Interim Analysis of ACE-011-REN-001: The First 28-Day Dose Cycle of Low and Medium Starting Doses of Sotatercept Compared to Placebo for Correction of Anemia in Hemodialysis Subjects

Mohamed D. Shabawy, James Cotton, Jeffrey Kaupke, Thomas D. Woodridge, Hem N. Singh, William T. Smith

INTRODUCTION

Anemia in chronic kidney disease (CKD) is a multifactorial condition involving low erythropoietin (EPO) production, renal and extrarenal iron deficiency and iron loss, hemodilution, and alterations in the bone marrow erythropoietic response to EPO.

METHODS

This was a randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with ESKD on hemodialysis. Sotatercept doses could have been delayed, reduced, or discontinued based on the subject’s absolute predialysis Hb level or change in Hb level observed after dosing.

RESULTS

Sotatercept was well tolerated with no observed changes in blood pressure (BP), and no consistent changes in safety laboratory or electrocardiographic parameters.

Conclusions

Sotatercept was well tolerated, with AEs similar to those observed with placebo and no trends toward increased BP.

REFERENCES

Interim Analysis of ACE-011-REN-001: The First 28-Day Dose Cycle of Low and Medium Starting Doses of Sotatercept Compared to Placebo for Correction of Anemia in Hemodialysis Subjects

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Table 3. Sotatercept PK in ESKD Subjects on Hemodialysis (Dose 1, Cycle 1)

<table>
<thead>
<tr>
<th>Serum Sotatercept (µg/mL)</th>
<th>Placebo (n=4)</th>
<th>Sotatercept 0.3 mg/kg (n=10)</th>
<th>Sotatercept 0.5 mg/kg (n=10)</th>
<th>Sotatercept 0.7 mg/kg (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, mean (SD)</td>
<td>2.4 (0.96)</td>
<td>3.5 (0.73)</td>
<td>3.8 (1.0)</td>
<td>3.6 (0.8)</td>
</tr>
</tbody>
</table>

Additional samples were obtained after Sotatercept dosing to evaluate PK parameters.

Table 1. Subject Disposition (FAS, N=20)

<table>
<thead>
<tr>
<th>Completers of Study Drug</th>
<th>Completers After D/C (Being Followed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Sotatercept 0.3 mg/kg</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

AEs in ≥2 subjects in a treatment group, n (%)

- Reduced: If a dose was delayed, OR if Hb <11 g/dL AND rate of rise of >2 g/dL (0.3, 0.5, and 0.7 mg/kg dose groups) or >1 g/dL (0.7/0.4 mg/kg dose group)

Hb Assessments

- PK parameters were similar to a phase I study in healthy postmenopausal women, with a long half-life (21 days).
- Sotatercept was not dialyzable.

- 30 Subjects with ESKD-related anemia: Hb ≥8 to ≤10 g/dL predialysis after ESA washout
- Kt/V ≥1.2 or urea reduction ratio ≥65%
- Baseline Hb levels were 9.7 g/dL in subjects receiving placebo, 9.3 g/dL in subjects receiving sotatercept 0.3 mg/kg, and 8.9 g/dL in subjects receiving sotatercept 0.5 mg/kg.

RESULTS

- At each interim analysis, blood samples were analyzed for the presence of anti-sotatercept antibodies.
- There were no other observed trends in laboratory, electrocardiogram, or vital sign parameters, including study visit and intra-dialytic BP, in either dose group of the study.
- No anti-drug antibodies, injection site reactions, or hypersensitivity reactions were observed.
- Baseline subject demographics and disease characteristics were generally similar across treatment groups.
- Subjects who did not require rescue were generally highest among subjects receiving sotatercept 0.5 mg/kg.
- Home BP measures in the first dose cycle revealed that all 3 groups had increases in group mean SBP, with the largest change in subjects receiving sotatercept.

CONCLUSIONS

- This interim analysis informed the data monitoring committee's decision to open enrollment for the high-dose group (sotatercept 0.7 mg/kg).
- Reduced: If a dose was delayed, OR if Hb <11 g/dL AND rate of rise of >2 g/dL (0.3, 0.5, and 0.7 mg/kg dose groups) or >1 g/dL (0.7/0.4 mg/kg dose group)

REFERENCES

3. Sherman ML, Borgstein NG, Mook L, et al. Multiple-dose, safety, pharmacokinetic, and pharmacodynamic study of sotatercept (ActRIIA-IgG1), a novel erythropoietic
INTRODUCTION

- The anemia seen in patients with end-stage kidney disease (ESKD) is largely due to decreased biosynthesis of erythropoietin from the kidney.1,2
- A number of erythropoiesis-stimulating agents (ESAs) have demonstrated efficacy in increasing hemoglobin (Hb) levels in patients with ESKD,1,2 but pose significant safety risks, including persistent hypertension, serious cardiovascular events, and increased risk of death.2,3
- Multiple observational studies have linked low Hb levels to poor cardiovascular outcomes.4 However, recent clinical studies have demonstrated that ESAs are unable to modify this risk when targeting a normal Hb level.1,2,5
- Sotatercept (ACE-011) is an ActRIIa/ActRIIB fusion protein trap that binds with high affinity to activin A and other members of the TGF superfamily and acts on late-stage erythroid progenitors to increase the production of mature erythrocytes into the circulation.5,6
- This 3-part, phase 1A, randomized, placebo-controlled, sequential dose-escalation study is the final to evaluate the pharmacokinetics (PK), safety, tolerability, and Hb effect of sotatercept in ESKD subjects with renal anemia receiving hemodialysis.
- In part 1, after a single subcutaneous dose (0.1 mg/kg) of sotatercept:7
  - PK parameters were similar to a phase 1 study in healthy postmenopausal women, with a long half-life (21 days).
  - Sotatercept was not dialyzable.
  - There was no evidence of a pharmacodynamic effect on Hb concentrations at the single, 0.1 mg/kg dose.
  - Sotatercept was well tolerated with no observed changes in blood pressure (BP), and no consistent changes in safety laboratory or electrocardiographic parameters.
- Part 2 is an ongoing, randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with ESKD on hemodialysis evaluating the PK, safety, tolerability, and Hb effects of sotatercept for the correction of ESKD-related anemia.
- We report the preliminary, interim analysis of the sotatercept 0.3 mg/kg (low dose) and 0.5 mg/kg (medium dose) treatment groups.
- Pending acceptable interim analysis results, additional patients may be randomized in a staggered parallel fashion to sotatercept 0.7 mg/kg once every 28 days (high dose) and sotatercept 0.7 mg/kg once every 14 days for 28 days followed by 0.4 mg/kg every 14 days for the remainder of the treatment period (Figure 1).

METHODS

Key Inclusion Criteria

- Adults receiving at least 3 hours of high-flux hemodialysis at each session for at least 12 weeks before screening and no planned changes to the hemodialysis regimen during the study period
- 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 at least 6 weeks before and during screening, excluding dose holds for high Hb (maximum dose: epoetin alfa >500 U/kg/wk; darbepoetin >195 U/kg/wk).
- ESKD-related anemia: Hb ≤10 g/dL predialysis after ESA washout
- Adequate iron status (transferrin saturation >20%)
- KVL ≤2 L or ursodiol reduction ≤50%
- Parathyroid hormone concentration ≤1.600 ng/mL; phosphorous ≤7 mg/dL; and total albumin-corrected calcium ≥8.0 to ≤10.5 mg/dL.

Key Exclusion Criteria

- Anemia due to non-renal causes
- ESKD due to malignancy or history of malignancy (excluding excised and cured non-melanoma skin cancer and cervical carcinoma in situ)
- Systemic hematologic disease
- Peritoneal dialysis or compromised venous access
- Uncontrolled diabetes mellitus (HbA1c >9%), hypertension (home systolic BP [SBP] >160 mm Hg, home diastolic BP [DBP] >90 mm Hg), or heart failure (New York Heart Association class ≥III)
- Alkaline transaminase and/or aspartate transaminase values >2 x the upper limit of normal; C-reactive protein >50 mg/L.
- 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).
- Eligible subjects were randomized to 2 arms (sotatercept or placebo) in a 3:1 ratio in 4 sequential dose groups (sotatercept 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg; or 0.1 mg/kg loading dose followed by 0.4 mg/kg).
  - This interim analysis informed the data monitoring committee’s decision to open enrollment for the high-dose group (sotatercept 0.7 mg/kg).
  - Sotatercept was well tolerated with no observed changes in blood pressure (BP), and no consistent changes in safety laboratory or electrocardiographic parameters.

Figure 1. Study Design

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.

*Hb ≤10.4 mg/dL, or 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.

Sotatercept mean concentration-vs.-time profiles for the 0.3 mg/kg and 0.5 mg/kg dose groups are shown in Figure 2. Sotatercept multidose PK was examined among all subjects who received at least 1 dose of study medication and who had evaluable PK data.

Table 1. Subject Disposition (FAS, N=20)

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Required Rescue (Hb &lt;9 g/dL)</th>
<th>Total</th>
<th>Cumulative days on study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>864</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>2046</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>634</td>
</tr>
</tbody>
</table>

Figure 2. Sotatercept Serum Concentration Over Time

The 28-day data may not be sufficient for accurate estimation in some subjects.

Table 2. Overview of AEs (Safety Population, N=20)

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo (n=8)</th>
<th>Sotatercept 0.3 mg/kg (n=6)</th>
<th>Sotatercept 0.5 mg/kg (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>3 (60.0)</td>
<td>8 (88.8)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (20.0)</td>
<td>2 (22.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any AE≥25%</td>
<td>1 (20.0)</td>
<td>2 (22.2)</td>
<td>1 (20.0)</td>
</tr>
</tbody>
</table>

Table 3. Mean Peak Hb Increase During the First 28-Day Dose Cycle (Per-Protocol Population)*

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Mean peak Hb increase (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
<td>0.1</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg</td>
<td>5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Due to Stopping Rule

- Hb increase ≥1.0 g/dL was achieved by 20% (placebo), 37.5% (sotatercept 0.3 mg/kg), and 40% (sotatercept 0.5 mg/kg) of subjects.
- Mean Hb concentration in subjects who received sotatercept 0.3 mg/kg and 0.5 mg/kg exhibited a greater increase from baseline in the first 15 days post-dose compared to placebo (vs. placebo); however, the increases were not sustained through the entire dose cycle.

Figure 3. Mean Hb Increase During the First 28-Day Dose Cycle (Per-Protocol Population)*

The 28-day data may not be sufficient for accurate estimation in some subjects.

Figure 4. Mean Peak Hemoglobin Increase During the First 28-Day Dose Cycle (Per-Protocol Population)*

Figure 5. Home BP Monitoring

With long-term treatment, home BP measures showed no consistent change from baseline among subjects in any of the treatment groups.

Figure 6A

Cumulative days on study

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Cumulative days on study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
<td>864</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg</td>
<td>6</td>
<td>2046</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg</td>
<td>5</td>
<td>634</td>
</tr>
</tbody>
</table>


Presented at: the National Kidney Foundation (NKF) 2014 Spring Clinical Meeting; April 22–26, 2014; Las Vegas, NV.

Sotatercept was well tolerated, with AEs similar to those observed with placebo and no trends toward increased BP.
The current report describes interim analysis of the sotatercept 0.3 mg/kg and 0.5 mg/kg dose groups for the purpose of determining safety of proceeding to the next treatment phase and 112-day follow-up phase.

Rescue treatment was recommended for subjects with Hb <9 g/dL after the first dose cycle, and those required to discontinue sotatercept could receive ESA treatment.

Subjects
- A total of 21 subjects were randomized and received study medication. One subject was randomized to sotatercept 0.5 mg/kg and received 1 dose of study medication; however, this subject did not have the first follow-up visit at the time of the interim database cutoff point and was not included in either the safety or efficacy population.

RESULTS

Subjects
- A total of 21 subjects were randomized and received study medication. One subject was randomized to sotatercept 0.5 mg/kg and received 1 dose of study medication; however, this subject did not have the first follow-up visit at the time of the interim database cutoff point and was not included in either the safety or efficacy population.

Mean peak Hb response in the first 28 days was dose-related, with the sotatercept 0.5 mg/kg dose having the highest mean peak Hb response.

Exposure to sotatercept was not associated with the development of anti-drug antibodies, injection site reactions, or hypersensitivity reactions.

Sotatercept was not dialyzable.

Baseline Hb levels were 9.7 g/dL in subjects receiving placebo, 9.3 g/dL in subjects receiving sotatercept 0.3 mg/kg, and 8.9 g/dL in subjects receiving sotatercept 0.5 mg/kg.

The mean Hb values were calculated by first determining the mean of 3 waking and 3 bedtime sets of Hb measures. Next, the mean waking and mean bedtime Hb values were calculated.

The final mean home BP value was calculated by first determining the mean of 3 waking and 3 bedtime sets of BP measures. Next, the mean waking and mean bedtime BP values from a single day were both used to calculate the day mean. Finally, the mean of the day means was calculated, and this comprised the final mean home BP.

Mean peak Hb response in the first 28 days was dose-related, with the sotatercept 0.5 mg/kg dose having the highest mean peak Hb response.

Exposure to sotatercept was not associated with the development of anti-drug antibodies, injection site reactions, or hypersensitivity reactions.

Sotatercept was not dialyzable.

Baseline Hb levels were 9.7 g/dL in subjects receiving placebo, 9.3 g/dL in subjects receiving sotatercept 0.3 mg/kg, and 8.9 g/dL in subjects receiving sotatercept 0.5 mg/kg.

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Home BP measures in the first dose cycle revealed that all 3 groups had increases in group mean SBP, with the largest change in subjects receiving sotatercept.

The final mean home BP value was calculated by first determining the mean of 3 waking and 3 bedtime sets of BP measures. Next, the mean waking and mean bedtime values from a single day were both used to calculate the day mean. Finally, the mean of the day means was calculated, and this comprised the final mean home BP.

Home BP measures and safety measures were summarized descriptively.
Rescue treatment was recommended for subjects with Hb <9 g/dL after the first dose cycle, and those required to discontinue sotatercept could receive ESA treatment.

Study Design

- The anemia seen in patients with end-stage kidney disease (ESKD) is largely due to decreased biosynthesis of erythropoietin from the kidneys.1-3
- Part 2 is an ongoing, randomized, single-blind, placebo-controlled, sequential dose-escalation study in subjects with ESKD on hemodialysis evaluating the PK, safety, treatment phase and 112-day follow-up phase.
- Subjects were enrolled after a screening period (Day –90 to Day –1) and randomized to treatment arms upon completion of baseline PK and safety assessments (Day 0). Subjects were then dosed q14d, up to 15 doses (Sotatercept 0.7 mg/kg SC q14d, up to 15 doses).

Safety

- An overview of AEs is provided in Table 4.
- A decrease in serum calcium levels during follow-up in subjects who had received sotatercept 0.3 mg/kg was noted, without AEs of hypocalcemia.
- There were no other observed trends in laboratory, electrocardiogram, or vital sign parameters, including study visit and intra-dialytic BP, in either dose group of sotatercept during long-term follow-up.
- No anti-drug antibodies, injection site reactions, or hypersensitivity reactions were observed.

Table 4. Overview of AEs (Safety Population, N=20)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>0.3 mg/kg</th>
<th>0.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Cumulative days on study</td>
<td>204</td>
<td>204</td>
<td>204</td>
</tr>
<tr>
<td>Any AE</td>
<td>12 (60.0%)</td>
<td>10 (50.0%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>≥1 serious AE</td>
<td>2 (10.0%)</td>
<td>2 (10.0%)</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (5.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs in ≥2 subjects in a treatment group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (5.0%)</td>
<td>2 (10.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Efficacy

Target Hb Increase (≥1 g/dL), and Target Hb Range (10–12 g/dL) During the First 28 Days

- Baseline Hb levels were 9.7 g/dL in subjects receiving placebo, 9.3 g/dL in subjects receiving sotatercept 0.3 mg/kg, and 8.9 g/dL in subjects receiving sotatercept 0.5 mg/kg.
- Hb increase ≥1.0 g/dL was achieved by 20% (placebo), 37.5% (sotatercept 0.3 mg/kg), and 40% (sotatercept 0.5 mg/kg) of subjects (Figure 3).
- The desired Hb range (10–12 g/dL) was achieved in 60% (placebo), 25% (sotatercept 0.3 mg/kg), and 60% (sotatercept 0.5 mg/kg) during the first dose cycle.
- Mean peak Hb increase in the first 28-day dose cycle was 0.1 g/dL in subjects receiving placebo, 0.5 g/dL in subjects receiving sotatercept 0.3 mg/kg, and 0.8 g/dL in subjects receiving sotatercept 0.5 mg/kg (Figure 4).
- Rescue therapy was required (Hb <9 g/dL) in 2 of 5 subjects after administration of placebo and 1 of 8 subjects after administration of sotatercept 0.3 mg/kg, while none required rescue after sotatercept 0.5 mg/kg (Figure 3).

Figure 3. Hb Increase During the First 28-Day Dose Cycle (Per-Protocol Population)*

*Two subjects with a major protocol violation were excluded from efficacy analyses.
Rescue treatment was recommended for subjects with Hb <9 g/dL after the first dose cycle, and those required to discontinue sotatercept could receive ESA treatment 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 to evaluate PK and safety before opening the next dose group.

Key Exclusion Criteria

- Parathyroid hormone concentration ≤1,000 pg/mL; phosphorous ≤7 mg/dL; and total albumin-corrected calcium ≥8.0 to ≤10.5 mg/dL
- ESKD-related anemia: Hb ≥8 to ≤10 g/dL predialysis after ESA washout

In part 1, after a single subcutaneous dose (0.1 mg/kg) of sotatercept:
- Sotatercept 0.3 mg/kg SC (n ~9) q28d,
- Placebo (n ~3)
- Sotatercept 0.5 mg/kg SC (n ~9) q28d,
- Sotatercept 0.7 mg/kg SC q14d up to 13 doses (n ~9)

Follow-up phase for

Table 3. Sotatercept PK in ESKD Subjects on Hemodialysis (Dose 1, Cycle 1)

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
<th>Sotatercept 0.3 mg/kg</th>
<th>Sotatercept 0.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, postdialysis mean, kg</td>
<td>75.8</td>
<td>79.4</td>
<td>81.0</td>
</tr>
<tr>
<td>Age, mean, years</td>
<td>58.4</td>
<td>59.9</td>
<td>60.7</td>
</tr>
</tbody>
</table>

Figure 1

Interim Analysis of ACE-011-REN-001: The First 28-Day Dose Cycle of Low and Medium Starting Doses

- Sotatercept exhibited dose-dependent increases in the serum drug exposure (Cmax and AUC), with a mean elimination half-life (t1/2,z) of 22 to 25 days.

Figure 2

Results

- Hb increase ≥1.0 g/dL was achieved by 20% (placebo), 37.5% (sotatercept 0.3 mg/kg), and 40% (sotatercept 0.5 mg/kg) of subjects.

Figure 3

Results

- There were no other observed trends in laboratory, electrocardiogram, or vital sign parameters, including study visit and intra-dialytic BP, in either dose group of ACE-011.

Figure 4

Mean Peak Hemoglobin Increase During the First 28-Day Dose Cycle (Per-Protocol Population)*

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Change from Baseline (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=5)</td>
<td>0.1</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg (n=8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg (n=5)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Figure 5

Hb Change From Baseline During Long-term Sotatercept Treatment Censored for Rescue

Home BP Measurements

- Home BP measures in the first dose cycle revealed that all 3 groups had increases in group mean SBP, with the largest change in subjects receiving sotatercept 0.5 mg/kg, while the largest change in DBP was in subjects receiving placebo. All the group mean changes were <10 mm Hg (Figure 6A and B).
- Findings were similar when analyzed for both the per-protocol population (Figure 6A) and FAS (Figure 6B).
- With long-term treatment, home BP measures showed no consistent change from baseline among subjects in any of the treatment groups (Figure 7).

Figure 6

Change From Baseline in Home BP at the End of Dose Cycle 1 in the (A) Per-Protocol Population* and (B) FAS

*Two subjects with a major protocol violation were excluded from efficacy analyses.

Change From Baseline in Hb Concentration

- Mean Hb concentration in subjects who received sotatercept 0.3 mg/kg and 0.5 mg/kg exhibited a greater increase from baseline in the first 15 days post-dose (vs. placebo); however, the increases were not sustained through the entire dose cycle.
- Hb levels throughout multiple dose cycles among subjects who did not require rescue were generally highest among subjects receiving sotatercept 0.5 mg/kg (Figure 6).

Table 4. Baseline Subject Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Weight, postdialysis mean, kg</th>
<th>Age, mean, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=5)</td>
<td>75.8</td>
<td>58.4</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg (n=8)</td>
<td>79.4</td>
<td>59.9</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg (n=5)</td>
<td>81.0</td>
<td>60.7</td>
</tr>
</tbody>
</table>

Table 5. Baseline Subject Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Baseline Subject Demographics and Disease Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=5)</td>
<td>Weight, postdialysis mean, kg 75.8</td>
</tr>
<tr>
<td>Sotatercept 0.3 mg/kg (n=8)</td>
<td>Weight, postdialysis mean, kg 79.4</td>
</tr>
<tr>
<td>Sotatercept 0.5 mg/kg (n=5)</td>
<td>Weight, postdialysis mean, kg 81.0</td>
</tr>
</tbody>
</table>

References

2. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis.
4. Wooldridge T, Kaplan M, Alcorn H Jr, et al. The pharmacokinetics and safety of a single-dose of sotatercept (ACE-011) in subjects on hemodialysis and the effects of home BP measures in the first dose cycle revealed that all 3 groups had increases in group mean SBP, with the largest change in subjects receiving sotatercept 0.5 mg/kg, while the largest change in DBP was in subjects receiving placebo. All the group mean changes were <10 mm Hg (Figure 6A and B).
- Findings were similar when analyzed for both the per-protocol population (Figure 6A) and FAS (Figure 6B).
- With long-term treatment, home BP measures showed no consistent change from baseline among subjects in any of the treatment groups (Figure 7).

Figure 7

Change From Baseline in Home BP at the End of Dose Cycle 1 in the (A) Per-Protocol Population* and (B) FAS

*Data exclude subjects with protocol violations and are censored for those who required rescue in the first dose cycle.
Figure 7. Change From Baseline Home BP Measurements (FAS) of (A) SBP and (B) DBP During long-term Sotatercept Treatment, Censored for Rescue

**REFERENCES**


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