TransCon™ Growth Hormone in the Treatment of Pediatric Growth Hormone Deficiency

RESULTS OF THE PHASE 3 heiGHt TRIAL

Paul Thornton MB BCh MRCPI, Paul Hofman MD, Aristides K. Maniatis MD, Elena Aghajanova MD PhD, Elena Chertok MD PhD, Maria Korpal-Szczyrska MD PhD, Elene Giorgadze MD PhD, Tatiana Kovalenko MD, Aimee D. Shu MD, David B. Karpf MD, Michael Beckert MD, Jonathan A. Leff MD, and the heiGHt Trial Investigators
Disclosures

Paul Thornton

- Research Investigator: Ascendis Pharma, Zealand Pharmaceuticals, Xeris Pharmaceuticals, OPKO, Pfizer, Novo Nordisk
- Consultant: Endo Pharmaceuticals, Xeris Pharmaceuticals
Growth Hormone Deficiency: Clinical Manifestations are More Than Just Height

<table>
<thead>
<tr>
<th>PEDIATRIC(^1)</th>
<th>ADULT(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Growth failure</td>
<td>• Abnormal body composition</td>
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<tr>
<td>• Abnormal body composition</td>
<td>• Decreased bone mineral density</td>
</tr>
<tr>
<td>• Abnormal metabolic profile</td>
<td>• Dyslipidemia</td>
</tr>
<tr>
<td>• Impaired exercise capacity</td>
<td>• Increased cardiovascular mortality and morbidity</td>
</tr>
<tr>
<td>• Decreased quality of life</td>
<td>• Decreased quality of life</td>
</tr>
</tbody>
</table>

Daily hGH addresses all these symptoms; Long-acting hGH must fully mimic daily hGH to address totality of disease

\(^1\) BMC Endocrine Disorders 2012, 12: 26
\(^2\) J Clin Endocrinol Metab 2006, 91: 1621–1634
TransCon™ hGH Phase 3 Program

- **Pivotal trial**
  - N = 161

- **Switch trial**
  - N = 146

- **Extension trial** (n~300)

- **Regulatory Filings**
Once-weekly prodrug designed to release unmodified hGH and mimic daily hGH:

- Tissue distribution
- Physiological levels
- Therapeutic effects: safety, efficacy, and tolerability
Phase 3 heiGHt Trial

161 treatment-naïve children with GHD dosed (2:1 randomization)

TransCon™ hGH (0.24 mg/kg/week)

Genotropin® (0.034 mg/kg/d = 0.24 mg/kg/week)

Key Inclusion Criteria
• Prepubertal children with GHD
• Height SDS ≤ -2.0
• IGF-1 SDS ≤ -1.0
• 2 GH stimulation tests (GH ≤ 10 ng/mL)
• Bone age ≥ 6 months behind chronological

Objective:
• Demonstrate non-inferiority

Key Endpoints
• Annualized height velocity at 52 weeks (primary endpoint)
• Annualized HV at earlier time points
• Change in HT SDS over 52 weeks
• Change in serum IGF-1/IGFBP-3 levels
• Change in IGF-1 SDS and IGFBP-3 SDS
• Normalization of IGF-1 SDS
• hGH and IGF-1 levels over 168 hours at week 13 (PK/PD subset)
## Demographics and Baseline Characteristics Comparable Between Arms

<table>
<thead>
<tr>
<th></th>
<th>TransCon™ hGH (N=105) Mean</th>
<th>Genotropin® (N=56) Mean</th>
<th>Total (N=161) Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.51</td>
<td>8.48</td>
<td>8.50</td>
</tr>
<tr>
<td>Bone Age (years)</td>
<td>5.84</td>
<td>5.98</td>
<td>5.88</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-2.89</td>
<td>-3.00</td>
<td>-2.93</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-0.32</td>
<td>-0.14</td>
<td>-0.25</td>
</tr>
<tr>
<td>Delta Mid-Parental Height SDS</td>
<td>-2.32</td>
<td>-2.55</td>
<td>-2.40</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>-2.08</td>
<td>-1.96</td>
<td>-2.04</td>
</tr>
<tr>
<td>Peak GH (ng/mL)</td>
<td>5.89</td>
<td>5.48</td>
<td>5.75</td>
</tr>
<tr>
<td>Caucasian (% in race)</td>
<td>95.2</td>
<td>92.9</td>
<td>94.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>81.9</td>
<td>82.1</td>
<td>82.0</td>
</tr>
</tbody>
</table>
TransCon™ hGH Met its Primary Endpoint of Non-inferiority and was Superior to Genotropin® in AHV at Week 52

<table>
<thead>
<tr>
<th></th>
<th>TransCon™ hGH (N=105)</th>
<th>Genotropin® (N=56)</th>
<th>Estimate of Treatment Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean AHV at Week 52 (cm/year)</td>
<td>11.2</td>
<td>10.3</td>
<td>0.86</td>
<td>0.0088</td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.23</td>
<td>0.30</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval (cm/year)</td>
<td>10.71 – 11.62</td>
<td>9.73 – 10.89</td>
<td>0.22 – 1.50</td>
<td></td>
</tr>
</tbody>
</table>

Favoring Genotropin®
Favoring TransCon™ hGH
Non-inferior and superior
Non-inferior but not superior
Non-inferior and inferior

-2.0cm 0cm 1.5cm
Treatment difference (TransCon™ hGH – Genotropin®)

Note: ANCOVA model was applied after missing data were imputed by multiple imputation method.
Change in Height SDS

LS Mean Change from Baseline (+/- SE)

Week 5  Week 13  Week 26  Week 39  Week 52

TransCon™ hGH
Genotropin®

ANCOVA model
Lower Incidence of Poor-Responders with TransCon™ hGH

Poor-responders defined as AHV < 8.0 cm/year

<table>
<thead>
<tr>
<th>At Week 52</th>
<th>TransCon™ hGH (N=104)* n (%)</th>
<th>Genotropin® (N=55)* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>100 (96.2)</td>
<td>49 (89.1)</td>
</tr>
<tr>
<td>Poor-Responder</td>
<td>4 (3.8)</td>
<td>6 (10.9)</td>
</tr>
</tbody>
</table>

* Excludes one subject/group with missing Week 52 data (98.8% subjects completed study)
IGF-1 Profile Over 1 Week of Testing at Week 13 (n = 11)

Mean SDS (+/- SE)

TransCon™ hGH (0.24 mg/kg/wk)

Baseline 0 1 2 3 4 5 6 7

Days (Week 13)

13th Dose
Estimated mean IGF-1 SDS of +0.4 (average trough to peak) for TransCon™ hGH compared to an approximate average IGF-1 SDS of 0.0 for Genotropin® may reflect the different AHV
Summary of Adverse Events: Safety Population

<table>
<thead>
<tr>
<th>Event</th>
<th>TransCon™ hGH N = 105 n (%)</th>
<th>Genotropin® N = 56 n (%)</th>
<th>Total N = 161 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent Adverse Events (TEAE)</td>
<td>81 (77.1%)</td>
<td>39 (69.6%)</td>
<td>120 (74.5%)</td>
</tr>
<tr>
<td>TEAEs Related to Study Drug</td>
<td>12 (11.4%)</td>
<td>10 (17.9%)</td>
<td>22 (13.7%)</td>
</tr>
<tr>
<td>Serious Adverse Events (AEs)</td>
<td>1 (1.0%)</td>
<td>1 (1.8%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Serious AEs Related to Study Drug</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs Leading to Any Action on Study Drug</td>
<td>2 (1.9%)</td>
<td>1 (1.8%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>TEAEs Leading to Discontinuation of Study Drug</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Adverse events for TransCon™ hGH consistent with the type and frequency observed with Genotropin®
- No serious adverse events related to study drug in either arm
- No treatment-emergent adverse events led to discontinuation of study drug in either arm
Preliminary Safety Analyses

• No neutralizing antibodies detected, and transient low level (< 10%) of low-titer non-neutralizing antibodies was similar between the two arms

• Mean fasting glucose and hemoglobin A1c values were stable and within the normal range for both arms

• Two subjects in each treatment arm experienced mild injection site reactions that were considered adverse events
AHV was significantly higher (p=0.0088) with TransCon™ hGH (11.2 cm) compared to daily Genotropin® (10.3 cm).

The incidence of poor responders was ~3x lower in the TransCon hGH arm compared to the daily Genotropin® arm.

IGF-1 SDS levels were modestly higher with TransCon™ hGH than with Genotropin®, reflecting the higher observed AHV in the TransCon™ hGH arm.

No neutralizing antibodies were detected, and the low level (<10 percent) of low-titer non-neutralizing antibodies was similar between groups.

No serious adverse events related to study drug and no treatment-emergent adverse events leading to discontinuation of study drug were observed in either arm.
Conclusions

- Treatment with TransCon™ hGH achieved the primary objective of non-inferiority in AHV at 52 weeks, and further showed superiority over Genotropin®

- AHV was greater for TransCon™ hGH than for the daily hGH at each visit, with the treatment difference reaching statistical significance at week 26 onward

- IGF-1 SDS scores were generally within the normal range following treatment for both groups

- Safety profile of TransCon™ hGH was consistent with daily Genotropin®
## Acknowledgements

The heiGHt Trial Investigators:

### North America
- Aristides Maniatis
- Brad Miller
- Brenden Hursh
- David Repaske
- Deborah Bowlby
- Deborah Counts
- Eva Tsalikian
- Gad Kletter
- Gail Mick
- Gnanagurudasan Prakasham
- Grace Tannin
- Holley Allen
- Jennifer Abuzzahab
- Joshua Yang
- Katie Woods
- Larry Deeb
- Larry Fox
- Laura Cohen
- Luis Gonzalez-Mendoza
- Lydia Snyder
- Mark Kummer
- Maya Hunter
- Naomi Neufeld
- Naznin Dixit
- Patricia Fechner
- Paul Saenger
- Richard Noto
- Robert Rapaport

### Europe & Eastern Europe
- Robin Nemery
- Roy Kim
- Samuel Casella
- Steven Chernausek
- Susan Kingery
- Teresa Quattrin
- Thomas Kelly
- Tim Flannery
- Wendy Brickman

### Europe
- Alicja Korpsz
- Artur Mazur
- Aysehan Akinci
- Carmen Barbu
- Chiara Mameli
- Corina Galesanu
- David Metreveli
- Dmitry Raduk
- Enea Aghajanova
- Elena Bashnina
- Elena Chertok
- Elena Kobalsina
- Elena Giorgadze
- Epis Vlachopapadopoulou
- Evgeniya Mikhailova
- Farida Valeeva
- Gulay Karaguzel
- Julia Skorodok

### Oceania
- Laura Guazzarotti
- Lorenzo Luguetti
- Lubov Samsonova
- Lyudmila Aleksyushina
- Maia Rekhviashvili
- Marco Cappa
- Margarita Kovarenko
- Maria Koral-Szczyska
- Mecyzlaw Walczak
- Mykola Aryayev
- Nataliya Zelinska
- Nihal Hatipoglu
- Nina Botoleva
- Oleg Malievskiy
- Olena Bolshova
- Otilia Marginane
- Sukran Darcan
- Tatiana Kovalenko
- Tatyana Taranushenko
- Teodora Eminnna Dragomir-Ananie
- Tetyana Chaychenko
- Valentia Peterkova
- Violeta Mhova Iotova
- Vladislav Simonov
- Yulia Samoilova
- Zehra Aycan

Special thank you to all of the participating children and their families, as well as study site staff.
Thank You