Safety and Hemoglobin Effect of the First 28-Day Dose Cycle of Sotatercept 0.7 mg/kg Compared With Lower Doses and Placebo for Correction of Anemia in Hemodialysis Subjects: Interim Analysis

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INTRODUCTION

- Patients with end-stage kidney disease (ESKD) often exhibit anemia, which is 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 ligand trap 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.[10,11]
- This 2-part, phase 2A, randomized, placebo-controlled study is the first trial to evaluate the pharmacokinetics (PK), safety, tolerability, and Hb effect of subcutaneous (SC) sotatercept in ESKD subjects with renal anemia undergoing hemodialysis.
- In Part 1 of the study, following administration of a single SC dose of sotatercept 0.1 mg/kg, PK parameters in subjects 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 home blood pressure (BP).[13]
- Part 2 of the study is an ongoing, randomized, single-blind, placebo-controlled, multiple-dose, 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 SC sotatercept for the correction of ESKD-related anemia.
- Subjects who maintained a stable dose of ESA for ≥6 weeks entered ESA washout until their Hb dropped to <10 g/dL and were then randomized to 4 escalating dose groups of SC sotatercept (0.3, 0.5, and 0.7 mg/kg every 28 days (up to 8 doses), and 0.7 mg/kg every 14 days (2 doses) followed by 0.4 mg/kg every 14 days (up to 13 doses), or placebo control, to evaluate both the dose level and schedule.
- Treatment failures (Hb <9 g/dL) were rescued with ESA or transfusion.
- The current interim analysis describes the assessment of PK, safety, and efficacy with SC sotatercept 0.3, 0.5, and 0.7 mg/kg compared with placebo. The interim analysis evaluated all data accrued for the sotatercept 0.3 and 0.5 mg/kg dose groups and the first 28-day dose cycle of the 0.7 mg/kg dose group for PK, Hb, and BP effects, and cumulative safety throughout the planned 225-day treatment phase (up to eight 28-day dose cycles) and 112-day follow-up phase.
- At the time of the abstract submission, enrollment in the sotatercept 0.7 mg/kg dose group was ongoing.

METHODS

Key Inclusion Criteria

- Adults receiving ≥3 hours of high-flux hemodialysis at each session for ≥12 weeks before screening
- Adequate Hb response (≥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

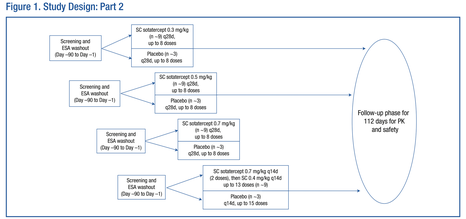
Key Exclusion Criteria

- 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 (RBC) 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 continued treatment with sotatercept 0.3, 0.5, or 0.7 mg/kg or placebo for up to 8 doses* unless they had treatment failure requiring rescue or discontinued early.
*At sotatercept 0.7/0.4 mg/kg, all randomized subjects continued treatment for up to 15 doses unless they had treatment failure requiring rescue 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.

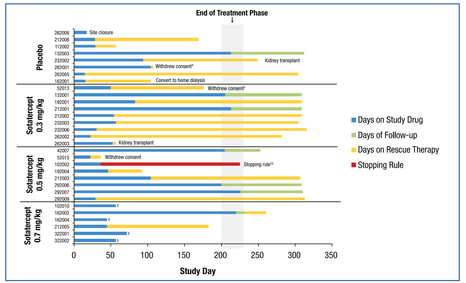
RESULTS

- A total of 31 subjects were randomized and received ≥1 dose of study medication and comprise the full analysis set and the safety population.
- Major protocol violations were noted for 3 subjects randomized to sotatercept. One subject in the sotatercept 0.3 mg/kg dose group received multiple doses of EPO before, at, and immediately after randomization; 1 subject in the sotatercept 0.5 mg/kg dose group did not qualify for enrollment based on home BP evaluation, and 1 subject in the sotatercept 0.7 mg/kg dose group did not receive a second dose at Day 28. These subjects were excluded from the prespecified per-protocol efficacy analyses.
- Baseline subject demographics and disease characteristics were generally similar across treatment groups (**Table 1**).
- The subject disposition is shown in **Figure 2**.
- Most study treatment discontinuations were due to the subject having treatment failure requiring rescue.

Table 1. Baseline Demographic and Clinical Characteristics of Randomized Subjects (Full Analysis Set, N=31)

	Placebo n=8	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8	Sotatercept 0.7 mg/kg n=6
Age, mean (range), years	55.1 (39-76)	59.9 (38-79)	56.9 (42-76)	63.0 (39-76)
Female, %	2 (25.0)	6 (66.7)	1 (12.5)	4 (66.7)
Race, n (%)				
White	1 (12.5)	3 (33.3)	4 (50.0)	5 (83.3)
Black	5 (62.5)	6 (66.7)	4 (50.0)	1 (16.7)
Asian	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic	0 (0.0)	2 (22.2)	4 (50.0)	2 (33.3)
Non-Hispanic	8 (100.0)	7 (77.8)	4 (50.0)	4 (66.7)
Postdialysis weight, mean, kg	82.4	78.6	79.1	84.5
Body mass index, mean, kg/m^2	28.1	27.8	26.5	29.9
Baseline Hb, mean (range), g/dL	9.5 (8.9-9.9)	9.3 (7.3-10.5)	8.9 (7.1-10.0)	9.2 (8.2-10.0)

Figure 2. Subject Disposition



*This subject receiving placebo had elevated serum EPO levels, suggesting off-protocol EPO administration.
†Protocol violation.
‡Subject met stopping rule criteria for elevated BP on Day 29; study treatment was discontinued, and ESA 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.
§Subject remains in the study, still ongoing.

Sotatercept PK

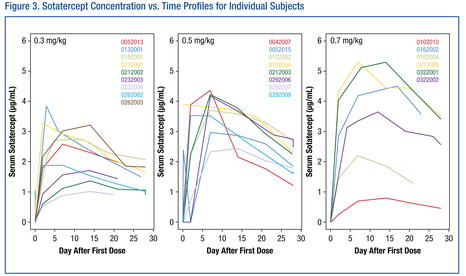
- PK data, based on analysis of all subjects randomized to sotatercept 0.3, 0.5, or 0.7 mg/kg, are presented in **Table 2**.
- Sotatercept exhibited dose-dependent increases in the serum drug exposure (maximum plasma concentration [C_{max}] and area under the concentration vs. time curve to infinity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

Table 2. Sotatercept PK in ESKD Subjects on Hemodialysis (Dose 1, Cycle 1)

	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8	Sotatercept 0.7 mg/kg n=5*
Parameter			
t_{max}, median (min–max), day	8 (3-14)	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_{day}, day•μg/mL	49.1 (42.2)	78.1 (21.3)	93.7 (45.2)
$t_{1/2}$, 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)

CV%=percent coefficient of variation; t_{max}=time to C_{max}; min–max=minimum–maximum; AUC_{∞}=AUC up to 28 days; CL/F=oral clearance; V_z/F=apparent volume of distribution.
*Sotatercept PK was not evaluated in 1 subject receiving sotatercept 0.7 mg/kg.
Note: 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.

Figure 3. Sotatercept Concentration vs. Time Profiles for Individual Subjects



Safety Assessments

- An overview of treatment-emergent adverse events (TEAEs) is summarized in **Table 3**. Subjects were followed for TEAEs up to 112 days after the last dose of study drug. Therefore, some TEAEs occurred after initiation of ESA for rescue.
- Most TEAEs were mild or moderate in severity, unrelated to study drug, relatively similar between groups, and generally consistent with subjects' medical histories.
- A small decrease in calcium levels during follow-up in subjects who had received sotatercept 0.3 mg/kg was noted, without TEAEs of hypocalcemia.
- There were no other observed trends in laboratory, electrocardiogram, or vital sign parameters, including study visit and intra-dialytic BP, in the sotatercept dose groups during long-term follow-up.
- One subject developed low levels of anti-drug antibodies without consequence to PK, Hb effect, or safety. No injection site reactions or hypersensitivity reactions were observed in any subjects.

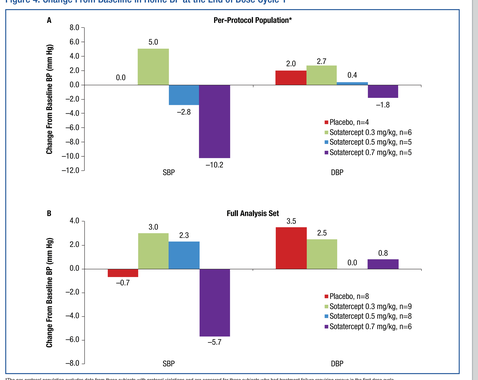
Table 3. Overview of TEAEs, Regardless of Relatedness or Causality (Safety Population, N=31)

	Placebo n=8	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8	Sotatercept 0.7 mg/kg n=6
Subjects, n (%)				
Days on study (cumulative)	1,320	2,371	1,845	645
Days on study drug (cumulative)	514	767	867	440
Any TEAE	5 (62.5)	8 (88.9)	6 (75.0)	6 (100.0)
Any TEAE related to study drug	2 (25.0)	2 (22.2)	0 (0.0)	1 (16.6)
Any severe TEAE	1 (12.5)	2 (22.2)	2 (25.0)	1 (16.6)
Any severe TEAE related to study drug	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
≥1 serious TEAE	2 (25.0)	4 (44.4)	1 (12.5)	2 (33.3)
Death	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs in ≥2 subjects in any treatment group, n (%)				
Fatigue	1 (12.5)	2 (22.2)	0 (0.0)	0 (0.0)
Pain	1 (12.5)	2 (22.2)	0 (0.0)	0 (0.0)
Constipation	1 (12.5)	2 (22.2)	1 (12.5)	0 (0.0)
Nausea	1 (12.5)	1 (11.1)	1 (12.5)	3 (50.0)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
Hypertension	1 (12.5)	3 (33.3)	0 (0.0)	1 (16.6)
Fall	2 (25.0)	1 (11.1)	0 (0.0)	1 (16.6)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
Increased blood phosphorous	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)

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, 0.5, and 0.7 mg/kg in the safety population (**Figure 4**).
- 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 (data not shown).

Figure 4. Change From Baseline in Home BP at the End of Dose Cycle 1

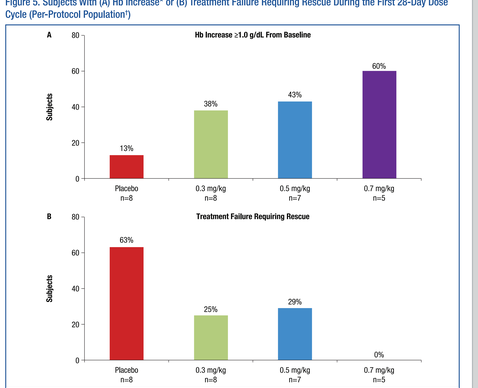


*The per-protocol population excludes data from those subjects with protocol violations and are censored for those subjects who had treatment failure requiring rescue in the first dose cycle.

Efficacy

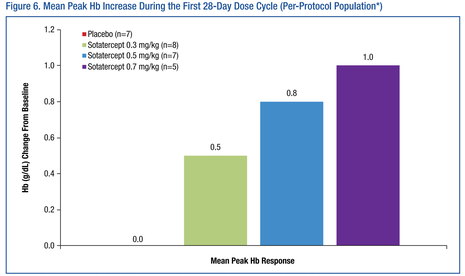
- Baseline Hb levels in the per-protocol population were similar to the full analysis set (**Table 1**): 9.5, 9.3, 8.9, and 9.2 g/dL in subjects receiving placebo, or sotatercept 0.3, 0.5, and 0.7 mg/kg, respectively.
- During the first 28-day dose cycle, an Hb increase of ≥1.0 g/dL was achieved by 13% (placebo), 38% (sotatercept 0.3 mg/kg), 43% (sotatercept 0.5 mg/kg), and 60% (sotatercept 0.7 mg/kg) of subjects (**Figure 5A**); rescue treatment was required by 63% (placebo), 25% (sotatercept 0.3 mg/kg), 29% (sotatercept 0.5 mg/kg), and 0% (sotatercept 0.7 mg/kg) of subjects (**Figure 5B**).
- The mean peak Hb increase in the first 28-day dose cycle was 0.0 g/dL in subjects receiving placebo, and 0.5, 0.8, and 1.0 g/dL in subjects receiving sotatercept 0.3, 0.5, and 0.7 mg/kg, respectively (**Figure 6**).
  - The ongoing washout of ESA effect (Hb decline before randomization) at the time of randomization was several times faster for the sotatercept groups compared with the placebo group and may have masked some of the treatment effect.

Figure 5. Subjects With (A) Hb Increase* or (B) Treatment Failure Requiring Rescue During the First 28-Day Dose Cycle (Per-Protocol Population†)



*Hb increase defined as ≥1.0 g/dL increase from baseline.
†The per-protocol population excludes data from those subjects with protocol violations and are censored for those subjects who had treatment failure requiring rescue in the first dose cycle.

Figure 6. Mean Peak Hb Increase During the First 28-Day Dose Cycle (Per-Protocol Population*)



*The per-protocol population excludes data from those subjects with protocol violations and are censored for those subjects who required rescue in the first dose cycle.

Long-term Change From Baseline Hb Concentration

- The Hb concentration in subjects who received sotatercept 0.3, 0.5, or 0.7 mg/kg exhibited a greater increase from baseline in the first 15 days post-treatment vs. placebo; however, the increases were not sustained through the entire dose cycle (data not shown), suggesting the need for a dosing regimen of once every 2 weeks instead of the once every 4 weeks used in this study.
- Hb levels throughout multiple dose cycles among subjects who did not have treatment failure requiring rescue were generally highest among subjects receiving sotatercept 0.5 mg/kg; longer-term evaluation of the sotatercept 0.7 mg/kg group is needed.

CONCLUSIONS

- Sotatercept exhibited dose linear PK characteristics, and a half-life of 21 to 26 days.
- All dose levels of sotatercept were well tolerated, with AEs similar to those observed with placebo and no trends toward increased BP.
- Exposure to sotatercept was not associated with injection site reactions or hypersensitivity reactions. One subject developed anti-drug antibodies without PK, pharmacodynamic, or safety consequences.
- In the first 28 days of sotatercept treatment, the proportion of subjects achieving the target Hb increase of ≥1 g/dL was dose dependent.
- Mean peak Hb response in the first 28 days was dose related, with the sotatercept 0.7 mg/kg dose group having the highest mean peak Hb response (1.0 g/dL).
- This interim analysis indicates adequate and dose-dependent Hb responses and safety of sotatercept at 0.3, 0.5, and 0.7 mg/kg in patients with ESKD on hemodialysis.
- Changes in Hb suggest a shorter dose cycle of once every 2 weeks instead of once every 4 weeks, as used in this study, may better maintain Hb levels in the target range.
- Based on these results, a phase 2 study of intravenous and SC administration of escalating dose levels of sotatercept every 14 days is ongoing (NCT01999582).

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