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

SP244

Mohamed El-Shahawy[1]; James Cotton[2]; Jeffrey Kaupke[3]; Thomas D. Wooldridge[4]; Michael Weiswasser[5]; William T. Smith[5]

[1]Academic Medical Research Institute, Los Angeles, CA, USA; [2]Tyler Nephrology Associates PC, Tyler, TX, USA; [3]Nephrology Specialist Medical Group, Orange, CA, USA; [4]Nephrology & Hypertension Associates LTD, Tupelo, MS, USA; [5]Celgene Corporation, Warren, NJ, USA

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 beta 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.
- 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,[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.
- 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 (2.4 [0.96] and 3.5 [0.73] µg/mL, respectively) and area under the plasma concentration-vs.-time curve (50.5 [17.4] and 73.2 [11.5] day•µg/mL, 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 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
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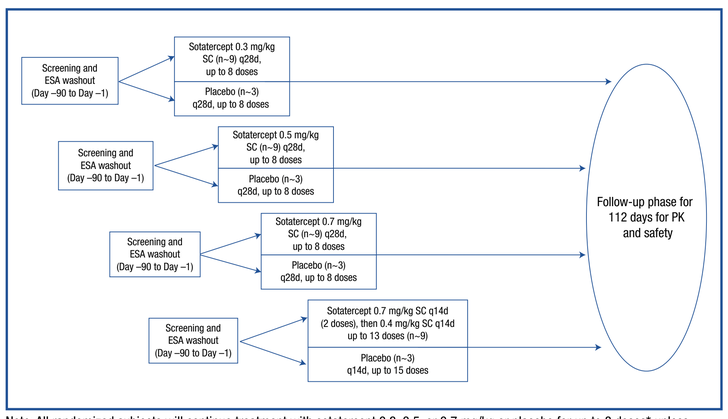
- Anticipated or scheduled living donor renal transplant

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.
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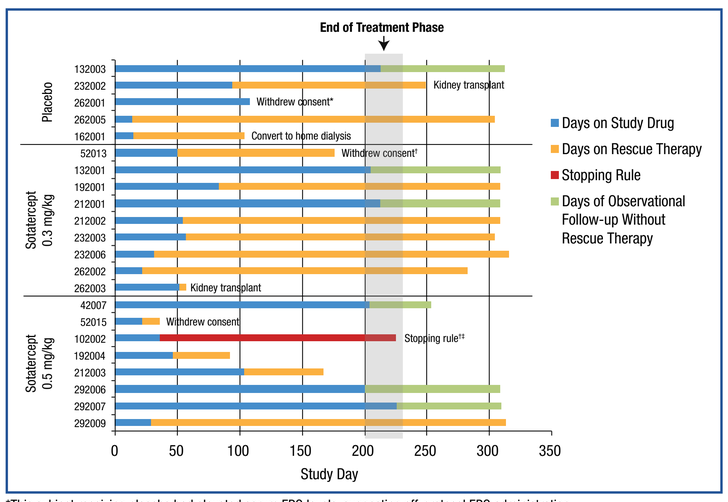
28 days after the 6th subject is dosed with sotatercept in each dose group (0.3, 0.5, and 0.7 mg/kg), an interim analysis will occur to evaluate PK and safety before opening the next dose group.

RESULTS

Subjects

- A total of 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



*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 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=22)

	Placebo n=5	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8
Age, mean (range), years	58.4 (39–76)	59.9 (36–79)	56.9 (42–76)
Female, n (%)	1 (20.0)	6 (66.7)	1 (12.5)
Race, n (%)			
White	1 (20.0)	3 (33.3)	4 (50.0)
Black	3 (60.0)	6 (66.7)	4 (50.0)
Asian	1 (20.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)			
Hispanic	0 (0.0)	2 (22.2)	4 (50.0)
Non-Hispanic	5 (100.0)	7 (77.8)	4 (50.0)
Postdialysis weight, mean, kg	75.8	79.4	79.1
Body mass index, mean, kg/m^2	25.4	27.8	26.5
Baseline Hb, mean (range), g/dL	9.7 (9.3–9.9)	9.3 (7.3–10.5)	8.9 (7.1–10.0)

- Major protocol violations were noted for 2 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. These subjects were excluded from the prespecified per-protocol efficacy analyses.
- Included in the per-protocol efficacy analysis population were:
  - 5 who received placebo.
  - 8 who received sotatercept 0.3 mg/kg.
  - 7 who received sotatercept 0.5 mg/kg.

Safety Assessments

- An overview of AEs is summarized in **Table 2**.
- A decrease in calcium levels was noted during follow-up in subjects who had received sotatercept 0.3 mg/kg, without AEs of hypocalcemia.
- No other observed trends in laboratory, electrocardiogram, or vital sign parameters were observed, 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.

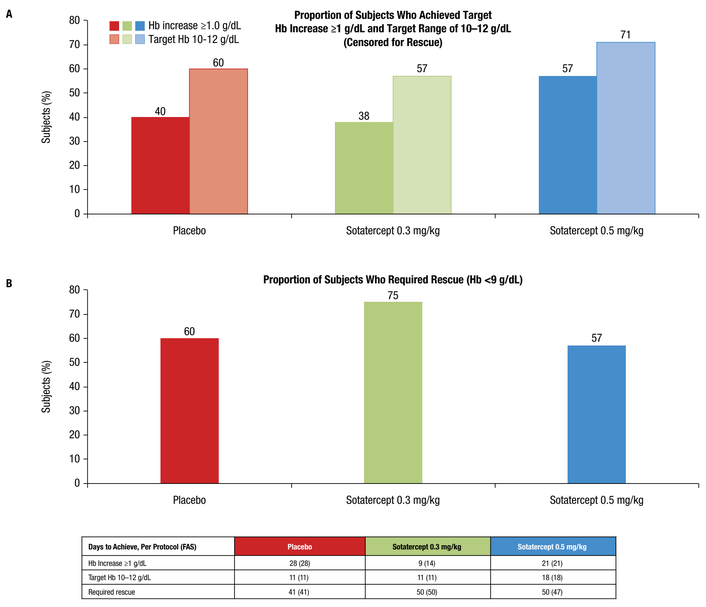
Table 2. Overview of AEs (Safety Population, N=22)

	Placebo n=5	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8
Days on study drug, mean	88	85	108
Subjects, n (%)			
Any AE	4 (80.0)	8 (88.9)	6 (75.0)
≥1 AE related to study drug	1 (20.0)	2 (22.2)	0 (0.0)
≥1 severe AE	2 (40.0)	2 (22.2)	2 (25.0)
≥1 serious AE	2 (40.0)	4 (44.4)	1 (12.5)
Death	1 (20.0)	0 (0.0)	0 (0.0)
AEs in ≥2 subjects in a treatment group, n (%)			
Fatigue	1 (16.6)	2 (22.2)	0 (0.0)
Pain	0 (0.0)	2 (22.2)	0 (0.0)
Constipation	1 (16.6)	2 (22.2)	0 (0.0)
Hypertension	0 (0.0)	3 (33.3)	0 (0.0)

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 mIU/dL (as high as 174 mIU/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 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.

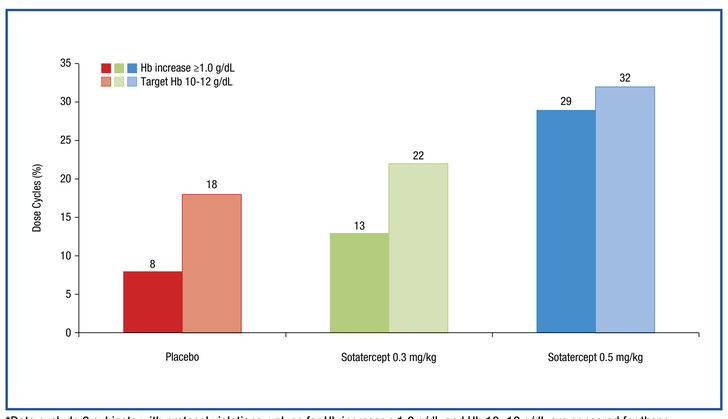
Figure 3. Hb Response at Any Time During the 225-Day Treatment Phase (Per-Protocol Population)*



Days to Achieve, Per Protocol (FAS)	Placebo	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg
Hb increase ≥1 g/dL	28 (28)	9 (14)	21 (21)
Target Hb 10–12 g/dL	11 (11)	11 (11)	18 (18)
Required rescue	41 (41)	50 (50)	50 (47)

*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 who required rescue treatment. One subject in the placebo group had elevated serum EPO levels, suggesting off-protocol EPO administration.

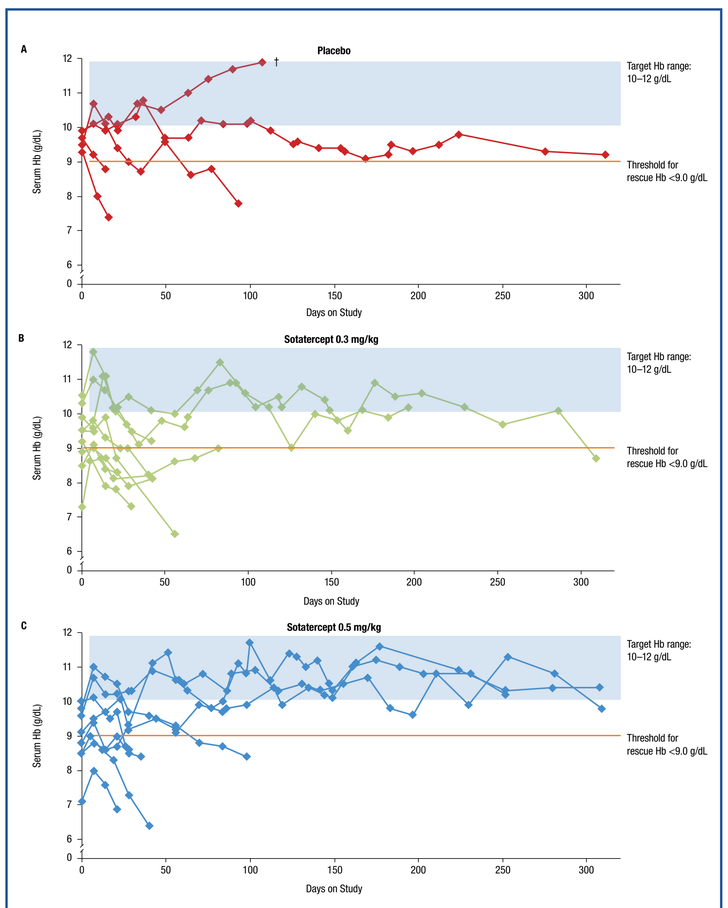
Figure 4. Percentage of Dose Cycles With Hb Response During the 225-Day Treatment Phase (Per-Protocol Population, Censored for Rescue)*



*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 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 more often sustained over 225 study days in subjects treated with sotatercept 0.5 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 Study (Per-Protocol Population, Censored for Rescue)*



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†Subject 262001 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, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg in the safety population (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, 6.0, 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 rescue 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.

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This study was sponsored by Celgene Corporation.

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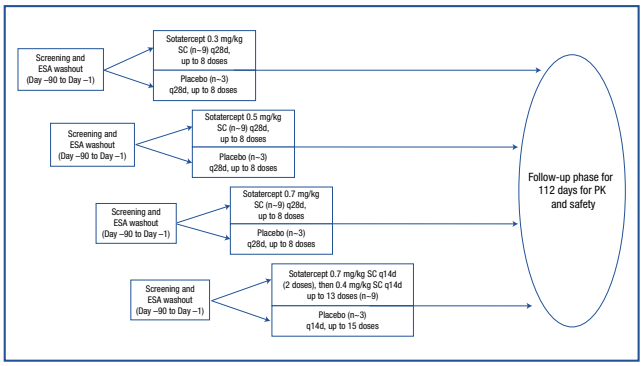

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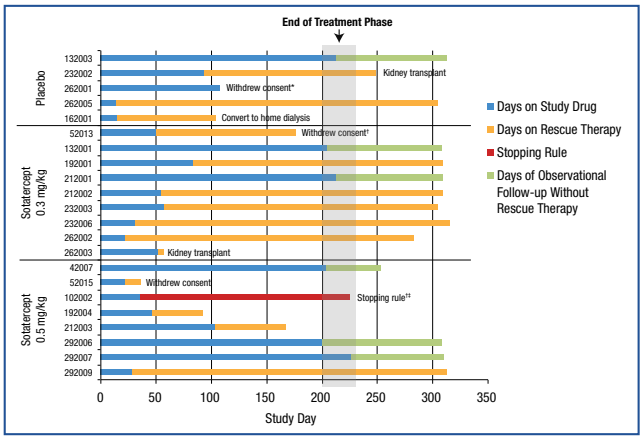

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Baseline Hb, mean (range), g/dL	9.7 (9.3–9.9)	9.3 (7.3–10.5)	8.9 (7.1–10.0)

- Major protocol violations were noted for 2 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. These subjects were excluded from the prespecified per-protocol efficacy analyses.
- Included in the per-protocol efficacy analysis population were:
  - 5 who received placebo.
  - 8 who received sotatercept 0.3 mg/kg.
  - 7 who received sotatercept 0.5 mg/kg.

Safety Assessments

- An overview of AEs is summarized in **Table 2**.
- A decrease in calcium levels was noted during follow-up in subjects who had received sotatercept 0.3 mg/kg, without AEs of hypocalcemia.
- No other observed trends in laboratory, electrocardiogram, or vital sign parameters were observed, 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.

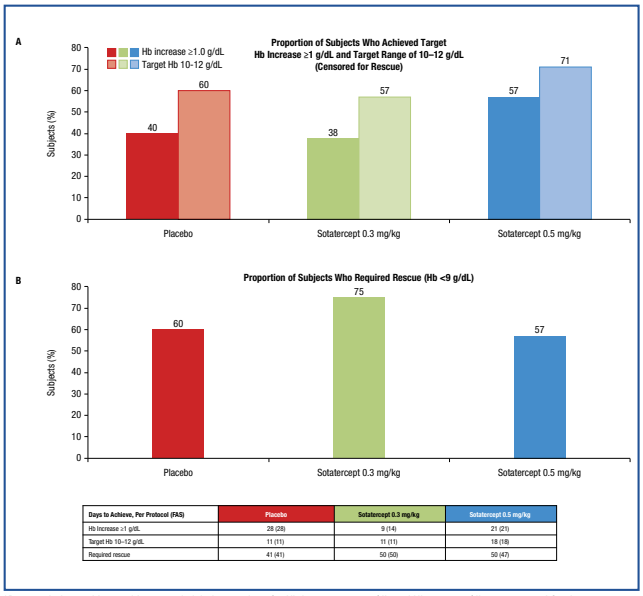
Table 2. Overview of AEs (Safety Population, N=22)

	Placebo n=5	Sotatercept 0.3 mg/kg n=9	Sotatercept 0.5 mg/kg n=8
Days on study drug, mean	88	85	108
Subjects, n (%)			
Any AE	4 (80.0)	8 (88.9)	6 (75.0)
≥1 AE related to study drug	1 (20.0)	2 (22.2)	0 (0.0)
≥1 severe AE	2 (40.0)	2 (22.2)	2 (25.0)
≥1 serious AE	2 (40.0)	4 (44.4)	1 (12.5)
Death	1 (20.0)	0 (0.0)	0 (0.0)
AEs in ≥2 subjects in a treatment group, n (%)			
Fatigue	1 (16.6)	2 (22.2)	0 (0.0)
Pain	0 (0.0)	2 (22.2)	0 (0.0)
Constipation	1 (16.6)	2 (22.2)	0 (0.0)
Hypertension	0 (0.0)	3 (33.3)	0 (0.0)

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 mIU/dL (as high as 174 mIU/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 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.

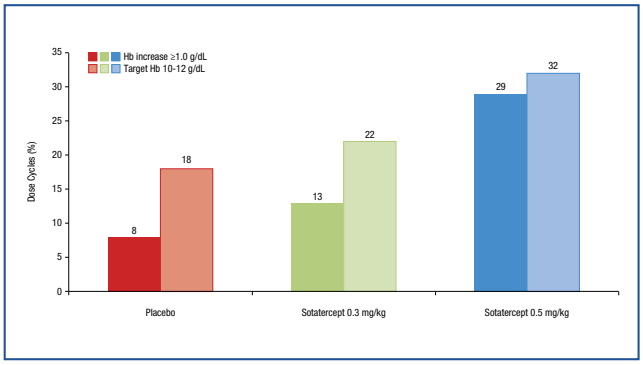
Figure 3. Hb Response at Any Time During the 225-Day Treatment Phase (Per-Protocol Population)*



Days to Achieve, Per Protocol (FAS)	Placebo	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg
Hb increase ≥1 g/dL	28 (28)	9 (14)	21 (21)
Target Hb 10–12 g/dL	11 (11)	11 (11)	18 (18)
Required rescue	41 (41)	50 (50)	50 (47)

*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 who required rescue treatment. One subject in the placebo group had elevated serum EPO levels, suggesting off-protocol EPO administration.

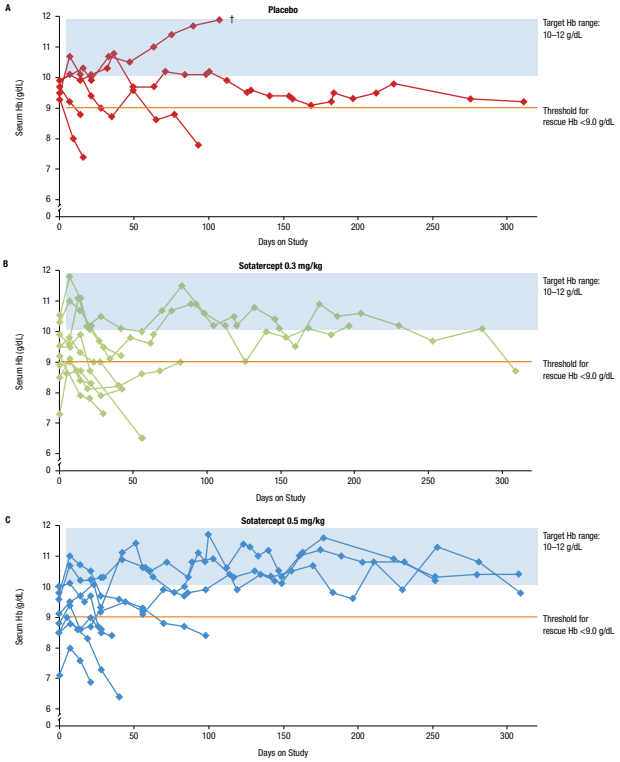
Figure 4. Percentage of Dose Cycles With Hb Response During the 225-Day Treatment Phase (Per-Protocol Population, Censored for Rescue)*



*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 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 more often sustained over 225 study days in subjects treated with sotatercept 0.5 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 Study (Per-Protocol Population, Censored for Rescue)*



*Data exclude 2 subjects with protocol violations and are censored for those who required rescue treatment.
†Subject 262001 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, sotatercept 0.3 mg/kg, and sotatercept 0.5 mg/kg in the safety population (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, 6.0, 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 rescue 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.

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This study was sponsored by Celgene Corporation.

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