Safety and Hemoglobin Effect of Sotatercept, Administered Intravenously and Subcutaneously, for Maintenance of Hemoglobin in Hemodialysis Subjects: Interim Analysis of a Phase 2 Study

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Presented at: the 48th Annual American Society of Nephrology Kidney Week; November 3-8, 2015; San Diego, CA.

This study was sponsored by Celgene Corporation.
Disclosures

- Frank Dellanna has received fees as a speaker for Mitsubishi, Otsuka, Roche, and Sandoz/Hexal
- Francisco Maduell has received fees as a speaker for Amgen, Baxter, Bellco, Fresenius, and Nipro
- Joan Fort has received fees as a speaker for Baxter
- Xavier Warling has nothing to disclose
- Hem Nalini Singh is an employee of and shareholder in Celgene Corporation
- William T. Smith is an employee of and shareholder in Celgene Corporation, and is a shareholder in Johnson & Johnson
Introduction

- Patients with ESKD exhibit anemia, primarily caused by decreased renal biosynthesis of erythropoietin\(^1\)

- Sotatercept (ACE-011) is an ActRIIA-IgG1 fusion protein that binds with high affinity to activin A and other members of the TGF-β superfamily that are negative regulators of erythropoiesis, thereby promoting the release of mature erythrocytes\(^2,3\)

- Sotatercept is being studied in ESKD subjects on HD in 2 ongoing studies:
  - For the correction of anemia in the ongoing REN-001 study in the US\(^4\)
    - REN-001 is also evaluating sotatercept’s effects on CKD-MBD; preliminary results show a slowing of progression of vascular calcification and increased cortical bone mass\(^5\)
  - Interim findings are presented here from an ongoing randomized study (REN-002) evaluating sotatercept, IV and SC, for maintenance of Hb in ESKD subjects on HD

ESKD=end-stage kidney disease; ActRIIA=type II activin A receptor; TGF-β=transforming growth factor-beta; HD=hemodialysis; CKD-MBD=chronic kidney disease and mineral/bone disorder; IV=intravenous; SC=subcutaneous; Hb=hemoglobin.

REN-002 Study Design

Screening randomization: 1:1
ESA-free period* (Day −30 to Day −1)

Sotatercept
IV 0.1 mg/kg
SC 0.13 mg/kg
each group: n ~6–9

Completed
q14d, up to 8 doses unless rescued† or discontinued early
Evaluate PK and safety 14 days after 6th subject is dosed with 3rd IV/SC dose; home BP monitored throughout

Sotatercept
IV 0.2 mg/kg
SC 0.26 mg/kg
each group: n ~6–9

Completed
q14d, up to 8 doses unless rescued† or discontinued early
Evaluate PK and safety 14 days after 6th subject is dosed with 3rd IV/SC dose; home BP monitored throughout

Intra-subject dose-escalation‡

Screening randomization: 2:1
ESA-free period* (Day −30 to Day −1)

Sotatercept
IV 0.1/0.2/0.3/0.4 mg/kg
(n ~12–18)

Currently enrolling

Sotatercept
SC 0.4/0.5 mg/kg
(n ~6–9)

Follow-up phase for 112 days for PK and safety

q14d, up to 8 doses unless rescued† or discontinued early
Evaluate PK and safety after 12 IV and 6 SC subjects are dosed with 3rd IV/SC dose; home BP monitored throughout

*ESA-free period of 5 to 10 days began following randomization, before first dose of sotatercept; duration was dependent on ESA and route of administration.
†If Hb was <9.0 g/dL, subjects were given rescue treatment with an ESA or blood transfusion and discontinued study drug, but remained in study for safety follow-up.
‡With sotatercept, IV or SC, dose could be increased if: 1) Hb increased <1 g/dL from baseline, or 2) Hb was <10 g/dL, within 7 days before dosing.

BP=blood pressure; ESA=erythropoiesis-stimulating agents; PK=pharmacokinetics.
Subject Disposition

- 36 subjects were randomized and received ≥1 dose of study medication

*Subject met stopping rule criteria for elevated blood pressure (BP). †Subject met stopping rule for elevated Hb (>13.0 g/dL for >7 days).
‡Findings for subjects in the highest sotatercept dosing groups (IV 0.1-0.4 mg/kg; n=2; SC 0.4-0.5 mg/kg; n=2) are not presented due to insufficient post-baseline follow-up data; enrollment in these groups is ongoing.
Baseline Demographic Characteristics of Randomized Subjects  
(Dose Groups 1 and 2)

<table>
<thead>
<tr>
<th></th>
<th>Sotatercept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV 0.1 mg/kg</td>
</tr>
<tr>
<td></td>
<td>n=7</td>
</tr>
<tr>
<td>Age, mean, years</td>
<td>59.0</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Postdialysis weight, mean, kg</td>
<td>78.7</td>
</tr>
<tr>
<td>Body mass index, mean, kg/m²</td>
<td>26.8</td>
</tr>
<tr>
<td>Hemoglobin, mean, g/dL</td>
<td>11.0</td>
</tr>
</tbody>
</table>
Sotatercept Pharmacokinetics by Route of Administration and Dose

- For 24 subjects with evaluable data (IV: n=12; SC: n=12), sotatercept AUC and $C_{\text{max}}$ are higher when administered IV vs. SC
- Mean AUC$_{\text{\infty}}$ is increased by ≤41% in response to a 100% increase in dose levels for both dosing routes of administration
- Mean $t_{1/2}$ in serum ranged from 12 to 26 days

### Sotatercept PK Parameters*

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>IV 0.1 mg/kg n=7</th>
<th>IV 0.2 mg/kg n=5</th>
<th>SC 0.13 mg/kg n=7</th>
<th>SC 0.26 mg/kg n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$, $\mu$g/mL</td>
<td>2.3 (28.5)</td>
<td>2.8 (69.8)</td>
<td>1.1 (38.0)</td>
<td>0.9 (20.9)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, day</td>
<td>NA</td>
<td>NA</td>
<td>8 (4–13)</td>
<td>12 (1–18)</td>
</tr>
<tr>
<td>AUC$_{\text{\infty}}$, day*$\mu$g/mL</td>
<td>48.2 (79.7)</td>
<td>67.7 (29.6)</td>
<td>34.5 (39.5)</td>
<td>45.5 (13.7)</td>
</tr>
<tr>
<td>CL or CL/F, mL/day</td>
<td>158 (109.8)</td>
<td>208 (39.8)</td>
<td>298 (56.4)</td>
<td>409 (32.5)</td>
</tr>
<tr>
<td>$t_{1/2}$, day$^\dagger$</td>
<td>18.6 (42.7)</td>
<td>12.2 (96.6)</td>
<td>26.0 (35.3)</td>
<td>22.9 (31.0)</td>
</tr>
</tbody>
</table>

Note: The n reflects the number of randomized subjects who underwent PK testing; actual number of subjects with data available for each parameter may vary. Pharmacokinetic parameters are estimated using a 2-compartment model unless stated otherwise.

*Data are expressed as median (min-max) for $T_{\text{max}}$ and geometric mean (CV%) for all other parameters.

$^\dagger$Estimated by non-compartmental method using concentrations after the last dose.

AUC=area under the concentration-vs.-time curve; $C_{\text{max}}$=maximum plasma concentration; $t_{1/2}$=terminal half-life; $T_{\text{max}}$=time to $C_{\text{max}}$; CL or CL/F=total clearance; NA=not applicable.
Safety
(Dose Groups 1 and 2)

- TEAEs were mostly mild, unrelated to study drug, and similar between treatment groups and generally consistent with subjects’ medical histories.
- No injection site or hypersensitivity reactions were observed.
- Home BP measurements showed no consistent route- or dose-dependent changes from baseline among subjects in any of the treatment groups (mean change from baseline to Day 99 post-dose, range: SBP: −25 to 12 mm Hg; DBP: −16 to 8 mm Hg).
- With sotatercept IV: in the 0.1 mg/kg IV group, 1 subject was discontinued after the first dose due to the stopping rule for elevated home BP; in the 0.2 mg/kg IV group, 1 subject experienced an AE of hypertension that led to study drug discontinuation while 1 subject experienced both an AE of hypertension and the BP stopping rule; changes in BP in these subjects were generally transient.
- 1 subject who received sotatercept IV 0.2 mg/kg was discontinued after the first dose due to the stopping rule for elevated Hb.

DBP=diastolic blood pressure; SBP=systolic blood pressure; TEAEs=treatment-emergent adverse events; AE=adverse event; Hb=hemoglobin.
## Safety
(Dose Groups 1 and 2)

### Subjects, n (%)

<table>
<thead>
<tr>
<th></th>
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<tr>
<td></td>
<td>IV 0.1 mg/kg</td>
</tr>
<tr>
<td></td>
<td>n=7</td>
</tr>
<tr>
<td>Any TEAE*</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>TEAE related to study drug</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

### TEAEs in ≥2 subjects in any treatment group, n (%)

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>IV 0.1 mg/kg</td>
</tr>
<tr>
<td></td>
<td>n=7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*TEAE is defined as any adverse event with a start date on or after date of first dose of study drug.

TEAE=treatment-emergent adverse event; AEs=adverse events.
Serum Hb Concentrations: Sotatercept IV

Sotatercept IV 0.1 mg/kg (n=7)

Threshold for rescue range: 10–12 g/dL

Sotatercept IV 0.2 mg/kg (n=9)

Threshold for rescue range: 10–12 g/dL

Hb = hemoglobin.
Serum Hb Concentrations: Sotatercept SC

Sotatercept SC 0.13 mg/kg (n=7)

Target Hb range: 10–12 g/dL
Threshold for rescue Hb <9.0

Sotatercept SC 0.26 mg/kg (n=9)

Target Hb range: 10–12 g/dL
Threshold for rescue Hb <9.0

Hb=hemoglobin.
Percentage of Subjects Achieving Target Hb (10–12 g/dL) or Requiring Rescue

*Subjects who achieved target Hb range without the need for rescue.

• The proportion of subjects who experienced ≥1 dose hold due to elevated Hb (>12.0 g/dL) was 28.6%, 44.4%, 42.9%, and 22.2% in the sotatercept IV 0.1 mg/kg, IV 0.2 mg/kg, SC 0.13 mg/kg, and SC 0.26 mg/kg dose groups, respectively.
• At the end of the treatment phase, subjects receiving higher doses of sotatercept, given either IV or SC, showed a mean increase in Hb from baseline.

*Analysis includes data as observed in subjects with baseline Hb and mean evaluation phase Hb, from samples obtained from Study Days 99 to 113.
Conclusions

- Sotatercept has an acceptable safety profile in ESKD subjects on HD and is well tolerated for up to eight 14-day dose cycles
  - There were no route- or dose-dependent changes in home BP measurements
- Sotatercept SC 0.26 mg/kg was associated with stable Hb levels
- Sotatercept IV 0.2 mg/kg SC 0.26 mg/kg were associated with lower rates of rescue with ESAs
- Sotatercept IV 0.2 mg/kg was associated with earlier discontinuations due to elevated Hb or BP stopping criteria
  - This led to a change in protocol to intra-subject dose escalation in the third dose groups to account for an early ESA effect, which diminishes over time after the switch to sotatercept
- Enrollment in the dose escalation groups (sotatercept IV 0.1-0.4 mg/kg and SC 0.4-0.5 mg/kg) is ongoing