Future of Growth Hormone Therapy

PENS 2017
Minneapolis, MN
April 27, 2017

Bradley S. Miller, MD, PhD
Associate Professor
Division of Endocrinology
Department of Pediatrics
University of Minnesota Masonic Children’s Hospital

Disclosure

• Dr. Miller is a consultant for Abbvie, Ferring, Genentech, Novo Nordisk, Pfizer, Sandoz and Versartis and has received research support from Alexion, Ascendis, Endo Pharmaceuticals, Genentech, Novo Nordisk, Sandoz, Shire, Tolmar, Ultragenyx and Versartis.
• I will be discussing off-label use of medications including products in development.

Learning Objectives

• Review of normal growth hormone structure and metabolism
• Mechanisms of prolonging growth hormone action
• Review of long-acting growth hormone preparations currently in development
Growth Hormone Structure

- 191 amino acids, 22 kiloDaltons
- 4 alpha helices, 2 disulfide bonds
- Binds to GH receptor dimers via 2 different binding sites that must sequentially bind to the receptors

Physiology of the GH/IGF-I Axis

GHRH = growth hormone releasing hormone
GH-R = growth hormone receptor
GHBP = growth hormone binding protein
IGF-1 = insulin-like growth factor 1
IGFBP-3 = insulin-like growth factor binding protein
IGF-R = insulin-like growth factor receptor
ALS = acid-labile subunit
GH Signaling

- Regulates
  - Growth
  - Metabolism
- Disruption
  - Growth
  - Metabolic
  - Immunologic
- Activation
  - Hematologic
  - Malignancies

ORF. Molecular Endocrinology 28: 1012–1025, 2014

IGF-1 Signaling

- Regulates
  - Growth
  - Proliferation
  - Metabolism
  - Apoptosis
- Disruption
  - Growth
  - Metabolic
  - Neurologic
- Activation
  - XS Growth
  - Soft Tissue
  - Malignancy


How Long does GH last?

- Clearance from circulation
  - Glomerular filtration/renal metabolism
  - Receptor-mediated uptake
  - Extracellular proteases?
- Half life after IV injection: 14-19 minutes
- Half life after SQ injection: 2.1 hours
- Half life after endogenous pulse: ~25 minutes

FDA-Approved Indications for Daily rhGH Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Product</th>
<th>mg/kg/week</th>
<th>mg/kg/week</th>
<th>mg/kg/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHD</td>
<td>Genotropin</td>
<td>0.175</td>
<td>0.1 - 0.3</td>
<td>22 - 45</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin AF</td>
<td>0.245</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin</td>
<td>0.25 - 0.47</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.175 - 0.25</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Syntha-Grow</td>
<td>0.175 - 0.47</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.25 - 0.47</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.3 - 0.67</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin</td>
<td>0.175 - 0.47</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.25 - 0.47</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin</td>
<td>0.3 - 0.67</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.3 - 0.67</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
</tr>
</tbody>
</table>

Approved Daily rhGH Doses

<table>
<thead>
<tr>
<th>Indication</th>
<th>Maker 1</th>
<th>mg/kg/week</th>
<th>mg/kg/week</th>
<th>mg/kg/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHD</td>
<td>Genotropin</td>
<td>0.175</td>
<td>0.1 - 0.3</td>
<td>22 - 45</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin AF</td>
<td>0.245</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin</td>
<td>0.25 - 0.47</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.175 - 0.25</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Syntha-Grow</td>
<td>0.175 - 0.47</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.25 - 0.47</td>
<td>0.24</td>
<td>34</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.3 - 0.67</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Nutropin</td>
<td>0.175 - 0.47</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.25 - 0.47</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>0.3 - 0.67</td>
<td>0.25</td>
<td>35</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
</tr>
<tr>
<td>NS</td>
<td>Humatrope</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
<td>up to 0.6</td>
</tr>
</tbody>
</table>

Not all brands have been approved for each indication. GH dose = mg/kg/week ; mg/kg/day
PWS = Prader-Willi syndrome; GHD = growth hormone deficiency; NS = Nonsuch syndrome
1 One range reflects FDA-approved doses for same indication by different companies
2 May be increased in peds to 1.5mg/kg/week (45mcg/kg/day)
Questions

• What are the benefits of GH therapy?
• Do the benefits outweigh the risks?
   – Primum non nocere (First, do no harm)

Goals of Growth Hormone Therapy

• Attain catch-up growth
• Normalize height during childhood
• Achieve normal height by onset of puberty
• Achieve normal adult height
• Achieve mid-parental target height
• Achieve optimal BMD, muscle mass and body composition

Growth Response to Daily rhGH

Goals of rhGH Therapy

• Have our therapeutic regimens represented adequate replacement of rhGH leading to normalization of growth?

Growth Response to Daily rhGH

Novo ANSWER Registry

Similar NAH Outcomes in the International Registries for GHD
The Use of IGF-1 for monitoring Growth Hormone Therapy

- Since the growth response is dependent upon the responsivity of the individual to both growth hormone and IGF-1, the practice of monitoring IGF-1 and adjusting the growth hormone dose based upon IGF-1 in conjunction with weight and growth velocity has been evolving.

The Use of IGF-1 for monitoring Growth Hormone Therapy

- Rationale - Studies demonstrated that adjusting growth hormone dose to target IGF-1 to +2 SDS improved growth first year growth response compared to standard weight based dosing and targeting IGF-1 to 0 SDS.

IGF-1-based Dosing

![Graph of IGF-1-based Dosing]

Daily rhGH Response

- Near Adult Height responses are nearing the goal of attaining genetic height potential.
- IGF-1 based therapy may bring us closer to that goal. However, adult height data for this practice are not published.

Short-Term Safety of Daily rhGH Therapy


Multiple FDA-mandated Phase IV studies to monitor safety of rhGH

Why a long-acting GH?

- Potential for Improvement
  -- Adherence
  -- Persistence
  -- Growth Response
Compliance with Daily rhGH

Parents of Children (age 5-12)

- “Noncompliant & Skeptical”: 23%
- “Occasionally Noncompliant But Committed”: 41%
- “Perfectly Compliant & Motivated”: 36%

Teens (age 13-17)

- “Noncompliant & Skeptical”: 33%
- “Occasionally Noncompliant But Committed”: 44%
- “Perfectly Compliant & Motivated”: 23%

Study of Adherence: Syringe and Vial

- n=177; 4 month period; New Zealand
- Number of vials returned as measure of compliance
- Good Compliance (≥85%) =34%
- Self-report (66%) vs. Recorded (34%)
- Returned vials associated with HVSDS

Adherence: Vial Collection

- N = 177
- Comparison of adherence levels:
  - Low: >3/week
  - Medium: 1-3/week
  - High: <1/week

Device Recorded Adherence

- easypod™ long-term observation
- n=75 (46 male); 343+/-201 days
- 91.2% Adherent
- Adherence reduced in pubertal (89.1%) compared to prepubertal (96.5%)
- Intra-individual comparison of Growth Velocity and adherence rate revealed no significant correlation

Hartmann, K et al, Horm Res Paediatr 80:1, 2013

Medication Persistence

- Novo Nordisk ANSWER Registry
- GHD (n=826)
- Reasons for Discontinuation
  - Final height achieved (34.9%)
  - Insurance issues (28.0%)
  - Patient and caregiver decision (16.2%)
  - Other (20.9%)

- Nonadherence (3.6%), provider recommendation (1.9%), adverse events (2.5%), lack of follow-up (1.5%), lack of response (0.1%)

Questions About Long-Acting Growth Hormone

• Will they provide physiologic growth hormone release?
• Will IGF-1 levels be similar to daily GH therapy?

How Long does GH last?

• Clearance from circulation
  — Glomerular filtration/renal metabolism
  — Receptor-mediated uptake
  — Extracellular proteases?
• Half life after IV injection: 14-19 minutes
• Half life after SQ injection: 2.1 hours
• Half life after endogenous pulse: ~25 minutes

How do we make an injection of growth hormone last longer?

• Delay absorption from the subcutaneous space
  — Incorporation into microspheres
• Slow clearance from circulation
  — Polyethylene glycol
    • Permanent Pegylation
    • Reversible Pegylation
  — Modify Binding to Serum Proteins
    • Change binding to Albumin
  — Fusion proteins
    • Synthetic polypeptides
    • Naturally occurring proteins
      — Human Chorionic Gonadotropin (hCG)
      — Albumin
    — Immunoglobulin Chains
Nutropin Depot  1999-2004

• Polylactide coglycolide microspheres (PLG)
• Same polymer used for depot leuprolide
• PLG degrades to lactic and glycolic acids
  — Excreted by kidney or metabolized to CO₂ and H₂O
• Initial release of GH by diffusion
• Secondary release by dissolution of microsphere
• Given twice monthly or monthly

Nutropin Depot

• Production discontinued in 2004
  — Manufacturing issues
  — Concern for adverse reactions
    • Large needle size (21G)
  — Concern for inadequate growth response
  — Concern for bone age advancement

Discontinued long acting GH products

• PEGylated GH
  — NNC126-0083 (Novo Nordisk): Insufficient activity for weekly dosing
  — ARX-201 (Ambrx, Inc.): Phase 2 trial completed 2009, no further trials
• Crystalline GH
  — ALTU-238 (Altus Pharmaceuticals): Phase 2 trial in adults completed, company out of business
LB03002

- BioPartners in conjunction with LG Life Sciences
- GH incorporated into Na hyaluronidate microspheres
  - Degraded in tissues by hyaluronidase
- Release rate altered by GH:hyaluronidate ratio
- Reconstituted in MCT oil
- Preclinical studies indicated weekly dosing

LB03002

- Phase III clinical trial in GHD children (n=177)
- Randomized to weekly LB03002 (0.5 mg/kg, n=91) vs. daily GH (30 mcg/kg, n=87) for 1 year
- All subjects received weekly LB03002 in year 2
- Subjects predominately from eastern Europe with severe GHD
  - Mean height SDS = -4.3
  - Mean IGF-1 SDS = -4.2
  - Mean GH peak = 2.1


LB03002

Table 3. All and Changes From Baseline During Once-Wkly LB0302 and Daily GH Treatment for the First Year, and Once-Wkly LB0302 in Both Groups for the Second Year

<table>
<thead>
<tr>
<th></th>
<th>LB03002</th>
<th>Daily GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Ht (cm)</td>
<td>151</td>
<td>163</td>
</tr>
<tr>
<td>Year 1 Ht (cm)</td>
<td>159 ± 2.90</td>
<td>171 ± 2.39</td>
</tr>
<tr>
<td>Year 2 Ht (cm)</td>
<td>166 ± 2.30</td>
<td>174 ± 2.26</td>
</tr>
<tr>
<td>Change Ht (cm)</td>
<td>-7.2 ± 2.30</td>
<td>-11.9 ± 3.49</td>
</tr>
<tr>
<td>Change Ht ≥ 18 to 34 months, mean ± SE</td>
<td>-7.2 ± 2.30</td>
<td>-11.9 ± 3.49</td>
</tr>
</tbody>
</table>

*Last mean 18/m to 34 months from LB0302 with final effect for treatment, age group, gender, and prior baseline height and if of average change.

**P < 0.01 to LB0302 throughout group.

LB03002

- Injection site reactions seen in 47% of LB03002 subjects vs. 22% of daily GH subjects
  - Swelling, pain, erythema, “discoloration” all more common with LB03002
  - 90% of injection site reactions considered mild or moderate
- A1c and FBG not different between groups
  - No change when switching from daily GH to LB03002
- Anti-GH antibodies in 40.7% of LB03002 subjects vs. 4.6% of daily GH subjects
  - Low binding activity, often transient, and no effect on 1st or 2nd year height velocity


LB03002

- Approved by Korean FDA as Declage
- Approved by EMA 8/13 as Somatropin Biopartners
- 0.5 mg/kg subcutaneously weekly
- Indication: GHD
- Not currently marketed outside Korea
- Under FDA review for extended period

Somapacitan (NNC0195-0092)

- Binds to Albumin in the Blood Stream
  - A single-point mutation is introduced into the hGH backbone to which a side chain with a terminal fatty acid with noncovalent albumin-binding properties is added (similar to Victoza® and Levemir®)
  - NNC0195-0092 (Novo Nordisk): Phase 1 trial in children completed in Europe
    - NCT01973244
  - Weekly Administration
    - Phase 2 in children comparing weekly NNC0195-0092 to daily rhGH enrolling now:
      - NCT02616562

www.ClinicalTrials.gov
**MOD-4023 CTP-hGH**

- Fusion protein from Prolor Biotech (now OPKO, partnered with Pfizer)
- 28 amino acid C-terminal peptide from hCG β chain
- Contains 4 glycosylation sites not present on LH, extending half-life

**MOD-4023 hGH-CTP Pharmacokinetic/Pharmacodynamic Model**

- 2-compartment model with first-order elimination
- Indirect model (IGF-1 is not directly related to MOD-4023)

---

**Somapacitan (NNC0195-0092)**

---

---

---
Model Development: Adults with Extensive Sampling

- Fits are generally good
- Apparent clearance is weight proportional
- No other covariates affect PK/PD

When should IGF-1 samples be obtained?

- IGF-1 profile simulated for each subject for Dose 6
- IGF-1 values mapped to IGF-1 SDS
- Mean over dosing interval calculated
- Mean compared to value at each day
- Sample at Day 4 optimally describes mean IGF-1 SDS
MOD-4023 hGH-CTP

Phase 2 trial in GH deficient children

- NCT01592500
- Greece, Hungary, Slovakia
- Low, medium, high dose arms + daily Genotropin arm
- Primary outcome: Height velocity at 1 year
- Weekly dosing with 31G needle

Baseline Characteristics (n=53)

<table>
<thead>
<tr>
<th></th>
<th>MOD-4023</th>
<th>MOD-4023</th>
<th>MOD-4023</th>
<th>Daily hGH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td>Cohort 3</td>
<td>Cohort 4</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>6.5±3</td>
<td>6.5±3</td>
<td>7.0±8</td>
<td>6.4±3</td>
</tr>
<tr>
<td>IH SDS</td>
<td>-3.6±2</td>
<td>-3.8±2</td>
<td>-3.6±2</td>
<td>-3.6±2</td>
</tr>
<tr>
<td>IH SDS – Thr SDS</td>
<td>-3.6±2</td>
<td>-3.6±2</td>
<td>-3.6±2</td>
<td>-3.6±2</td>
</tr>
<tr>
<td>MS SDS</td>
<td>-1.9±3</td>
<td>-1.8±3</td>
<td>-1.8±3</td>
<td>-1.8±3</td>
</tr>
<tr>
<td>Peak GH (ng/ml)</td>
<td>11.0±1</td>
<td>10.8±1</td>
<td>10.8±1</td>
<td>10.8±1</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>-1.7±3</td>
<td>-1.6±3</td>
<td>-1.6±3</td>
<td>-1.6±3</td>
</tr>
</tbody>
</table>


MOD-4023 and IGF-1 SDS Profiles

MOD-4023 hGH-CTP

IGF-1 SDS Profile (Day 4)

MOD-4023 hGH-CTP

Phase 2 Annualized HV from 6 months

<table>
<thead>
<tr>
<th>Dose</th>
<th>hGH Content (mg/kg/w)</th>
<th>n</th>
<th>Mean (cm/yr)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg/kg/w</td>
<td>MOD-4023</td>
<td>11</td>
<td>12.2</td>
<td>3.7</td>
</tr>
<tr>
<td>0.48 mg/kg/w</td>
<td>MOD-4023</td>
<td>9</td>
<td>12.3</td>
<td>2.6</td>
</tr>
<tr>
<td>0.66 mg/kg/w</td>
<td>MOD-4023</td>
<td>12</td>
<td>13.6</td>
<td>5.3</td>
</tr>
<tr>
<td>0.24 mg/kg/w</td>
<td>Genotropin</td>
<td>9</td>
<td>14.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Comparable to ~10 cm/yr in similar GHD patient populations (based upon peak GH and age) published by Bakker (2008) and Ranke (2010).


MOD-4023 hGH-CTP

12 month Height Velocity (n=53)

MOD-4023 hGH-CTP

Safety Concerns

- No severe or serious adverse events
- No lipoatrophy
- No clinically significant local tolerability issues
- No neutralizing antibodies or related adverse events

MOD-4023 CTP-hGH

- Phase 3 clinical trial (NCT02968004) currently recruiting comparing weekly MOD-4023 CTP-hGH to daily GH.

TransCon hGH

- Being developed by Ascendis Pharma.
- Predictable drug release from carrier based upon pH- and temperature-dependent self-cleavage of TransCon linker.
- Delivers un-modified rhGH molecule.
TransCon hGH:
Phase 2 Trial in Children Annualized Height Velocity (6 month)

- Weekly Administration
- Injection site reactions were generally mild and transient and occurred in only a few patients.
- Dose-proportional increase in IGF-I levels into the normal range.

Chatelain, P, et al, JCEM 2017; doi: 10.1210/jc.2016-3776
www.ascendispharma.com/technology

<table>
<thead>
<tr>
<th>Dose Mean (cm/yr)</th>
<th>TransCon hGH 11.9</th>
<th>TransCon hGH 13.9</th>
<th>TransCon hGH 14.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14 mg/kg/w</td>
<td>11.5</td>
<td>12.9</td>
<td>13.9</td>
</tr>
<tr>
<td>0.21 mg/kg/w</td>
<td>Not in Abstract</td>
<td>11.5</td>
<td>14.5</td>
</tr>
<tr>
<td>0.30 mg/kg/w</td>
<td>12.9</td>
<td>13.9</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Phase 3 clinical trial (NCT02781727) currently enrolling comparing weekly TransCon hGH to daily GH.

Somavaratan (VRS-317)

- Fusion protein from Versartis, Inc.
- XTEN sequences of hydrophilic amino acids designed to lack secondary structure and have low antigenicity
- Increase solubility and stability of GH molecule


www.Clinicaltrials.gov
Somavaratan (VRS-317)

- hGH = 22 kDa, VRS-317 = 119 kDa
- XTEN₁ = Increase hydrodynamic diameter
- XTEN₂ = Decrease receptor binding affinity and receptor mediated clearance
- In vitro potency decreased 12 fold
- In vivo potency increased 3-5 fold due to prolonged exposure to receptors


Somavaratan (VRS-317)

- Phase 1 single ascending dose study in GH deficient adults (n=50)
- $T_{1/2} = 131$ hours (5.5 days) at highest dose


Somavaratan in Children

A Randomized Safety and Efficacy Study of Somavaratan (VRS-317), a Long-Acting rhGH, in Pediatric Growth Hormone Deficiency

Wayne V. Moore, Hung JH Nguyen, Gad B. Kletter, Bradley S. Miller, Douglas Popkin, David Ng, Jerome A. Moore, Eric Humphris, Jeffrey L. Cleland, and George M. Bright
Somavaratan in Children

Table 1. Baseline Body Characteristics at Entry of Study Phase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Group</th>
<th>Placebo Group</th>
<th>Placebo Group</th>
<th>Placebo Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>5.1 ± 0.8</td>
<td>5.2 ± 0.8</td>
<td>5.1 ± 0.8</td>
<td>5.2 ± 0.8</td>
<td>5.1 ± 0.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>121 ± 3.5</td>
<td>121 ± 3.5</td>
<td>121 ± 3.5</td>
<td>121 ± 3.5</td>
<td>121 ± 3.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.7 ± 3.2</td>
<td>24.7 ± 3.2</td>
<td>24.7 ± 3.2</td>
<td>24.7 ± 3.2</td>
<td>24.7 ± 3.2</td>
</tr>
</tbody>
</table>

Note: Baseline characteristics represent values at the start of each phase of the study.

Somavaratan Clearance in Children

Somavaratan Action in Children
Somavaratan Action in Children

- 1.15 mg/kg Weekly
- 2.5 mg/kg Twice-Monthly
- 5.0 mg/kg Monthly

Maximal GFI-1 SDS
Maximal Change from Baseline
Mean Change from Baseline


Somavaratan Impact on Growth in Children
6 month data

- ITT Analysis
- N = 25

Annualized Height Velocity (cm/yr)
(Mean ± SD)


Somavaratan Impact on Growth:
12 month HV vs. Historical Controls

Annualized Height Velocity (cm/year)

- Monthly 1.15 mg/kg (n=70)
- 2.5 mg/kg bi-Monthly (n=90)
- 5.0 mg/kg Monthly (n=85)

Somavaran Impact on Growth: 3 years

Starting Doses

Mean Height SDS ±±±±

Baseline Phase 3 Dose

Year 1 Year 2 Year 3

n = 64 48 57 48 48 48

All Evaluable Patients


Somavaratan Height SDS: Comparison With Norditropin® ANSWER Registry

Baseline Year 1 Year 2 Year 3 Year 4 Year 5

Mean Height SDS ±±±±

Somavaran


Somavaran IGF-I SDS

Baseline Year 1 Year 2 Year 3

Mean IGF-I SDS ±±±±

Somavaran

### IGF-I SDS:
Comparison of Peak Levels with Norditropin® ANSWER Registry

![Graph showing IGF-I SDS comparison](image)


### Somavaratan Safety: 3 years
Treatment-Related Adverse Events (AEs) Occurring in >1 Subject

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Months 0-6 (n=64)</th>
<th>Months 6-36 (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>34 (53)</td>
<td>24 (40)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>31 (48)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>6 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Muscle/tendon pain</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Increased IGF-I*</td>
<td>0</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*As reported by treating physician

- No related SAEs, no nodule formation
- Related AEs were generally mild-to-moderate and transient
- Frequency of AEs declined substantially after initial 6 month exposure period
- Dose increase and new formulation gave no change in incidence, type, duration or severity of AE
- Subject withdrawals at expected rate in long-term clinical studies

![Table showing adverse event incidence](image)


### Somavaratan (VRS-317)

- Phase 3 clinical trial (NCT02339090) underway comparing semi-monthly Somavaratan (VRS-317) to daily GH.
  - Phase 3 results expected Fall 2017

![Clinical trial information](image)

www.Clinicaltrials.gov
GENEXINE GX-H9

- hGH linked to a fragment of Fc region of human immunoglobulin
  - Phase 2 trial in children
  - Weekly Administration

LAPS rhGH

- hGH linked to a fragment of the common region of human immunoglobulin via PEG-linker
  - HM10560A: Phase 2 trial in adults completed, safety and efficacy data presented at ENDO 2015
    - NCT01822340
      - Hanmi Pharmaceutical Co (S. Korea)
    - Weekly Administration

Will weekly/twice monthly injections improve compliance?

- Other medications have shown significant improvement in compliance when changing from twice daily to daily, daily to weekly, etc.
- Volume and pain of injection may be key factors.
- Injection Device characteristics will be important
- Missing a dose will likely have a higher negative impact on growth.
Will the risk of side effects change with long-acting growth hormone?

Theoretical Concerns for Long-Acting Growth Hormones
• Changes in the growth hormone molecule will alter the signaling of the molecule at the GH receptor.
• Persistent exposure of the vasculature to high levels of the long-acting growth hormone molecules may change the risk of cardiovascular disease.

What Unique Concerns arise with long-acting GH?
• Effects related to the modified GH molecule
  – Immunogenicity
  – Limited access of modified GH to target tissue
  • Are large fusion proteins able to access target tissue (adipose, growth plate, etc.)
  – Fusion protein specific effects
  – Possible larger injection volume
• Lack of experience with new therapy.
• Lack of knowledge of dose adjustments necessary for individualization of therapy.
  – Amount of dose adjustment necessary for targeted increase or decrease in IGF-1 response.
What Unique Concerns arise with long-acting GH?

• Potential differences in growth response and metabolic activity of GH due to lack of pulsatility.
• Potential increase in risk of malignancy due to persistent GH exposure.

Last Thoughts

• Long acting GH has been sought for many years
• Many attempts, many unsuccessful
• Multiple products appear to be progressing through trials at present
• Most are weekly, one is semi-monthly
• Growth response data will need to be carefully compared based upon trial population

Last Thoughts

• Most products appear to be safe in short term
  – No differences in FBG, A1c
  – IGF-1 maintained in normal range
  – Antibody formation low and/or of low affinity
  – Injection site problems continue, appear to be mild/transient per company reports
• Will need long-term safety data
Need for Long-Term Safety Data

• Due to long-term metabolic, cardiovascular and neoplasia concerns, long-term safety data is increasingly important for patients receiving growth hormone therapy.
• What will be the requirement by
  – Regulatory Agencies?
  – Public?
• Final Height Data?
• Long-term follow-up program?