**Introduction**

- Subjects who met stopping rule criteria for elevated BP on Day 29; study treatment was discontinued, and rescue therapy was administered.
- *This subject receiving placebo had elevated serum EPO levels, suggesting off-protocol EPO administration.*

**Methods**

1. **Subjects**
   - Randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with ESKD on hemodialysis (consistent with subjects enrolled in Part 1 evaluating the PK, safety, tolerability, and efficacy of sotatercept for the correction of ESA washout).
   - Patients with ESKD exhibit anemia, primarily caused by decreased renal erythropoiesis to increase the production of mature erythrocytes.

2. **Objectives**
   - Assess the safety, tolerability, and efficacy of sotatercept for the correction of ESA washout.
   - Evaluate the PK of sotatercept in subjects with ESKD on hemodialysis.

3. **Study Design**
   - Open-label, single-blind, placebo-controlled, sequential dose-escalation design with 28 days to assess PK and safety.
   - Group 1: 0.3 mg/kg;
   - Group 2: 0.5 mg/kg.
   - Group 3: 0.7 mg/kg.

4. **Subjects**
   - Subjects on continuous outpatient home HD therapy for ≥8 weeks before screening.
   - Albuminuria measured over the prior 3 months.
   - Subjects not receiving multiple doses of EPO before, at, and immediately after randomization; one 0.5 mg/kg subject received multiple doses of EPO before, at, and immediately after randomization.
   - Subjects not receiving multiple doses of ESA (epoetin alfa, darbepoetin) for ≥6 weeks before and during screening, excluding ESA washout.

5. **Safety Assessments**
   - AEs in the per-protocol population are described in Table 2.
   - Changes in safety laboratory values were monitored during the study.

6. **PK Assessments**
   - The sampling frequency for PK assessments was weekly throughout the planned 225-day treatment phase (up to eight 28-day dose cycles).
   - Subjects received multiple doses of sotatercept throughout the planned 225-day treatment phase.

7. **Efficacy**
   - Baseline subject demographics and disease characteristics were generally similar across the treatment groups.
   - Baseline Hb levels in the per-protocol population were similar to the FAS (Table 1).
   - Hb increase ≥1 g/dL.
   - Days to achieve target Hb range (10–12 g/dL).

8. **Conclusions**
   - Subjects treated with sotatercept 0.5 mg/kg had a lower target range of 10–12 g/dL, with the target level (1 g/L) compared with placebo, despite dose escalation being limited with increasing total daily of sotatercept.
   - Based on the observations from the 0.3 mg/kg and 0.5 mg/kg groups, subjects with ESKD on hemodialysis are currently being enrolled to receive 0.7 mg/kg.

**References**

- Pierson SD, Colburn HN, et al. Multiple-dose, safety, pharmacokinetic, and efficacy study of sotatercept (ACE-011) in subjects on hemodialysis and the effects of its murine analog on renal function and erythropoiesis. Presented at American Society of Nephrology Kidney Week, November 5, 2014; San Diego, CA.
- The pharmacokinetics and safety of a single dose of sotatercept (ACE-011) in subjects with ESKD on hemodialysis and the effects of the dose on the erythropoiesis of patients receiving epoetin alfa. Presented at American Society of Nephrology Kidney Week, November 5, 2014; San Diego, CA.

**Figure 1. B and H Response at Any Time During the 225-Day Treatment Phase (FAS Population)**

**Table 1. Demographic and Clinical Characteristics of Randomized Subjects (FAS, N=22)**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Race</th>
<th>Dialysis vintage (days)</th>
<th>Baseline Hb (g/dL)</th>
<th>Baseline EPO (μg/mL)</th>
<th>Baseline ESA (μg/mL)</th>
<th>Baseline creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>7</td>
<td>52.4 ± 13.8</td>
<td>5</td>
<td>0</td>
<td>167.9 ± 108.9</td>
<td>9.7 ± 1.3</td>
<td>6.5 ± 2.0</td>
<td>1.7 ± 1.0</td>
<td>5.2 ± 1.0</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>7</td>
<td>52.0 ± 14.6</td>
<td>5</td>
<td>0</td>
<td>167.9 ± 108.9</td>
<td>9.7 ± 1.3</td>
<td>6.5 ± 2.0</td>
<td>1.7 ± 1.0</td>
<td>5.2 ± 1.0</td>
</tr>
<tr>
<td>0.7 mg/kg</td>
<td>8</td>
<td>52.0 ± 14.6</td>
<td>4</td>
<td>4</td>
<td>167.9 ± 108.9</td>
<td>9.7 ± 1.3</td>
<td>6.5 ± 2.0</td>
<td>1.7 ± 1.0</td>
<td>5.2 ± 1.0</td>
</tr>
</tbody>
</table>

**Table 2. Overview of AEs (Safety Population, N=22)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>0.3 mg/kg</th>
<th>0.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Number of events</td>
<td>38</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>% of population</td>
<td>5.0</td>
<td>7.1</td>
<td>8.3</td>
</tr>
</tbody>
</table>

**Figure 2. Subject Disposition**

**Figure 3. Hb Response at Any Time During the 225-Day Treatment Phase (FAS Population)**

**Figure 4. Percentage of Dose Cycles With Hb Response During the 225-Day Treatment Phase (FAS Population)**

**Figure 5. Serum Hb Concentrations During the Study (Per-Protocol Population, Censored for Rescue)**

**Figure 6. Days of Observational Phase (Per-Protocol Population)**

**Figure 7. Days on Study Drug**

**Figure 8. Baseline Subject Demographics and Disease Characteristics Were Generally Similar Across the Treatment Groups**

**Figure 9. Baseline Subject Demographics and Disease Characteristics Were Generally Similar Across the Treatment Groups**

**Figure 10. Baseline Subject Demographics and Disease Characteristics Were Generally Similar Across the Treatment Groups**

This study was sponsored by Celgene Corporation.
Long-term Effects of Sotatercept Compared With Placebo for Correction of Anemia in Hemodialysis Subjects: Interim Analysis of ACE-011-REN-001 Phase 2A Study

Mohamed El-Shahawy1, James Cotton2, Jeffrey Kaupke3, Thomas D. Wooldridge4, Michael Weiswasser5, William T. Smith5

SP244

Subjects treated with sotatercept 0.5 mg/kg. Subjects treated with sotatercept 0.3 mg/kg had a mean (SD) increase in Hb of 0.9 (0.3) g/dL, with no observed changes in blood pressure (BP).13

• Included in the per-protocol efficacy analysis population were:

Baseline Hb, mean (range), g/dL

Placebo 9.7 (9.3–9.9) Sotatercept 0.3 mg/kg 9.3 (7.3–10.5) Sotatercept 0.5 mg/kg 8.9 (7.1–10.0)

• Major protocol violations were noted for 2 subjects randomized to sotatercept. One 0.3 mg/kg subject was well tolerated, with no observed changes in blood pressure (BP).13

• The analysis also revealed adequate tolerability and dose-related Hb responses with sotatercept observed and no rescue required with sotatercept 0.5 mg/kg during the first 28-day dose cycle.14

† Threshold for rescue Hb <9.0 g/dL

Days on Study

≥1 AE related to study drug 1 (20.0) 2 (22.2) 0 (0.0)

Days on study drug, mean 88 85 108

Parents receiving ≥3 hours of high-flux hemodialysis at each session for ≥12 weeks before screening were eligible.

• ESKD-related anemia: predialysis Hb of ≥8 to <10 g/dL after ESA washout

≥1 AE related to study drug 1 (20.0) 2 (22.2) 0 (0.0)

• Adequate iron status (transferrin saturation ≥20%)

• Parathyroid hormone concentration ≤1,000 pg/mL; phosphorous ≤7 mg/dL; and total calcium level ≤10 mg/dL

• Kt/V ≥1.2 or urea reduction ratio ≥65%

• ESKD due to malignancy or history of malignancy

• Subjects with a hemoglobin (Hb) level ≥12 g/dL within 90 days prior to screening

• Adults receiving ≥3 hours of high-flux hemodialysis at each session for ≥12 weeks before screening were eligible.

• ESKD-related anemia: predialysis Hb of ≥8 to <10 g/dL after ESA washout

Days on Study

≥1 AE related to study drug 1 (20.0) 2 (22.2) 0 (0.0)

Days on study drug, mean 88 85 108

• The ongoing washout of ESA effect (Hb decline before randomization) at the time of randomization was 3.5 times slower for the placebo group compared with both of the doses of sotatercept.12

• ESKD due to malignancy or history of malignancy

• Subjects with a hemoglobin (Hb) level ≥12 g/dL within 90 days prior to screening were eligible.

• ESKD-related anemia: predialysis Hb of ≥8 to <10 g/dL after ESA washout

Days on Study

≥1 AE related to study drug 1 (20.0) 2 (22.2) 0 (0.0)

Days on study drug, mean 88 85 108

Note: All randomized subjects will continue treatment with sotatercept 0.3, 0.5, or 0.7 mg/kg or placebo for up to 8 doses* unless rescued or discontinued early.

During the 225-day treatment phase (up to 8 dose cycles):

– The proportions of subjects achieving Hb increase ≥1 g/dL, achieving the target Hb range (10–12 g/dL), and requiring rescue are shown in Figure 3. Findings were similar for the FAS.

– Hb increase ≥1 g/dL was maintained for 8%, 13%, and 29% of all possible dose cycles (n×8 for each group) in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively.

4. During the 225-day treatment phase (up to 8 dose cycles):

– The proportions of subjects achieving Hb increase ≥1 g/dL, achieving the target Hb range (10–12 g/dL), and requiring rescue are shown in Figure 3. Findings were similar for the FAS.

– Hb increase ≥1 g/dL was maintained for 8%, 13%, and 29% of all possible dose cycles (n×8 for each group) in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively.

Note: All randomized subjects will continue treatment with sotatercept 0.3, 0.5, or 0.7 mg/kg or placebo for up to 8 doses* unless rescued or discontinued early.

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• Hb increase ≥1 g/dL was maintained for 8%, 13%, and 29% of all possible dose cycles (n×8 for each group) in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively.
INTRODUCTION

- Patients with end-stage kidney disease (ESKD) exhibit anemia, primarily caused by decreased renal biosynthesis of erythropoietin (EPO).1,2
- Erythropoiesis-stimulating agents (ESAs) effectively increase hemoglobin (Hb) levels in patients with ESKD, but pose significant safety risks, including persistent hypertension, serious cardiovascular events, and increased risk of death.3,4
- Although low Hb levels are linked to poor cardiovascular outcomes in ESKD patients, ESAs do not modify this risk when targeting Hb levels ranging from 13.0 to 15.0 g/dL.5,6,7
- Sotatercept (ACE-011) is an ActivINα-IgG1 fusion protein that binds with high affinity to activin A and other members of the transforming growth factor beta superfamily and acts during late-stage erythropoiesis to increase the production of mature erythropoietins.8,9

This 2-part, phase 2A, randomized, placebo-controlled study is the first trial to evaluate the pharmacokinetics (PK), safety, tolerability, and Hb effect of sotatercept in ESKD subjects with renal anemia receiving hemodialysis.

- Subjects who maintained a stable dose of ESA for at least 6 weeks entered ESA washout until their Hb dropped to <10 g/dL, and were then randomized to sotatercept or placebo control.
- In Part 1 of the study, following administration of a single subcutaneous dose of sotatercept 0.1 mg/kg, PK parameters in patients with ESKD were similar to those observed previously in healthy postmenopausal women,10,11 with a long half-life (21 days). Sotatercept was not dialyzable as it has well tolerated, with no observed changes in blood pressure (BP).12,13
- Part 2 of the study is an ongoing, randomized, single-blind, placebo-controlled, multiple-dose, sequential dose-escalation trial in subjects with ESKD on hemodialysis (consistent with subjects enrolled in Part 1) evaluating the PK, safety, tolerability, and efficacy of sotatercept for the correction of ESKD-related anemia.

In a preliminary, interim analysis of Part 2, sotatercept 0.3 mg/kg and 0.5 mg/kg exhibited dose-dependent increases in mean (SD) maximum plasma concentration (Cmax) (0.96 and 3.5 ± 0.73 μg/mL, respectively) and area under the plasma concentration-vs.-time curve (AUC0–t) (50.5 ± 17.4 and 33.2 ± 11.5 μg/mL · h, respectively), with a mean (SD) terminal elimination half-life of 22.3 (3.0) and 24.5 (8.9) days, respectively.14

The analysis also revealed adequate tolerability and dose-related Hb responses with sotatercept 0.3 mg/kg and 0.5 mg/kg treatment scheduled every 28 days, with higher mean peak Hb response observed and no rescue required with sotatercept 0.5 mg/kg during the first 28-day dose cycle.14

The current interim analysis describes the assessment of efficacy and safety with sotatercept 0.3 mg/kg and 0.5 mg/kg throughout the planned 225-day treatment phase (up to eight 28-day dose cycles) and 112-day follow-up phase.

Enrollment in the sotatercept 0.7 mg/kg dose group is ongoing.

METHODS

Key Inclusion Criteria

- Adults receiving ≥3 hours of high-flux hemodialysis at each session for ≥12 weeks before screening
- Adequate Hb response (Hb ≥10 to ≥12 g/dL, predialysis mean of 3 consecutive Hb concentrations) to stable doses of ESA (epoetin alfa, darbepoetin) for ≥6 weeks before and during screening, excluding dose modifications for high Hb (maximum dose: epoetin alfa ≤500 IU/kg/week; darbepoetin ≤90 μg/week)
- ESKD-related anemia: predialysis Hb ≤8 to <10 g/dL after ESA washout
- Adequate iron status (transferrin saturation ≥20%)
- Kt/V ≥1.2 or urea reduction ratio ≥65%
- Parathyroid hormone concentration ≤1,000 pg/mL; phosphorus ≤7 mg/dL; and total albumin-corrected calcium ≥8.8 to ≤10.5 mg/dL

Key Exclusion Criteria

- Anemia due to non-renal causes
- ESKD due to malignancy or history of malignancy
- Systemic hemato logic disease
- Peritoneal dialysis or compromised venous access
- Uncontrolled diabetes mellitus (HbA1C ≥9%), hypertension (home systolic BP ≥160 mm Hg, home diastolic BP ≥90 mm Hg), or heart failure (New York Heart Association class ≥3)
- Alanine transaminase and/or aspartate transaminase values >2× the upper limit of normal; C-reactive protein >50 mg/L at screening
- Red blood cell transfusion <8 weeks before screening
- Anticipated or scheduled living donor renal transplant

Study Design

This was a randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with ESKD on hemodialysis (Figure 1).

Figure 1. Study Design: Part 2

Note: All randomized subjects will continue treatment with sotatercept (0.3, 0.5, or 0.7 mg/kg) or placebo for up to 8 doses* unless rescued or discontinued early.

*0.7 mg/kg: 4 mg/kg, all randomized subjects will continue treatment for up to 15 doses unless rescued or discontinued early.

28 days after the 8th subject is dosed with sotatercept in each dose group (0.3, 0.5, and 0.7 mg/kg), an interim analysis will occur to evaluate PK and safety before opening the next dose group.
RESULTS

Subjects
- A total of 22 subjects were randomized and received ≥1 dose of study medication and comprise the full analysis set (FAS) and safety population:
  - 5 who received placebo.
  - 9 who received sotatercept 0.3 mg/kg.
  - 8 who received sotatercept 0.5 mg/kg.
- Subject disposition is illustrated in Figure 2.
- Most study treatment discontinuations were due to the subject receiving rescue treatment; no subject was discontinued from study treatment due to an adverse event (AE).
- Baseline subject demographics and disease characteristics were generally similar across the treatment groups (Table 1).

Figure 2. Subject Disposition

![SubjectDisposition](image)

*This subject receiving placebo had elevated serum EPO levels, suggesting off-protocol EPO administration.

**Subject met stopping rule criteria for elevated BP on Day 39; study treatment was discontinued, and rescue therapy was administered on Day 36, with continued follow-up. Subject was randomized in error with non-qualifying BP, based on incomplete evaluations, at baseline.
28 days after the 6th subject is dosed with sotatercept in each dose group (0.3, 0.5, and 0.7 mg/kg), an interim analysis will occur. Key Exclusion Criteria:

- Parathyroid hormone concentration ≤1,000 pg/mL; phosphorous ≤7 mg/dL; and total calcium ≤9.7 mg/dL
- Adequate Hb response (Hb ≥10 to ≤12 g/dL predialysis mean of 3 consecutive Hb concentrations) to rescue therapy
- Subjects who maintained a stable dose of ESA for at least 6 weeks entered ESA washout until their Hb increased ≥1.0 g/dL
- Patients with end-stage kidney disease (ESKD) exhibit anemia, primarily caused by decreased renal synthesis of erythropoietin (EPO), which leads to decreased hematopoiesis and decreased levels of mature red blood cells. Serum Hb concentrations within the target range of 10–12 g/dL were generally more often sustained in the placebo group compared to the sotatercept groups as the proportion of subjects who went off-protocol EPO administration. This is the only subject in any dose group with a significant increase in serum EPO levels, suggesting undocumented off-protocol EPO administration. This subject was excluded from the per-protocol efficacy analyses.

### Table 1. Overview of AEs (Safety Population, N=22)

<table>
<thead>
<tr>
<th>Subjects (FAS, N=22)</th>
<th>Placebo (n~3)</th>
<th>Sotatercept 0.3 mg/kg (n~9)</th>
<th>Sotatercept 0.5 mg/kg (n~10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on study drug, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on rescue AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Overview of AEs (Safety Population, N=22)

<table>
<thead>
<tr>
<th>Subjects (FAS, N=22)</th>
<th>Placebo (n~3)</th>
<th>Sotatercept 0.3 mg/kg (n~9)</th>
<th>Sotatercept 0.5 mg/kg (n~10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n (%):</td>
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<tr>
<td>Days on study drug, n</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subjects, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on rescue AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Efficacy

- Baseline Hb levels in the per-protocol population were similar to the FAS (Table 1): 9.7, 9.2, and 8.9 g/dL in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively.
- The rates of ESA-effect washout during the pre-randomization washout phase for the FAS were 0.02, 0.07, and 0.07 g/dL/day in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively.
- One placebo subject who responded (achieved target range and target increase) while on study drug (placebo) and who experienced a dose delay also had elevated serum EPO levels, suggesting undocumented off-protocol EPO administration. This is the only subject in any dose group with a serum EPO level >20 mL/dL (as high as 74 mL/dL) while on study drug.
- During the 225-day treatment phase (up to 8 dose cycles):—Dose delays with dose reductions for Hb >11 g/dL occurred in several subjects: placebo (n=1), sotatercept 0.3 mg/kg (n=1), and sotatercept 0.5 mg/kg (n=2). Total days in dose delay were 14, 14, and 43 days, respectively.
- The proportions of subjects achieving Hb increase ≥1.0 g/dL, achieving the target Hb range (10–12 g/dL), and requiring rescue are shown in Figure 3. Findings were similar for the FAS.
- Hb increase ≥1.0 g/dL was maintained for 8%, 13%, and 29% of all possible dose cycles (n×8 for each group) in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively (Figure 4). Findings were similar for the FAS.
- The target Hb range (10–12 g/dL) was maintained for 18%, 22%, and 32% of all possible dose cycles in subjects receiving placebo, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg, respectively (Figure 4). Findings were similar for the FAS.
Figure 3. Hb Response at Any Time During the 225-Day Treatment Phase (Per-Protocol Population)*

A

Proportion of Subjects Who Achieved Target Hb Increase ≥1 g/dL and Target Range of 10–12 g/dL, Censored for Rescue

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Achieving Target</th>
<th>No. Achieving Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg</td>
<td>36</td>
<td>57</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg</td>
<td>57</td>
<td>71</td>
</tr>
</tbody>
</table>

B

Proportion of Subjects Who Required Rescue (Hb <9 g/dL)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Requiring Rescue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>66</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg</td>
<td>75</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg</td>
<td>57</td>
</tr>
</tbody>
</table>

*Data exclude 2 subjects with protocol violations; values for Hb increase ≥1 g/dL and Hb 10–12 g/dL are censored for those who required rescue treatment. One subject in the placebo group had elevated serum EPO levels, suggesting off-protocol EPO administration.

Figure 4. Percentage of Dose Cycles With Hb Response During the 225-Day Treatment Phase (Per-Protocol Population, Censored for Rescue)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Increase ≥1 g/dL</th>
<th>No. Increase 10–12 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

*Data exclude 2 subjects with protocol violations; values for Hb increase ≥1 g/dL and Hb 10–12 g/dL are censored for those who required rescue treatment. One subject in the placebo group had elevated serum EPO levels, suggesting off-protocol EPO administration.
Subjects met stopping rule criteria for elevated BP on Day 29; study treatment was discontinued, and rescue therapy was administered.

Figure 2. Subject Disposition

- At 0.7/0.4 mg/kg, all randomized subjects will continue treatment for up to 15 doses unless rescued or discontinued early.

- Anticipated or scheduled living donor renal transplant
- ESKD due to malignancy or history of malignancy
- Parathyroid hormone concentration ≤1,000 pg/mL; phosphorous ≤7 mg/dL; and total protein >50 mg/L at screening
- Adults receiving ≥3 hours of high-flux hemodialysis at each session for ≥12 weeks before screening
- Enrollment in the sotatercept 0.7 mg/kg dose group is ongoing.

Erythropoiesis-stimulating agents (ESAs) effectively increase hemoglobin (Hb) levels in patients with ESKD-related anemia. Patients with end-stage kidney disease (ESKD) exhibit anemia, primarily caused by decreased renal dependent increases in mean (SD) maximum plasma concentration (2.4 [0.96] and 3.5 [0.73] μg/mL, respectively; mean change SBP mm Hg: 2.25, 3.0, and 2.3, respectively; mean change DBP mm Hg: 7.5, 2.5, and 0.0, respectively). Findings were similar in the per-protocol population, censored for rescue (mean change SBP mm Hg: 0.0, 0.0, and −1.5, respectively; mean change DBP mm Hg: 2.0, 3.3, and −0.5, respectively).

During the 225-day, long-term treatment phase, home BP measurements showed no consistent or dose-dependent change from baseline among subjects in any of the treatment groups.

**CONCLUSIONS**

- Sotatercept has an acceptable safety profile and is well tolerated over 225 days (up to eight 28-day dose cycles), with no dose-dependent changes in home BP measurements.
- In the first 28-day dose cycle, mean peak Hb response was dose-related and the proportions of subjects requiring rescuer was lowest in those on active treatment.
  - The ongoing washout of ESA effect (Hb decline before randomization) at the time of randomization was 3.5 times slower for the placebo group compared with both of the sotatercept groups and may have masked some of the treatment effect.
- Sotatercept 0.5 mg/kg treatment was associated with dose-dependent Hb improvements (achieving target increase >1 g/dL and target range 10–12 g/dL) that were generally sustained over multiple dosing cycles.
  - Sotatercept 0.5 mg/kg meaningfully increased the total number of potential dose cycles in the target range (10–12 g/dL), and with the target increase (>1 g/dL) compared with placebo, despite dose escalation being prohibited and having the lowest baseline Hb levels.
- Based on the observations from the 0.3 mg/kg and 0.5 mg/kg groups, subjects with ESKD on hemodialysis are currently being enrolled to receive sotatercept 0.7 mg/kg.
†Protocol violation.
Subjects to evaluate PK and safety before opening the next dose group.
28 days after the 6th subject is dosed with sotatercept in each dose group (0.3, 0.5, and 0.7 mg/kg), an interim analysis will occur.

Note: All randomized subjects will continue treatment with sotatercept 0.3, 0.5, or 0.7 mg/kg or placebo for up to 8 doses* unless:

- This was a randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with ESKD and anemia.
- Red blood cell transfusion <8 weeks before screening.
- Alanine transaminase and/or aspartate transaminase values >2× the upper limit of normal; C-reactive protein >10 mg/L.
- Albumin-corrected calcium ≥8.0 to ≤10.5 mg/dL.
- Baseline sCr >12 mg/dL.
- Kt/V ≥1.2 or urea reduction ratio ≥65%.
- Patients with end-stage kidney disease (ESKD) exhibit anemia, primarily caused by decreased renal erythropoiesis.
- Female, n (%) 1 (20.0) 6 (66.7) 1 (12.5).
- Pain 0 (0.0) 2 (22.2) 0 (0.0).
- No anti-drug antibodies, injection site reactions, or hypersensitivity reactions were observed.

*Data exclude 2 subjects with protocol violations; values for Hb increase ≥1.0 g/dL and Hb 10–12 g/dL are censored for those dropouts.


This study was sponsored by Celgene Corporation.

Presented at: the 51st ERA-EDTA Congress; May 31–June 3, 2014; Amsterdam, The Netherlands.