Safety and Efficacy of Somavaratan (VRS-317), a Long-Acting rhGH, in Children with Growth Hormone Deficiency (GHD): 3-Year Update of the VERTICAL & VISTA Trials (NCT01718041, NCT02068521)

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Disclosures

• Bradley S. Miller, MD, PhD, has received grants from Alexion Pharmaceuticals, Inc., Endo Pharmaceuticals, Genentech, Inc., Novo Nordisk A/S, Orphan Reach/Tolmar, Inc., Sandoz International GmbH, Shire Human Genetic Therapies, Inc. and Versartis, Inc. He has also received honoraria from Ferring Pharmaceuticals, Inc., Genentech, Inc., Novo Nordisk A/S, Sandoz International GmbH, and Versartis, Inc.

• Wayne V. Moore, MD, Patricia Y. Fechner, MD, Huong Jil Nguyen, MD, Quentin L. Van Meter, MD, and John S. Fuqua, MD, are Investigators and have received research support from Versartis, Inc.

• David Ng, PhD, is an employee of ResearchPoint Global, a CRO contracted by Versartis, Inc.

• Eric Humphriss, MBA, and R. William Charlton, MD, are employees and hold equity interest in Versartis, Inc.

• George Bright, MD, is a consultant and holds equity interest in Versartis, Inc.

• Somavaratan (VRS-317) is an investigational agent.
Recombinant Human Growth Hormone (rhGH) for Treatment of Pediatric Growth Hormone Deficiency (GHD)

• Therapeutic potential of daily rhGH is well established and has been the primary treatment for pediatric GHD for three decades\(^1,^2\)

• Current challenges with daily rhGH preparations include burden of daily subcutaneous injections\(^3\)
  – Noncompliance has been reported in up to 77% of adults and children with GHD\(^4,^5\)
  – Reduced efficacy (decreasing HV-SDS) is significantly associated with number of missed doses per week\(^3,^5,^6\)

“[Long-acting growth hormone] compounds may represent an advance over daily GH injections because of increased convenience and differing pharmacodynamic properties, providing the potential for improved adherence and outcomes.”

Growth Hormone Research Society – 2016\(^7\)

HV-SDS, height velocity-standard deviation score
Somavaratan (VRS-317)

- In clinical development for treatment of children and adults with GHD
- XTENylation increases half-life through reduced renal and receptor-mediated clearance
- Drug peak and AUC exposure proportional to dose
- Twice-monthly dosing

### VERTICAL/VISTA Study Design

**NAÏVE TO TREATMENT PRE-PUBERTAL CHILDREN WITH GHD* IN US**

**Phase 2a (Repeat Dose)**

<table>
<thead>
<tr>
<th>Somavaratan Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 mg/kg</td>
<td>Monthly</td>
</tr>
<tr>
<td>2.5 mg/kg</td>
<td>Twice-Monthly</td>
</tr>
<tr>
<td>1.15 mg/kg</td>
<td>Weekly</td>
</tr>
</tbody>
</table>

**Long-Term Safety Study**

<table>
<thead>
<tr>
<th>Somavaratan Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 mg/kg</td>
<td>Monthly</td>
</tr>
<tr>
<td>2.5 mg/kg</td>
<td>Twice-Monthly</td>
</tr>
<tr>
<td>3.5 mg/kg</td>
<td>Twice-Monthly</td>
</tr>
</tbody>
</table>

Same Total Somavaratan Dose Per Month

*GHD confirmed by short stature (height-SDS), 2 or more growth hormone stimulation tests, IGF-I SDS, and delayed bone age

**From the beginning of the second treatment year, all subjects received 3.5 mg/kg somavaratan twice-monthly, based on growth and IGF-I responses observed in Year 1**

**Objective:** To evaluate long-term somavaratan treatment outcomes in PGHD

**NOTE:** As of April 2015, dose formulation changed from 50 to 100 mg/mL

Data cutoff: December 8, 2016

## Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Subjects Enrolled in Phase 2a (N = 64)</th>
<th>Subjects Still in Year 3 (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Age, years, mean (SD)</td>
<td>7.8 (2.4)</td>
<td>7.6 (2.4)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27 (42%)</td>
<td>24 (50%)</td>
</tr>
<tr>
<td>Male</td>
<td>37 (58%)</td>
<td>24 (50%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>53 (83%)</td>
<td>39 (81%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3 (5%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Height SDS, mean (SD)</td>
<td>-2.6 (0.6)</td>
<td>-2.6 (0.6)</td>
</tr>
<tr>
<td>IGF-I SDS, mean (SD)</td>
<td>-1.7 (0.8)</td>
<td>-1.8 (0.8)</td>
</tr>
<tr>
<td>Stimulated GH&lt;sub&gt;max&lt;/sub&gt;, ng/mL, mean (SD)</td>
<td>5.4 (2.6)</td>
<td>5.4 (2.5)</td>
</tr>
<tr>
<td>Bone Age, years, mean (SD)</td>
<td>6.4 (2.4)</td>
<td>6.1 (2.4)</td>
</tr>
</tbody>
</table>

Baseline characteristics are consistent with a pediatric population with moderate GHD.
IGF-I SDS

Somavaratan 3.5 mg/kg twice-monthly from start of 2nd treatment year

Mean initial GH doses in ANSWER were 46.6 ± 12.4 µg/kg/day and 49.6 ± 16.8 µg/kg/day at year 5

NOTE: VISTA results overlaid on top of ANSWER Registry data for comparative purposes. No direct head-to-head comparison has been conducted.

ANSWER, American Norditropin Studies: Web-Enabled Research Program.

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

Mean IGF-I SDS (±SD) across years:
- Somavaratan: n = 64
- ANSWER Registry: n = 2222

IGF-I peak responses and excursions nearly identical to daily rhGH dose in US practice

$a$Somavaratan 3.5 mg/kg twice-monthly from start of 2nd treatment year

$b$Mean initial GH doses in ANSWER were 46.6 ± 12.4 µg/kg/day and 49.6 ± 16.8 µg/kg/day at year 5

NOTE: VISTA results overlaid on top of ANSWER Registry data for comparative purposes. No direct head-to-head comparison has been conducted.

ANSWER, American Norditropin Studies: Web-Enabled Research Program.

Results: Height Velocity (HV) and Height SDS

Increasing the somavaratan dose to 3.5 mg/kg twice-monthly resulted in Year 3 HV comparable to Year 1 and continued improvement in height SDS.
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Increasing the somavaratan dose to 3.5 mg/kg twice-monthly resulted in Year 3 HV comparable to Year 1 and continued improvement in height SDS.
Height SDS: Comparison With Norditropin ANSWER Registry

Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5

-3.5 | -3.0 | -2.5 | -2.0 | -1.5 | -1.0 | -0.5 | 0.0

Somavaratan: 3.5 mg/kg twice-monthly from start of 2nd treatment year

Mean initial GH doses in ANSWER were 46.6 ± 12.4 µg/kg/day and 49.6 ± 16.8 µg/kg/day at year 5

NOTE: VISTA results overlaid on top of ANSWER Registry data for comparative purposes. No direct head-to-head comparison has been conducted.

ANSWER, American Norditropin Studies: Web-Enabled Research Program.

Results: Bone Age/Chronological Age

Bone age/chronological age ratios are consistent with observed changes in daily rhGH registry studies in children with GHD.¹

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Somavaratan 3.5 mg/kg twice-monthly from start of 2nd treatment year

³Mean initial GH doses in ANSWER were 46.6 ± 12.4 µg/kg/day and 49.6 ± 16.8 µg/kg/day at year 5

NOTE: VISTA results overlaid on top of ANSWER Registry data for comparative purposes. No direct head-to-head comparison has been conducted.

ANSWER, American Norditropin Studies: Web-Enabled Research Program.
Results: Metabolism

- Body composition of moderate GHD and non-GHD children is similar\(^1\)
  - Therefore, development in children receiving GH replacement therapy should be comparable to non-GHD children
  - Catch-up growth accompanied by expected and normal increased weight for height
- Somavaratan baseline BMI was within normal range
- Normal $\Delta$BMI SDS over 3 years of somavaratan therapy
  - $\Delta$Height SDS 1.5 exceeds $\Delta$BMI SDS 0.64 over 3 years
- No clinically significant changes in mean HbA\(_{1c}\) were observed with increased exposure to somavaratan
  - Mean HbA\(_{1c}\) was 5.2%, 5.3%, and 5.3% at Months 6, 18, and 30, respectively, compared with 5.2% at study entry\(^*\)
- No development of overt diabetes mellitus

*\(n = 59, 58, 54, \) and 43 for VISTA study entry and Months 6, 18, and 30, respectively
Results: Safety

Treatment-Related Adverse Events (AEs) Occurring in >1 Subject

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</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>2 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Musculoskeletal 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>

ITT Population; Reported in >1 Subjects on Somavaratan for up to 36 months
*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

Somavaratan Safety and Tolerability Profile was Comparable to Daily rhGH
Summary & Conclusions

• Phase 3 somavaratan dose selection supported by 3 year VERTICAL/VISTA study results for subjects switched to 3.5 mg/kg twice-monthly

• Mean peak IGF-I SDS at 3.5 mg/kg twice-monthly was in upper half of normal range over the study duration

• Catch-up growth supported by mean increase in bone age exceeding years on study

• Overall change in height and weight in line with normal body composition changes

• Improvement in HT SDS continued in Year 3

• Long-term IGF-I, HT SDS, and HV findings comparable to ANSWER registry data for daily rhGH

• Phase 3 dose was safe and well tolerated in this study

• Frequency and severity of treatment-related adverse events indicate no safety concerns

3-year experience in line with daily rhGH: Catch-up growth, IGF-I response, bone maturation, metabolic parameters, and safety
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