Safety and Hemoglobin Effect of Sotatercept, Administered Intravenously and Subcutaneously, for Maintenance of Hemoglobin in Hemodialysis Subjects: Interim Analysis of a Phase 2 Study

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Disclosures

- Frank Dellanna has received fees as a speaker for Mitsubishi, Otsuka, Roche, and Sandoz/Hexal
- Francisco Maduell has received fees as a speaker for Amgen, Baxter, Bellco, Fresenius, and Nipro
- Joan Fort has received fees as a speaker for Baxter
- Xavier Warling has nothing to disclose
- Hem Nalini Singh is an employee of and shareholder in Celgene Corporation
- William T. Smith is an employee of and shareholder in Celgene Corporation, and is a shareholder in Johnson & Johnson

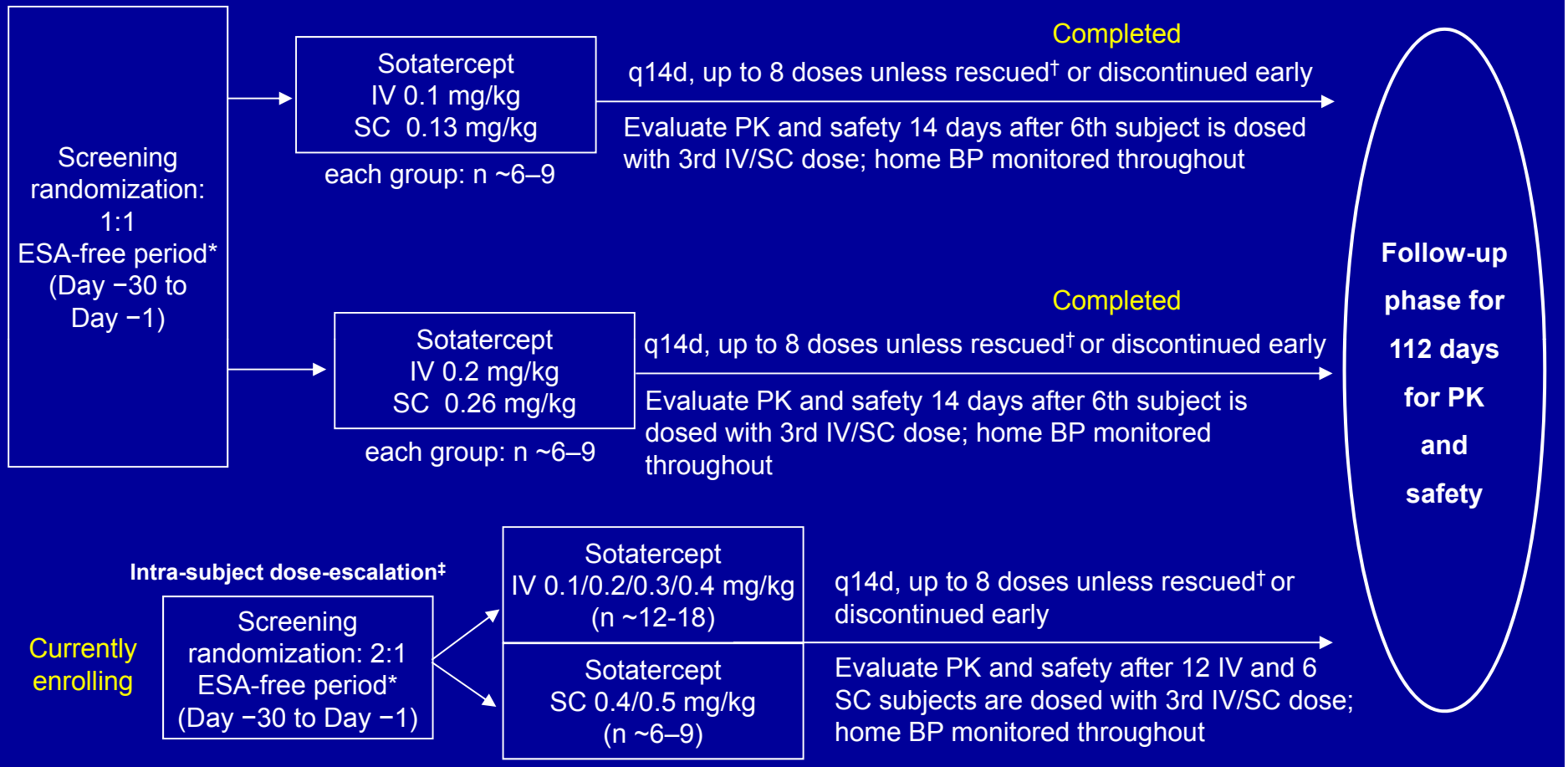
Introduction

- Patients with ESKD exhibit anemia, primarily caused by decreased renal biosynthesis of erythropoietin[1]
- Sotatercept (ACE-011) is an ActRIIA-IgG1 fusion protein that binds with high affinity to activin A and other members of the TGF-β superfamily that are negative regulators of erythropoiesis, thereby promoting the release of mature erythrocytes[2,3]
- Sotatercept is being studied in ESKD subjects on HD in 2 ongoing studies:
  - For the correction of anemia in the ongoing REN-001 study in the US[4]
    - REN-001 is also evaluating sotatercept's effects on CKD-MBD; preliminary results show a slowing of progression of vascular calcification and increased cortical bone mass[5]
  - Interim findings are presented here from an ongoing randomized study (REN-002) evaluating sotatercept, IV and SC, for maintenance of Hb in ESKD subjects on HD

ESKD=end-stage kidney disease; ActRIIA=type II activin A receptor; TGF-β=transforming growth factor-beta; HD=hemodialysis; CKD-MBD=chronic kidney disease and mineral/bone disorder; IV=intravenous; SC=subcutaneous; Hb=hemoglobin.

1. McGonigle RJS, et al. *Kidney Int.* 1984;25:437-444. 2. Iancu-Rubin C, et al. *Exp Hematol.* 2013;41:155-166. 3. Carrancio S, et al. *Br J Haematol*. 2014;165:870-882. 4. Smith W, et al. ERA. 2015 [poster FP-661]. 5. Smith W. et al. ERA. 2015 [poster SP645].

REN-002 Study Design



***ESA-free period of 5 to 10 days began following randomization, before first dose of sotatercept; duration was dependent on ESA and route of administration.**

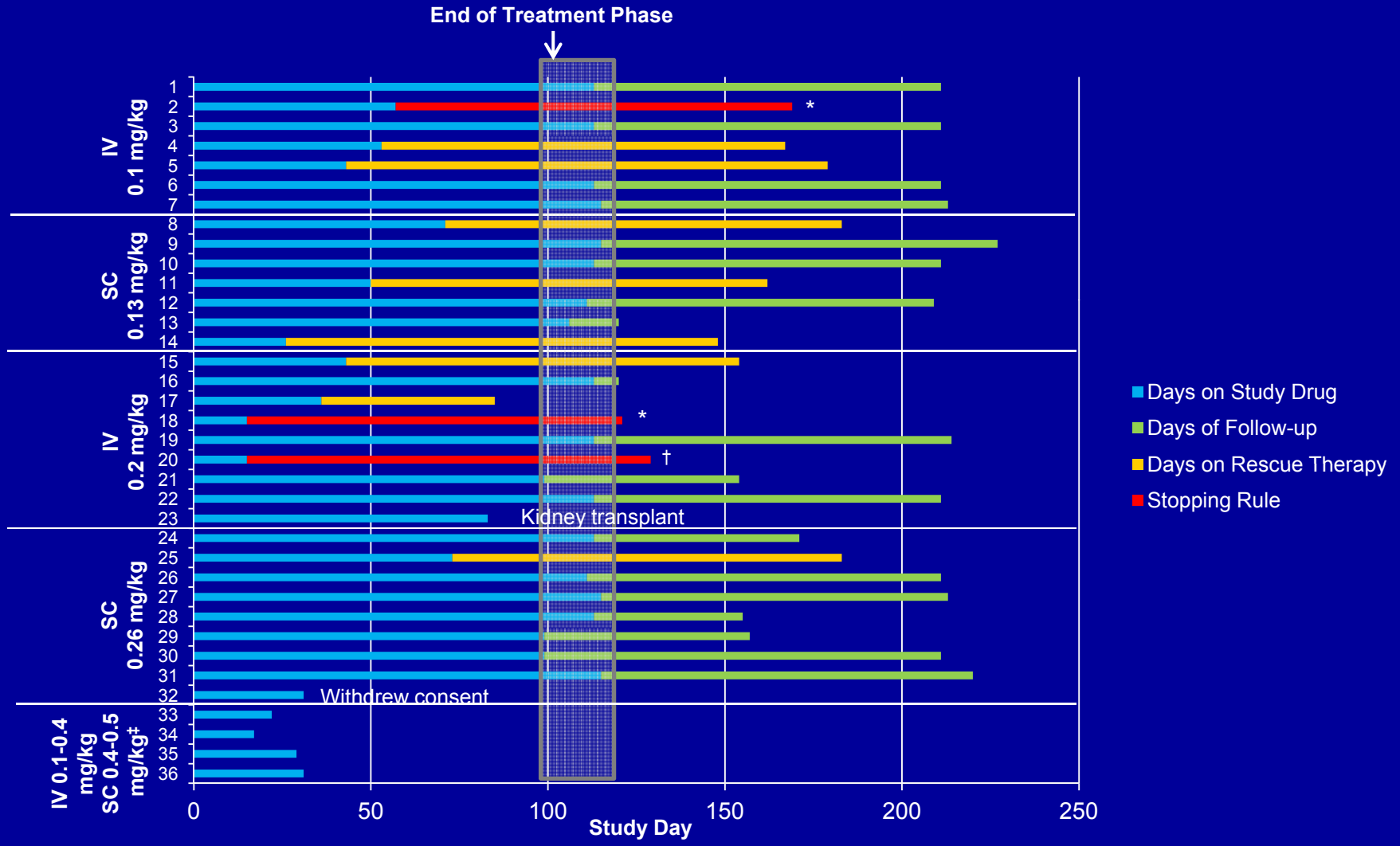
†If Hb was <9.0 g/dL, subjects were given rescue treatment with an ESA or blood transfusion and discontinued study drug, but remained in study for safety follow-up.

‡With sotatercept, IV or SC, dose could be increased if: 1) Hb increased <1 g/dL from baseline, or 2) Hb was <10 g/dL, within 7 days before dosing.

BP=blood pressure; ESA=erythropoiesis-stimulating agents; PK=pharmacokinetics.

Subject Disposition

- 36 subjects were randomized and received ≥1 dose of study medication



*Subject met stopping rule criteria for elevated blood pressure (BP). †Subject met stopping rule for elevated Hb (>13.0 g/dL for >7 days).

‡Findings for subjects in the highest sotatercept dosing groups (IV 0.1-0.4 mg/kg: n=2; SC 0.4-0.5 mg/kg: n=2) are not presented due to insufficient post-baseline follow-up data; enrollment in these groups is ongoing.

Baseline Demographic Characteristics of Randomized Subjects

(Dose Groups 1 and 2)

	Sotatercept			
	IV 0.1 mg/kg n=7	**IV 0.2 mg/kg n=9**	**SC 0.13 mg/kg n=7**	**SC 0.26 mg/kg n=9**
Age, mean, years	59.0	59.4	62.3	61.9
Female, n (%)	4 (57.1)	4 (44.4)	3 (42.9)	3 (33.3)
Race, n (%)				
White	4 (57.1)	6 (66.7)	5 (71.4)	8 (88.9)
Black/African-American	1 (14.3)	1 (11.1)	1 (14.3)	0 (0.0)
Asian	2 (28.6)	2 (22.2)	0 (0.0)	1 (11.1)
Other	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Ethnicity, n (%)				
Hispanic	0 (0.0)	1 (11.1)	1 (14.3)	0 (0.0)
Non-Hispanic	7 (100.0)	8 (88.9)	6 (85.7)	9 (100.0)
Postdialysis weight, mean, kg	78.7	73.8	79.9	80.4
Body mass index, mean, kg/m^2	26.8	26.4	28.7	27.8
Hemoglobin, mean, g/dL	11.0	11.3	10.7	11.0

Sotatercept Pharmacokinetics by Route of Administration and Dose

- For 24 subjects with evaluable data (IV: n=12; SC: n=12), sotatercept AUC and C_{max} are higher when administered IV vs. SC
- Mean AUC_{∞} is increased by ≤41% in response to a 100% increase in dose levels for both dosing routes of administration
- Mean $t_{1/2}$ in serum ranged from 12 to 26 days

	Sotatercept			
PK Parameters*	**IV 0.1 mg/kg n=7**	**IV 0.2 mg/kg n=5**	**SC 0.13 mg/kg n=7**	**SC 0.26 mg/kg n=5**
C_{max}, μg/mL	2.3 (28.5)	2.8 (69.8)	1.1 (38.0)	0.9 (20.9)
T_{max}, day	NA	NA	8 (4–13)	12 (1–18)
AUC_{∞}, day•μg/mL	48.2 (79.7)	67.7 (29.6)	34.5 (39.5)	45.5 (13.7)
CL or CL/F, mL/day	158 (109.8)	208 (39.8)	298 (56.4)	409 (32.5)
$t_{1/2}$, day†	18.6 (42.7)	12.2 (96.6)	26.0 (35.3)	22.9 (31.0)

Note: The n reflects the number of randomized subjects who underwent PK testing; actual number of subjects with data available for each parameter may vary. Pharmacokinetic parameters are estimated using a 2-compartment model unless stated otherwise.

*Data are expressed as median (min-max) for T_{max} and geometric mean (CV%) for all other parameters.
†Estimated by non-compartmental method using concentrations after the last dose.

AUC=area under the concentration-vs.-time curve; C_{max}=maximum plasma concentration; $t_{1/2}$=terminal half-life; T_{max}=time to C_{max}; CL or CL/F=total clearance; NA=not applicable.

Safety
(Dose Groups 1 and 2)

- TEAEs were mostly mild, unrelated to study drug, and similar between treatment groups and generally consistent with subjects' medical histories
- No injection site or hypersensitivity reactions were observed
- Home BP measurements showed no consistent route- or dose-dependent changes from baseline among subjects in any of the treatment groups (mean change from baseline to Day 99 post-dose, range: SBP: −25 to 12 mm Hg; DBP: −16 to 8 mm Hg)
- With sotatercept IV: in the 0.1 mg/kg IV group, 1 subject was discontinued after the first dose due to the stopping rule for elevated home BP; in the 0.2 mg/kg IV group, 1 subject experienced an AE of hypertension that led to study drug discontinuation while 1 subject experienced both an AE of hypertension and the BP stopping rule; changes in BP in these subjects were generally transient
- 1 subject who received sotatercept IV 0.2 mg/kg was discontinued after the first dose due to the stopping rule for elevated Hb

DBP=diastolic blood pressure; SBP=systolic blood pressure; TEAEs=treatment-emergent adverse events; AE=adverse event; Hb=hemoglobin.

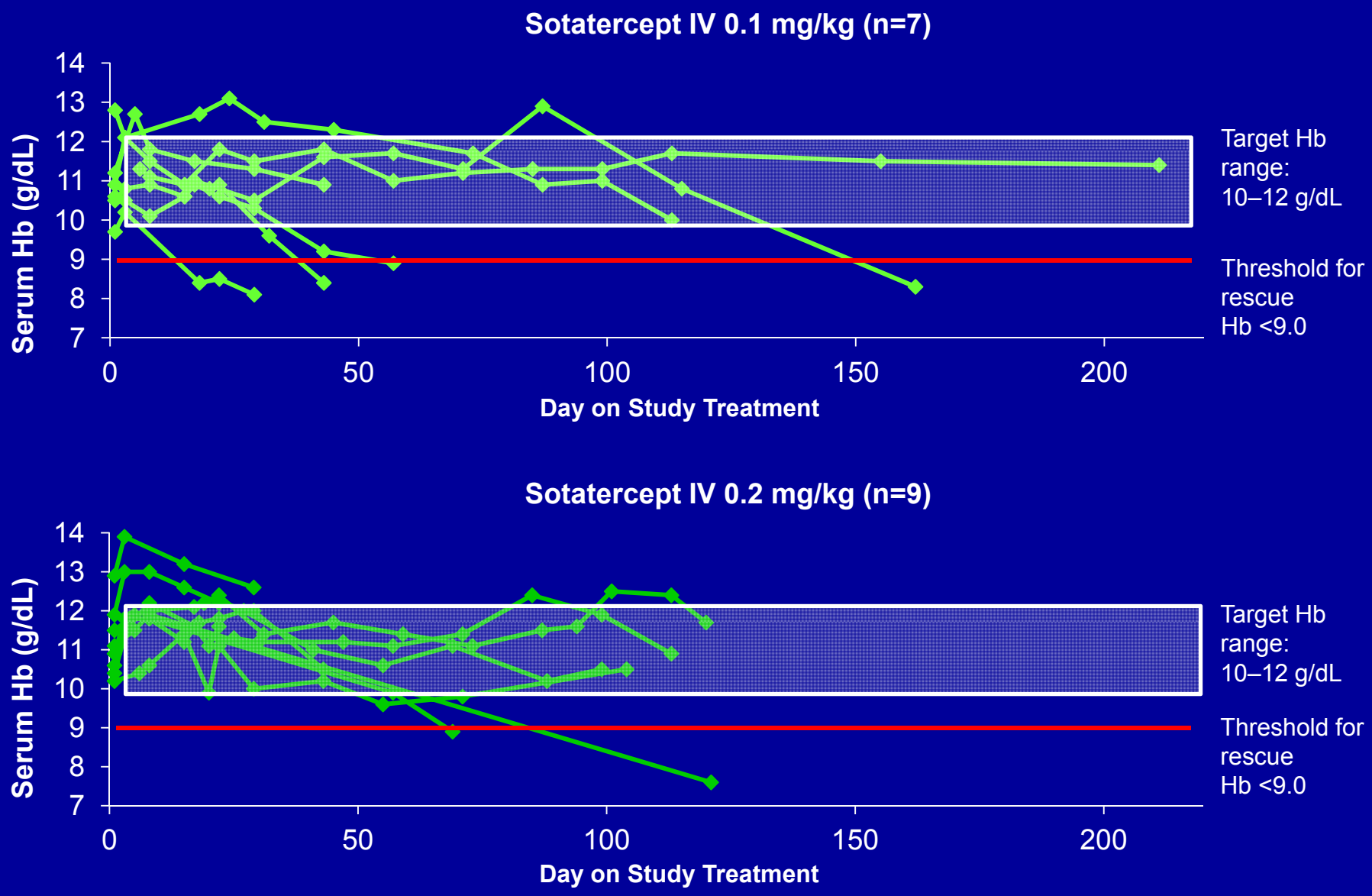
Safety
(Dose Groups 1 and 2)

	Sotatercept			
	IV 0.1 mg/kg n=7	**IV 0.2 mg/kg n=9**	**SC 0.13 mg/kg n=7**	**SC 0.26 mg/kg n=9**
Subjects, n (%)				
Any TEAE*	7 (100.0)	7 (77.8)	6 (85.7)	7 (77.8)
TEAE related to study drug	1 (14.3)	1 (11.1)	1 (14.3)	0 (0.0)
Severe TEAE	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
Serious TEAE	2 (28.6)	1 (11.1)	0 (0.0)	1 (11.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs in ≥2 subjects in any treatment group, n (%)				
Hypertension	0 (0.0)	2 (22.2)	0 (0.0)	1 (11.1)
Muscle spasm	0 (0.0)	0 (0.0)	1 (14.3)	2 (22.2)

*TEAE is defined as any adverse event with a start date on or after date of first dose of study drug.

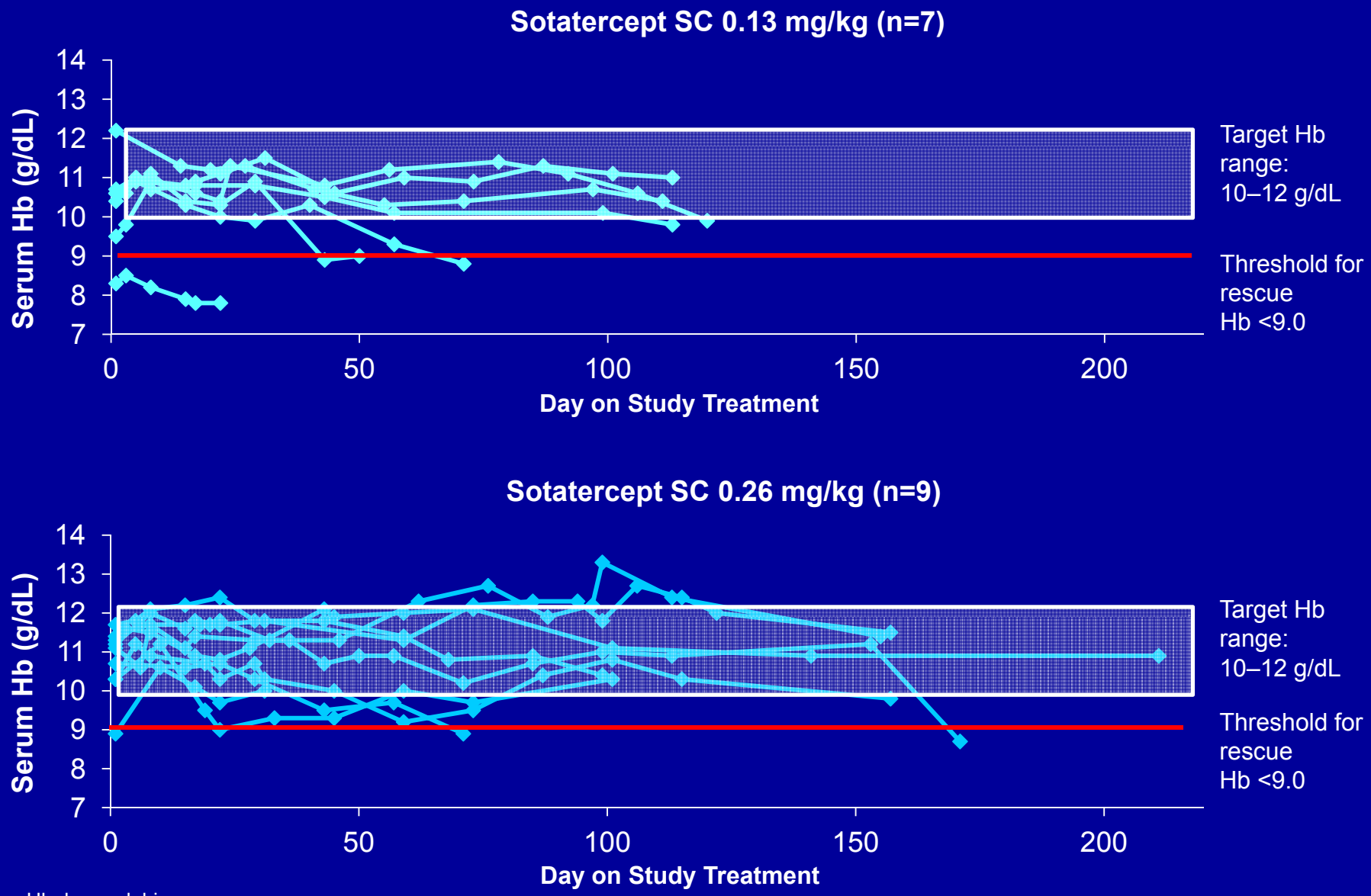
TEAE=treatment-emergent adverse event; AEs=adverse events.

Serum Hb Concentrations: Sotatercept IV



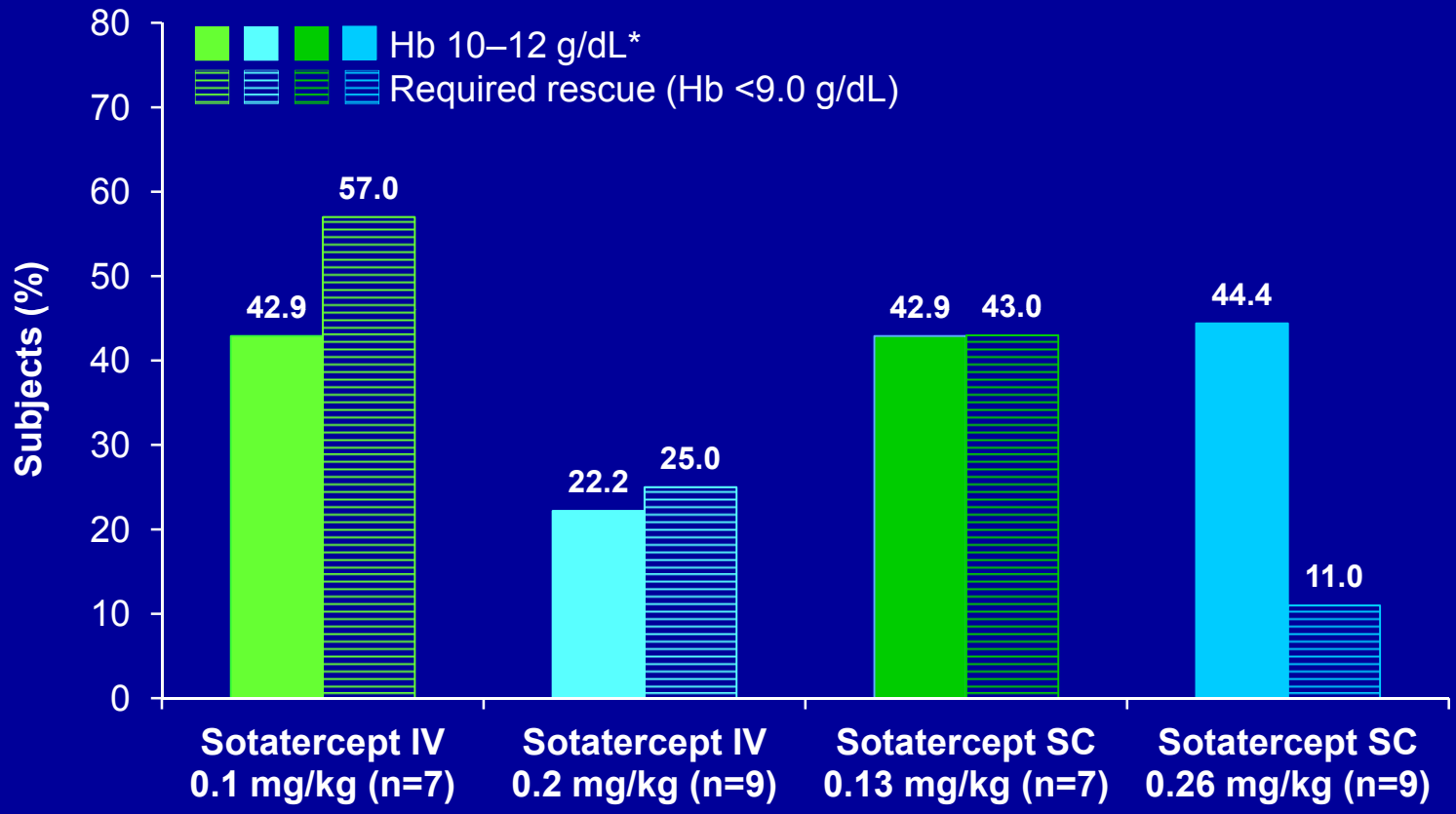
Hb=hemoglobin.

Serum Hb Concentrations: Sotatercept SC



Hb=hemoglobin.

Percentage of Subjects Achieving Target Hb (10–12 g/dL) or Requiring Rescue

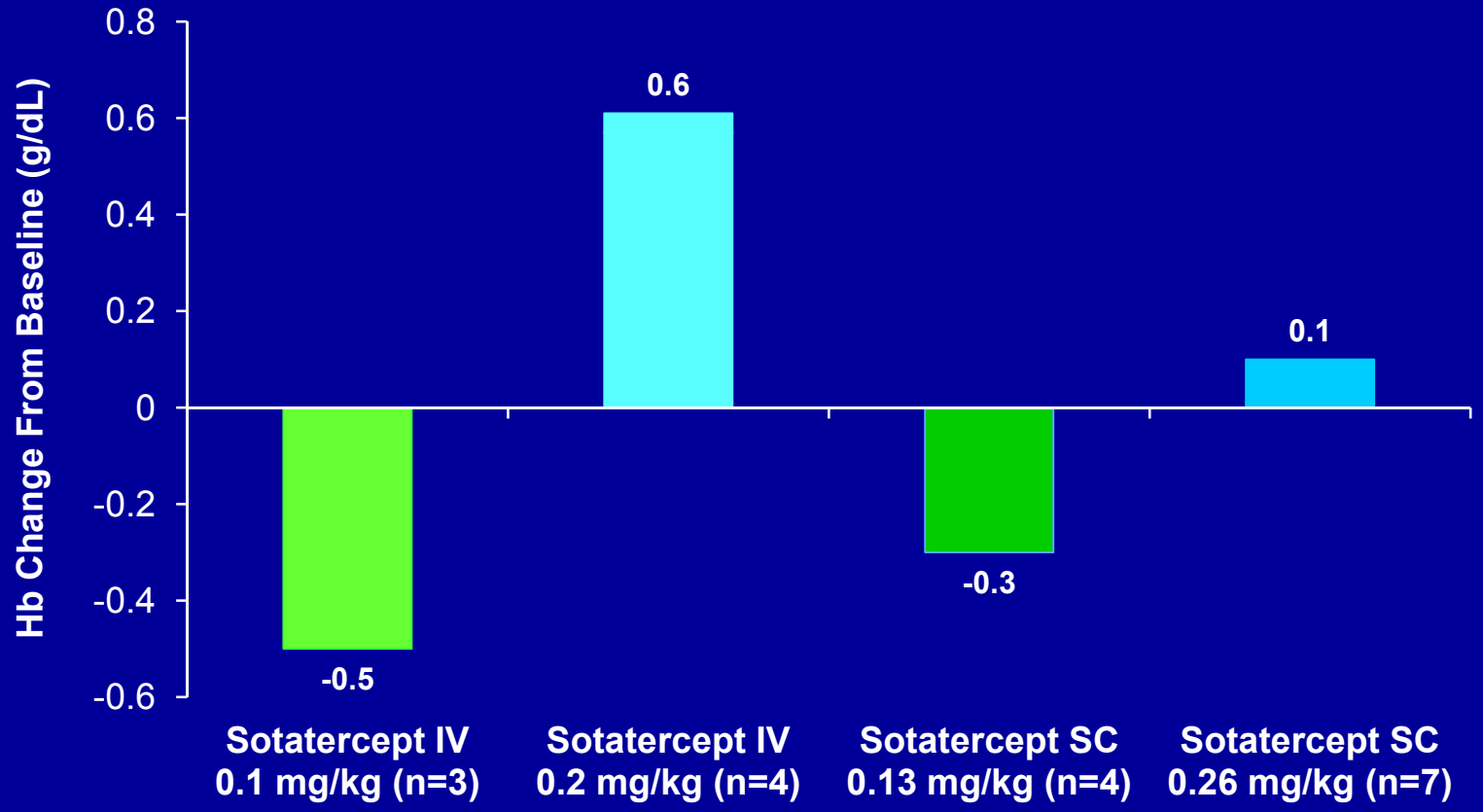


*Subjects who achieved target Hb range without the need for rescue.

- The proportion of subjects who experienced ≥1 dose hold due to elevated Hb (>12.0 g/dL) was 28.6%, 44.4%, 42.9%, and 22.2% in the sotatercept IV 0.1 mg/kg, IV 0.2 mg/kg, SC 0.13 mg/kg, and SC 0.26 mg/kg dose groups, respectively

Hb Change From Baseline to Evaluation Phase (Censored for Rescue)*

- At the end of the treatment phase, subjects receiving higher doses of sotatercept, given either IV or SC, showed a mean increase in Hb from baseline



*Analysis includes data as observed in subjects with baseline Hb and mean evaluation phase Hb, from samples obtained from Study Days 99 to 113.

Conclusions

- Sotatercept has an acceptable safety profile in ESKD subjects on HD and is well tolerated for up to eight 14-day dose cycles
  - There were no route- or dose-dependent changes in home BP measurements
- Sotatercept SC 0.26 mg/kg was associated with stable Hb levels
- Sotatercept IV 0.2 mg/kg SC 0.26 mg/kg were associated with lower rates of rescue with ESAs
- Sotatercept IV 0.2 mg/kg was associated with earlier discontinuations due to elevated Hb or BP stopping criteria
  - This led to a change in protocol to intra-subject dose escalation in the third dose groups to account for an early ESA effect, which diminishes over time after the switch to sotatercept
- Enrollment in the dose escalation groups (sotatercept IV 0.1-0.4 mg/kg and SC 0.4-0.5 mg/kg) is ongoing