GH/kg/week)</th>
<th>Annualized height velocity (cm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.16 mg</td>
<td>9.0 cm</td>
</tr>
<tr>
<td>0.21 mg</td>
<td>9.4 cm</td>
</tr>
<tr>
<td>0.26 mg</td>
<td>9.9 cm</td>
</tr>
<tr>
<td>0.30 mg</td>
<td>10.3 cm</td>
</tr>
</tbody>
</table>

The mean body mass index SDS was stable, similar to daily GH. Adverse events were mild to moderate without lipolysis, also comparable to daily GH. Data from the phase 3 trial in pediatric GHD is expected in 2019.