Long-term Effects of Sotatercept Compared With Placebo for Correction of Anemia in Hemodialysis Subjects: Interim Analysis of ACE-011-REN-001

FP661

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INTRODUCTION

- Patients with end-stage kidney disease (ESKD) exhibit anemia, primarily caused by decreased renal biosynthesis of erythropoietin (EPO).[1-3]
- 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.[4,5]
- Although low Hb levels are linked to poor cardiovascular outcomes in ESKD patients,[6] ESAs do not modify this risk when targeting Hb levels ranging from 13.0 to 15.0 g/dL.[5,7-9]
- Sotatercept (ACE-011) is an ActRIIA-IgG1 fusion protein that binds with high affinity to activin A and other members of the transforming growth factor-β superfamily and acts during late-stage erythropoiesis to increase the production of mature erythrocytes.[10-12]
- 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.
- 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,[12] with a long half-life (21 days). Sotatercept was not dialyzable and was well tolerated, with no observed changes in blood pressure (BP).[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.
- The current interim analysis describes the assessment of efficacy and safety with subcutaneous sotatercept 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg throughout the planned 225-day treatment phase (up to eight 28-day dose cycles) and 112-day follow-up phase.
- At the time of abstract submission, enrollment in a sotatercept dose group using a 14-day dose cycle was ongoing. For this group, subcutaneous sotatercept 0.7 mg/kg is given every 14 days for 2 doses, then 0.4 mg/kg every 14 days for up to 13 doses.

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 holds for high Hb (maximum dose: epoetin alfa ≤500 IU/kg/week; darbepoetin ≤95 µg/week)
- ESKD-related anemia: predialysis Hb of ≥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; phosphorous ≤7 mg/dL; and total albumin-corrected calcium ≥8.0 to ≤10.5 mg/dL

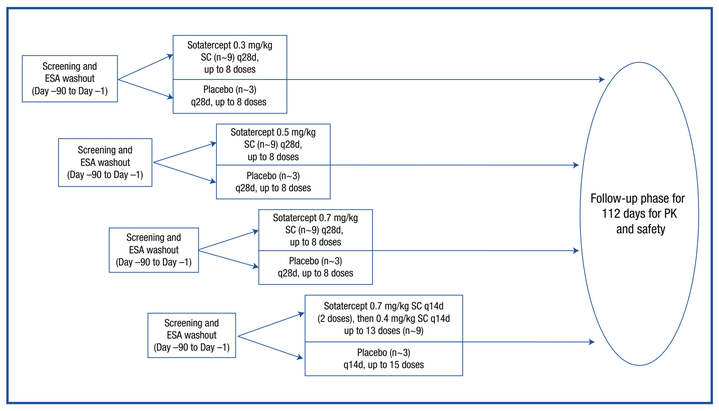
Key Exclusion Criteria

- Anemia due to non-renal causes
- ESKD due to malignancy or history of malignancy
- 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 ≥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.
*At 0.7/0.4 mg/kg, all randomized subjects will continue treatment for up to 15 doses unless rescued or discontinued early.
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.

RESULTS

Subjects

- A total of 35 subjects were randomized and received ≥1 dose of study medication and comprise the full analysis set (FAS) for efficacy and safety analyses:
  - 9 who received placebo.
  - 9 who received sotatercept 0.3 mg/kg.
  - 8 who received sotatercept 0.5 mg/kg.
  - 9 who received sotatercept 0.7 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

*One placebo patient who withdrew consent on Study Day 108 died on Study Day 148; 1 placebo patient who was receiving rescue therapy died on Study Day 186.
†Subject met stopping rule criteria for elevated BP on Day 29; 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 evaluation, at baseline.

Table 1. Demographic and Clinical Characteristics of Randomized Subjects (FAS, N=35)

	Placebo n=9	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8	Sotatercept 0.7 mg/kg n=9
Age, mean (range), years	52.9 (35-76)	59.9 (36-79)	56.9 (42-76)	61.7 (39-76)
Female, %	3 (33.3)	6 (66.7)	1 (12.5)	7 (77.8)
Race, n (%)				
White	2 (22.2)	3 (33.3)	4 (50.0)	7 (77.8)
Black	5 (55.6)	6 (66.7)	4 (50.0)	1 (11.1)
Asian	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
Ethnicity, n (%)				
Hispanic	1 (11.1)	2 (22.2)	4 (50.0)	2 (22.2)
Non-Hispanic	8 (88.9)	7 (77.8)	4 (50.0)	7 (77.8)
Postdialysis weight, mean, kg	79.8	78.6	79.1	80.8
Body mass index, mean, kg/m^2	27.6	27.8	26.5	28.7
Baseline Hb, mean (range), g/dL	9.5 (8.9-9.9)	9.3 (7.3-10.5)	8.9 (7.1-10.0)	9.3 (8.2-10.0)

- Major protocol violations were noted for 3 subjects randomized to sotatercept. One 0.3 mg/kg subject received multiple doses of EPO before, at, and immediately after randomization; one 0.5 mg/kg subject did not qualify for enrollment based on home BP evaluation; and one 0.7 mg/kg subject received the baseline dose and was accidentally dosed placebo in the second dose cycle. These subjects were excluded from the per-protocol population.

Safety Assessments

- An overview of AEs is summarized in **Table 2**.
- Serious AEs were generally considered unrelated to the study drug, did not lead to discontinuation, and resolved with continued therapy. No deaths were reported in the sotatercept groups.
- Two deaths occurred in the placebo group; neither was considered related to study medication.
  - One subject who withdrew consent on Study Day 108 died on Study Day 148 due to cardiomyopathy.
  - One subject who was receiving rescue therapy died on Study Day 186 due to worsening coronary artery disease.
- A decrease in calcium levels was noted during follow-up in subjects who had received sotatercept 0.3 mg/kg and 0.7 mg/kg, without AEs of hypocalcemia.
- There were minor but persistent increases in lactate dehydrogenase during the first 5 dose cycles, predominantly in the 3 active treatment groups. After the fifth dose cycle, the differences were less apparent.
- There was also a very minor but persistent decrease in follicle-stimulating hormone in the sotatercept 0.7 mg/kg group (range: -2.0 to -11.0 IU/L) that was not observed in other dose groups. This is an expected pharmacodynamic effect.
- No other trends in laboratory, electrocardiogram, or vital sign parameters were observed, including study visit and intra-dialytic BP, in any dose group of sotatercept during long-term follow-up.
- One subject developed low-level anti-drug antibody titers without consequence to PK, Hb effect, or safety. No injection site or hypersensitivity reactions were observed in any subjects.

Table 2. Overview of AEs (N=35)

Subjects, n (%)	Placebo n=9	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8	Sotatercept 0.7 mg/kg n=9
Days on study drug, mean	64	85	108	145
Any TEAE	7 (77.8)	8 (88.9)	6 (75.0)	9 (100.0)
Any TEAE related to study drug	3 (33.3)	2 (22.2)	0 (0.0)	5 (55.6)
Any severe TEAE	2 (22.2)	2 (22.2)	2 (25.0)	2 (22.2)
Any severe TEAE related to study drug	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
≥1 serious TEAE	3 (33.3)	4 (44.4)	1 (12.5)	6 (66.7)
Death	2* (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs in ≥2 subjects in any treatment group, n (%)				
Fatigue	2 (22.2)	2 (22.2)	0 (0.0)	1 (11.1)
Pain	1 (11.1)	2 (22.2)	0 (0.0)	0 (0.0)
Constipation	1 (11.1)	2 (22.2)	1 (12.5)	0 (0.0)
Nausea	1 (11.1)	1 (11.1)	1 (12.5)	3 (33.3)
Hypertension	1 (11.1)	4 (44.4)	0 (0.0)	5 (55.6)
Fall	2 (22.2)	1 (11.1)	0 (0.0)	1 (11.1)
Type 2 diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
Increased blood phosphorous	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
Anemia	0 (0.0)	1 (11.1)	0 (0.0)	2 (22.2)

*One placebo patient died on Study Day 186 while receiving rescue therapy due to worsening coronary artery disease; 1 placebo patient who withdrew consent on Study Day 108 died on Study Day 148 due to cardiomyopathy.

Pharmacokinetics

- Available PK data for subjects randomized to subcutaneous sotatercept 0.3 mg/kg, 0.5 mg/kg, or 0.7 mg/kg are presented in **Table 3**.
- Sotatercept exhibited dose-dependent increases in the serum drug exposure (maximum plasma concentration [C_{max}] and area under the concentration-vs.-time curve to infinity [AUC_{∞}]), with a mean elimination half-life ($t_{1/2,z}$) of 21 to 26 days.

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

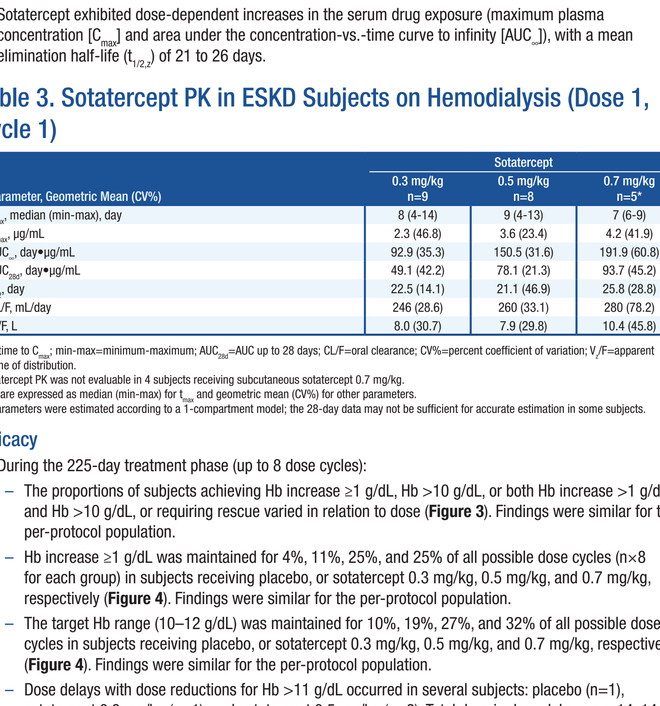
Parameter, Geometric Mean (CV%)	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8	Sotatercept 0.7 mg/kg n=5*
t_{max}, median (min-max), day	8 (4-14)	9 (4-13)	7 (6-9)
C_{max}, µg/mL	2.3 (46.8)	3.6 (23.4)	4.2 (41.9)
AUC_{∞}, day•µg/mL	92.9 (35.3)	150.5 (31.6)	191.9 (60.8)
AUC_{28d}, day•µg/mL	49.1 (42.2)	78.1 (21.3)	93.7 (45.2)
$t_{1/2,z}$, day	22.5 (14.1)	21.1 (46.9)	25.8 (28.8)
CL/F, mL/day	246 (28.6)	260 (33.1)	280 (78.2)
V_z/F, L	8.0 (30.7)	7.9 (29.8)	10.4 (45.8)

t_{max}=time to C_{max}; min-max=minimum-maximum; AUC_{28d}=AUC up to 28 days; CL/F=oral clearance; CV%=percent coefficient of variation; V_z/F=apparent volume of distribution.
*Sotatercept PK was not evaluable in 4 subjects receiving subcutaneous sotatercept 0.7 mg/kg.
Data are expressed as median (min-max) for t_{max} and geometric mean (CV%) for other parameters.
All parameters were estimated according to a 1-compartment model; the 28-day data may not be sufficient for accurate estimation in some subjects.

Efficacy

- During the 225-day treatment phase (up to 8 dose cycles):
  - The proportions of subjects achieving Hb increase ≥1 g/dL, Hb >10 g/dL, or both Hb increase >1 g/dL and Hb >10 g/dL, or requiring rescue varied in relation to dose (**Figure 3**). Findings were similar for the per-protocol population.
  - Hb increase ≥1 g/dL was maintained for 4%, 11%, 25%, and 25% of all possible dose cycles (n×8 for each group) in subjects receiving placebo, or sotatercept 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg, respectively (**Figure 4**). Findings were similar for the per-protocol population.
  - The target Hb range (10–12 g/dL) was maintained for 10%, 19%, 27%, and 32% of all possible dose cycles in subjects receiving placebo, or sotatercept 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg, respectively (**Figure 4**). Findings were similar for the per-protocol population.
  - 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.
- 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 mIU/dL (as high as 174 mIU/dL) while on study drug.

Figure 3. Proportions of Subjects With Hb Response or Rescue During the 225-Day Treatment Phase (FAS)*

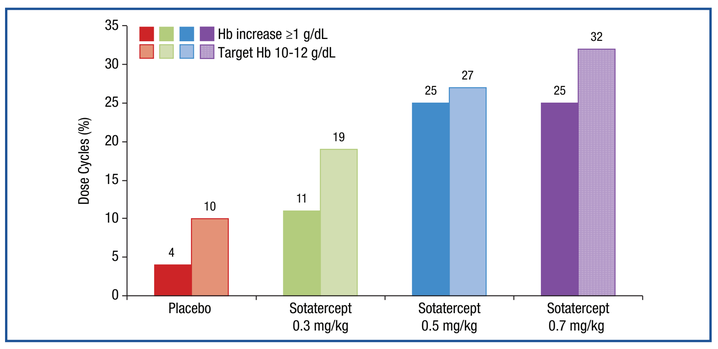


Days to Achieve, mean (FAS)	Placebo	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 0.7 mg/kg
Hb increase ≥1 g/dL	35.0	8.3	19.8	65.7
Hb >10 g/dL	10.0	4.3	17.2	35.1
Hb increase ≥1 g/dL and Hb >10 g/dL	35.0	10.0	19.8	91.3

	Placebo	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 0.7 mg/kg
Days to Rescue, mean (FAS)	49.1	68.8	46.4	99.4

*Values for Hb increase ≥1 g/dL, Hb >10 g/dL, or both Hb >1 g/dL and Hb >10 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.

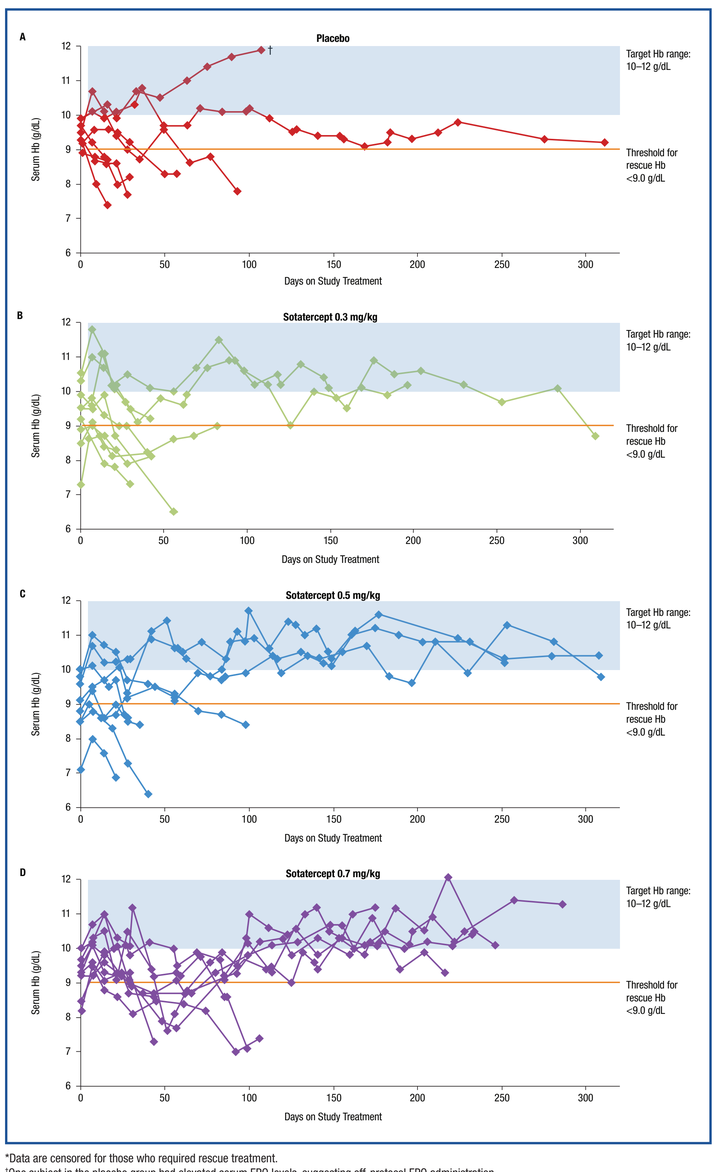
Figure 4. Percentage of All Possible Dose Cycles During the 225-Day Treatment Phase With Hb Response (FAS)*



*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.

- Serum Hb concentrations within the target range of 10–12 g/dL were generally sustained over 225 study days in subjects treated with sotatercept 0.5 mg/kg or 0.7 mg/kg. Subjects treated with sotatercept 0.3 mg/kg displayed lower and less consistent serum Hb concentrations (**Figure 5**).

Figure 5. Serum Hb Concentration During the 225-Day Treatment Phase (FAS, Censored for Rescue)*



*Data are censored for those who required rescue treatment.
†One subject in the placebo group had elevated serum EPO levels, suggesting off-protocol EPO administration.

Home BP Measurements

- At the end of the first dose cycle, home BP measurements revealed small changes from baseline in SBP and DBP that were generally similar in magnitude in subjects receiving placebo or sotatercept 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg in the safety population (mean change in SBP: –0.1, 5.2, 4.7, –1.4 mm Hg, respectively; mean change in DBP: 2.4, 3.6, 4.0, 2.4 mm Hg, 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).
- There were no dose-dependent changes in home BP measurements. Ten subjects had TEAEs of hypertension. However, the distribution and severity of events was not dose-dependent. All events were of mild to moderate severity, and most have resolved, with transient, non-persistent increases in BP. Many events occurred weeks after the last dose of study drug and/or after rescue with epoetin was initiated.
- In the first 28-day dose cycle, mean peak Hb response was dose-related and the proportions of subjects requiring rescue was lowest in those on active treatment.
- Sotatercept 0.7 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.
- Time to rescue appeared to be longer in the higher dose group, as 2/4 subjects receiving 0.7 mg/kg were rescued in the first 3 dose cycles. In the placebo, 0.3 mg/kg, and 0.5 mg/kg dose groups, 17/18 subjects were rescued in the first 3 dose cycles. Additionally, subjects receiving placebo appeared to be inherently less anemic as a group; the highest baseline Hb level occurred in the placebo group compared with the sotatercept groups, and some placebo group subjects achieved Hb target without documented active treatment. By contrast, some subjects with an adequate response to sotatercept required rescue because of their lower baseline Hb level and rapid rate of Hb decline before randomization.
- Based on the observations from the sotatercept 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg dose groups, subjects with ESKD on hemodialysis are currently being enrolled to receive sotatercept on a 14-day dosing schedule, beginning with 2 loading doses of 0.7 mg/kg, followed by 0.4 mg/kg every 14 days.

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