Somavaratan, a Long-acting Recombinant Human Growth Hormone, for the Treatment of Adults with Growth Hormone Deficiency: Results of VITAL, an Open-label, Dose-finding, International, Phase 2 Study (NCT02526420)

Kevin CJ Yuen, MD, MBChB, FRCP


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• BMKB: Received research grants from Novo Nordisk; Opko; and Versartis, Inc., and has acted as consultant to Novo Nordisk; Pfizer; and Versartis, Inc.

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• MK-H: Consultant, Versartis, Inc.

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• MB: Investigator for Pfizer, Inc.; OPKO; Genexine; and IDS. Speaker for Pfizer, Inc.; Sandoz; and Diasorin. Ad hoc consultant for Versartis, Inc.; OPKO; Sandoz; and Genexine.

• CJS: Medical advisory board member and investigator for Versartis, Inc.

• KSD: Nothing to disclose
Daily administration of GH injections can affect compliance

- Questionnaire on daily GH to 158 adult GHD patients
- High level of noncompliance
- Even in “highly compliant” segment, up to 21 doses missed over 3 months
- Discomfort with injection was one factor strongly correlated with noncompliance

Report from the GRS Workshop on long-acting GH:

- LAGHs have different pharmacodynamic properties
- Offer convenience
- Potential for increased adherence and improved outcomes
- LAGH may be an advance over daily GH, with detailed study needed

Today we will show results from the phase 2 study of somavaratan (VRS-317) in AGHD

Somavaratan: A novel, long-acting form of rhGH

- Rapid absorption with long serum half-life due to delayed clearance\(^1,2\)
- A phase 1 PK/PD study of single-dose administration in AGHD demonstrated:\(^2\)
  - Extended elimination half-life
  - Durable IGF-I response
- Drug peak and AUC exposure proportional to dose\(^2,3\)

rhGH
Same sequence as approved products

IGF-I = insulin-like growth factor 1; PK/PD = pharmacokinetic/pharmacodynamic; rhGH = recombinant human growth hormone.

Phase 2 somavaratan study objectives

Versartis International Trial in Adults with Long-acting Growth Hormone (VITAL)

• Evaluate:
  – Starting dose
  – Dose titration plan
  – Safety

• Determine IGF-I response with 30-day dosing
Methods: Patient selection

Key Criteria

Inclusion
• Aged 23 to 70 years
• Adult GHD diagnosed according to established guidelines¹
• Body-mass index of 19.0–35.0 kg/m²
• Stable pituitary condition and hormone replacement
• rhGH therapy washed out ≥ 14 days

Exclusion
• History of:
  – Diabetes mellitus or inadequate glucose control
  – Malignancy
  – Migraines
• Current significant medical condition
• Untreated adrenal insufficiency or free thyroxine outside the normal reference range

Patients were allocated into 3 starting dose cohorts based on age and oral estrogen use:

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 35 years</td>
<td>Age &lt; 35 years</td>
<td>Females on oral estrogen, regardless of age</td>
</tr>
<tr>
<td>0.6 mg/kg/month</td>
<td>0.8 mg/kg/month</td>
<td>1.0 mg/kg/month</td>
</tr>
</tbody>
</table>
Dosing based on a single ascending dose study in adults

Mean change in IGF-I SDS

Normalization of IGF-I SDS

X Placebo

▲ 0.05 mg/kg

■ 0.10 mg/kg

□ 0.20 mg/kg

● 0.40 mg/kg

○ 0.80 mg/kg

Study design

- Patients received 5 monthly SQ doses of somavaran in clinic.
- Target IGF-I SDS (mean of pre-dose and Day 8): 0 to 1.5.
- 4 dose adjustments were permitted until 2 consecutive means were within the target range.

IGF-I = insulin-like growth factor; SDS = standard deviation score; SQ = subcutaneous.
Results: Patient disposition

Screened
n = 49

Screen Failure
n = 13

Treated
n = 36

Cohort A (n = 22)
Age ≥ 35 years
0.6 mg/kg/month

Completed
n = 21 (96%)

Cohort B (n = 6)
Age < 35 years
0.8 mg/kg/month

Completed
n = 4 (67%)

Cohort C (n = 8)
Females on estrogen
1.0 mg/kg/month

Completed
n = 7 (88%)
### Patient baseline characteristics (N=36)

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>COHORT</th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 22)</td>
<td>(n = 6)</td>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>54 ± 10</td>
<td>30 ± 2</td>
<td>38 ± 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (64)</td>
<td>4 (67)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 4</td>
<td>27 ± 5</td>
<td>27 ± 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87 ± 17</td>
<td>79 ± 19</td>
<td>76 ± 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline IGF-I SDS</td>
<td>-0.53 ± 1.32</td>
<td>-2.89 ± -2.89</td>
<td>-2.29 ± 1.69</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

BMI = body-mass index; IGF-I = insulin-like growth factor 1; SDS = standard deviation score; min, max = minimum, maximum.
IGF-I response to the first and fifth injection across 30 days

Mean IGF-I SDS for all patients

- Robust IGF-I response at Day 8
- IGF-I returned to baseline by Day 22

Dose 1, n: 36 36 36 35
Dose 5, n: 33 33 32 31
IGF-I response by cohort

Mean IGF-I SDS after Dose 1

- Cohort A (n=22)
- Cohort B (n=6)
- Cohort C (n=8)

In each cohort, IGF-I returned to baseline by Day 22
More frequent administration needed
Somavaratan starting dose and titration

Somavaratan dose for each injection

Mean dose, mg (SE)

Cohort A
n = 22

Cohort B
n = 6

Cohort C
n = 8
## Target IGF-I SDS after Dose 5

### Patients with Mean IGF-I SDS between Pre-dose and Day 8 within target range (0 to 1.5)

<table>
<thead>
<tr>
<th>COHORT</th>
<th>DOSE, mg (min, max)</th>
<th>A (n = 22)</th>
<th>B (n = 6)</th>
<th>C (n = 8)</th>
<th>OVERALL (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>51.3</td>
<td>62.7</td>
<td>75.9</td>
<td>58.7</td>
</tr>
<tr>
<td></td>
<td>(31.5, 60.0)</td>
<td>(45.2, 80.0)</td>
<td>(55.0, 95.4)</td>
<td>(31.5, 95.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>37.1</td>
<td>79.0</td>
<td>172.3</td>
<td>70.9</td>
</tr>
<tr>
<td></td>
<td>(13.4, 61.8)</td>
<td>(41.5, 137.8)</td>
<td>(50.0, 400.0)</td>
<td>(13.4, 400.0)</td>
<td></td>
</tr>
</tbody>
</table>
### Treatment-related adverse events (AEs) occurring in > 1 subject

<table>
<thead>
<tr>
<th>AEs</th>
<th>COHORT</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (n = 22)</td>
<td>B (n = 6)</td>
<td>C (n = 8)</td>
<td>OVERALL (n = 36)</td>
<td></td>
</tr>
<tr>
<td>All AEs n (%)</td>
<td>7 (32)</td>
<td>5 (83)</td>
<td>3 (38)</td>
<td>15 (42)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (14)</td>
<td>1 (17)</td>
<td>0</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (9)</td>
<td>0</td>
<td>0</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (9)</td>
<td>1 (17)</td>
<td>1 (13)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>1 (5)</td>
<td>1 (17)</td>
<td>0</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (13)</td>
<td>2 (6)</td>
<td></td>
</tr>
</tbody>
</table>

- Nearly all patients experienced ≥ 1 AE, with 55% presenting no related AEs
- No related SAEs were reported
- Related AEs were generally mild, transient, and consistent with the safety profile of daily rhGH

AE = adverse event; rhGH = recombinant human growth hormone; SAE = serious adverse event.
Summary and conclusions

• Somavaratan was safe in adults
• Somavaratan induced a robust IGF-I response in adult patients with GHD
• IGF-I levels returned to pre-dose levels by day 22
• This study provided the needed information to optimize somavaratan treatment in AGHD, including the:
  – Starting dose
  – Titration plan
  – Dosing frequency
• Lower starting somavaratan doses administered twice-monthly are being investigated in the extension study* and will be used in a phase 3 study

*NCT02719990, protocol 15VR8
Acknowledgements

Thanks to:

- Patients who participated
- Nurses and study coordinators
- Versartis for study funding
- JB Ashtin for editorial assistance
Backup Slides
### Glucose and hemoglobin A1c

<table>
<thead>
<tr>
<th>MONTH 5 RESULTS</th>
<th>A (n = 22)</th>
<th>B (n = 6)</th>
<th>C (n = 8)</th>
<th>OVERALL (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting plasma glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (4.5)</td>
<td>0</td>
<td>0</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Normal</td>
<td>19 (86.4)</td>
<td>5 (83.3)</td>
<td>6 (75.0)</td>
<td>30 (83.3)</td>
</tr>
<tr>
<td>High</td>
<td>1 (4.5)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (4.5)</td>
<td>0</td>
<td>2 (25.0)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td><strong>Hemoglobin A1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>21 (95.5)</td>
<td>6 (100)</td>
<td>7 (87.5)</td>
<td>31 (94.4)</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (4.5)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>2 (5.6)</td>
</tr>
</tbody>
</table>

Data are n (%).
Somavaratan dose titration

- Used the SDS of the mean of IGF-I values from pre-dose and Day 8 (7 days after dosing)
- Adjusted until 2 consecutive means of pre-dose and Day 8 target IGF-I SDS were within the target range

<table>
<thead>
<tr>
<th>Prespecified Dose Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEAN IGF-I SDS</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Upward Dose Titration*, % Dose Increase</td>
</tr>
<tr>
<td>–0.50 to –0.01</td>
</tr>
<tr>
<td>–0.51 to –2.00</td>
</tr>
<tr>
<td>&lt; –2.00</td>
</tr>
<tr>
<td>Downward Dose Titration, % Dose Decrease</td>
</tr>
<tr>
<td>1.51 to 2.00</td>
</tr>
<tr>
<td>2.01 to 3.00</td>
</tr>
<tr>
<td>&gt; 3.00</td>
</tr>
</tbody>
</table>

*Maximum allowable dose is 5.0 mg/kg
IGF-I SDS returned to pre-dose levels by Day 22

Mean IGF-I SDS After Dose 5

- Cohort A, n: 22
- Cohort B, n: 22
- Cohort C, n: 21

Day 1
Cohort A: 22
Cohort B: 22
Cohort C: 21

Day 8
Cohort A: 4
Cohort B: 4
Cohort C: 4

Day 22
Cohort A: 7
Cohort B: 7
Cohort C: 7

IGF-I SDS = insulin-like growth factor 1 standard deviation score.
Dose effect on IGF-I response

- Subjects who received higher total doses tended to have higher IGF-I responses

<table>
<thead>
<tr>
<th>COHORT</th>
<th>$r$</th>
<th>MODEL $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.652</td>
<td>0.425</td>
</tr>
<tr>
<td>B</td>
<td>0.844</td>
<td>0.713</td>
</tr>
<tr>
<td>C</td>
<td>0.339</td>
<td>0.115</td>
</tr>
<tr>
<td>Total</td>
<td>0.148</td>
<td>0.022</td>
</tr>
</tbody>
</table>

IGF-I = insulin-like growth factor 1; SDS = standard deviation score.
## Treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>A (n = 22)</th>
<th>B (n = 6)</th>
<th>C (n = 8)</th>
<th>OVERALL (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs, n</td>
<td>90</td>
<td>35</td>
<td>43</td>
<td>168</td>
</tr>
<tr>
<td>Patients who experienced AEs, n (%)</td>
<td>21 (96)</td>
<td>5 (100)</td>
<td>8 (100)</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Severity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>6 (27)</td>
<td>3 (50)</td>
<td>3 (38)</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (59)</td>
<td>3 (50)</td>
<td>5 (63)</td>
<td>21 (58)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Life threatening</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>3 (14)</td>
<td>0</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Nearly all patients experienced ≥ 1 AE
- Most AEs were mild or moderate in intensity