Quantitative Computed Tomography Results for Bone Mass and Abdominal Aortic Vascular Calcification in Hemodialysis Subjects Treated With Escalating Dose Levels of Sotatercept: Interim Analysis of ACE-011-REN-001

SP645

William T. Smith[1]; Hartmut Malluche[2]; Keith Hruska[3]

[1]Celgene Corporation, Warren, NJ, USA; [2]University of Kentucky, Lexington, KY, USA; [3]Washington University St Louis, St Louis, MO, USA

INTRODUCTION

- Renal osteodystrophy (ROD) and vascular calcification (VC) are integral components of chronic kidney disease-mineral/bone disorder (CKD-MBD). CKD-MBD is strongly associated with greatly increased morbidity and mortality in end-stage kidney disease (ESKD).[1]
- Activin A is a transforming growth factor-β superfamily protein that is found at high levels in bone; its signaling is through the type II activin A receptor (ActRIIA).[2-4] Inhibin, an inhibitor of activin A signaling, is produced in the ovaries and stimulates bone growth.[2,5] Decreased inhibin expression is associated with post-menopausal bone loss.[5]
  - Non-clinical studies suggest that RAP-011 (the murine ActRIIA-IgG1 ligand trap that inhibits ActRIIA signaling) modulates the balance between bone formation and bone resorption activity by blocking signaling through the ActRIIA receptor.[2,6,7]
  - In a 5/6 nephrectomy mouse model of CKD that exhibits bone loss, bone mass measurements were significantly improved with 8 weeks of RAP-011 treatment, compared with the control mice.[6]
- In a mouse model of *ldlr*-/- high-fat fed, 5/6 nephrectomy for VC, RAP-011 inhibited bone resorption and increased bone volume. RAP-011 also inhibited Smad-dependent signaling, blocked aortic osteoblastic transition, increased vascular smooth muscle protein levels, and decreased CKD-stimulated VC.[8] These effects appear to be mediated by RAP-011 inhibition of CKD-stimulated endothelial to mesenchymal transition.[9]
- Sotatercept (ACE-011), a human ActRIIA-IgG1 ligand trap that inhibits ActRIIA signaling, improved total hip bone mineral density (BMD) with a 2.4% increase compared with a 0.7% decrease with placebo after 4 months in a post-menopausal healthy volunteer clinical trial.[10]
- Sotatercept is being studied in subjects on hemodialysis (HD) for the correction of anemia and improvement of measures of CKD-MBD. Sotatercept blocks activin A signaling and may reduce osteoclastogenesis, promote osteoblast maturation in bone, and reduce arterial osteoblastic transition.[8,9]
- The current exploratory analysis in HD subjects evaluated the effect of sotatercept on BMD and VC using quantitative computed tomography (QCT)[10-12] and expands the dataset.[13]
- At the time of abstract submission, enrollment in a sotatercept dose group using a 14-day dose cycle was ongoing.
- Interim results for safety and hemoglobin (Hb) effects are presented elsewhere.[14]

METHODS

- In an ongoing study of sotatercept in HD subjects for the correction of anemia, subjects responding to an erythropoietin-stimulating agent (ESA) were washed out of their ESA effect until Hb was <10 g/dL, and then randomized (3:1) to receive escalating dose levels of SC sotatercept (0.3 mg/kg, 0.5 mg/kg, or 0.7 mg/kg) or placebo every 28 days for up to 8 dose cycles. The study design and dosing are described in detail elsewhere.[14] Treatment failures (Hb <9 g/dL) were treated with ESA and/or red blood cell transfusion (rescue therapy).
- QCT of the hip, lumbar spine, and abdominal aorta was obtained at baseline and after the 225-day treatment phase.
  - Trabecular volumetric BMD (vBMD) (mg/cm^3) was determined for 2 vertebrae within L1-4 (typically L1-2).
  - The left proximal femurs were analyzed for vBMD of the cortical, trabecular, and integral bone compartments of the total hip, femoral neck, and trochanteric regions.
  - VC of the abdominal aorta was assessed using software that semi-automatically segmented the area and volume of calcifications within the region adjacent to the top of L1 through the bottom of L4. The number and location of slices was maintained across visits per subject. Agatston and square root transformed volumetric scores were determined as described elsewhere.[10,11] Lower total Agatston and square root transformed total volume scores (mm^3) indicate lower levels of VC.
  - All image quality control and blinded analyses were performed centrally by PAREXEL imaging (PAREXEL International Corp, Waltham, MA).
  - Results are based on all available data from the 21 subjects who had paired QCT assessments.

RESULTS

Subjects

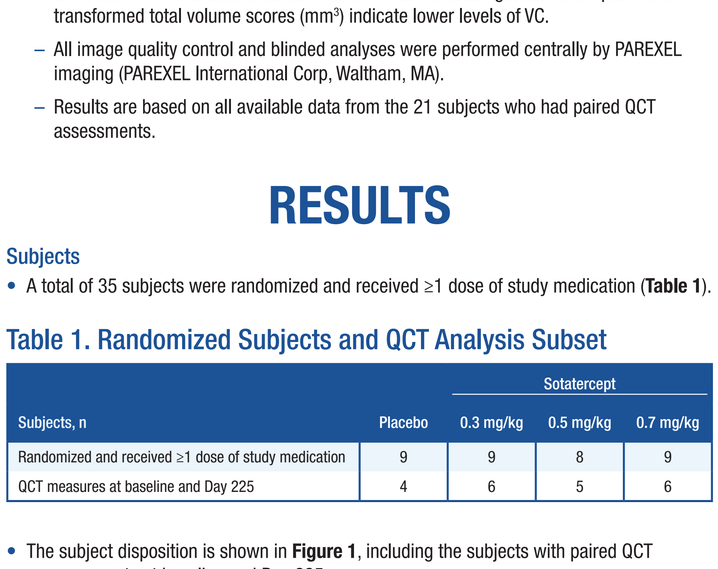
- A total of 35 subjects were randomized and received ≥1 dose of study medication (**Table 1**).

Table 1. Randomized Subjects and QCT Analysis Subset

Subjects, n	Placebo	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 0.7 mg/kg
Randomized and received ≥1 dose of study medication	9	9	8	9
QCT measures at baseline and Day 225	4	6	5	6

- The subject disposition is shown in **Figure 1**, including the subjects with paired QCT measurements at baseline and Day 225.
  - Most subjects who were discontinued from study treatment had treatment failure requiring rescue (generally because of Hb <9 g/dL; most common in the placebo and sotatercept 0.3 mg/kg groups); no subject discontinued treatment because of an adverse event (AE).
  - Of the 21 subjects with paired QCT measurements, 12 required rescue therapy due to Hb treatment failure during the treatment phase, 9 of whom required rescue within the first 3 dose cycles.
- Among subjects with paired QCT measurements, baseline demographic and clinical characteristics were generally similar across treatment groups (**Table 2**); however, there was a substantially longer time on dialysis in the placebo group, which was also the youngest group. There were also differences between groups in baseline biomarker and Agatston scores (**Table 3**).

Figure 1. Subject Disposition



Note: "•" indicates the subjects with paired QCT measurements at baseline and Day 225.
*One placebo subject who withdrew consent on Study Day 108 died on Study Day 148; 1 placebo subject who was receiving rescue therapy died on Study Day 186.
†Subject met stopping rule criteria for elevated blood pressure 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 blood pressure, based on incomplete evaluation, at baseline.

Table 2. Baseline Demographic and Clinical Characteristics of Subjects With Paired QCT Measurements

	Placebo n=4	Sotatercept 0.3 mg/kg n=6	Sotatercept 0.5 mg/kg n=5	Sotatercept 0.7 mg/kg n=6
Age, mean, years	51.3	57.3	60.8	63.0
Female, n (%)	1 (25.0)	4 (66.7)	0 (0.0)	4 (66.7)
Race, n (%)				
White	1 (25.0)	3 (50.0)	3 (60.0)	5 (83.3)
Black	2 (50.0)	3 (50.0)	2 (40.0)	1 (16.7)
Asian	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic	0 (0.0)	2 (33.3)	3 (60.0)	2 (33.3)
Non-Hispanic	4 (100.0)	4 (66.7)	2 (40.0)	4 (66.7)
Postdialysis weight, mean, kg	65.5	80.3	79.4	84.5
Body mass index, mean, kg/m^2	24.2	27.7	26.9	29.9
Diabetes, n (%)	2 (50.0)	5 (83.3)	5 (100.0)	5 (83.3)
Parathyroidectomy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time on dialysis, mean, months	165.8	43.3	22.4	68.1
Non-calcium phosphate binder, n (%)*	4 (100.0)	3 (50.0)	3 (60.0)	3 (50.0)
Calcium-based phosphate binder, n (%)*	1 (25.0)	4 (66.7)	4 (80.0)	4 (66.7)
Calcimimetic, n (%)*	1 (25.0)	2 (33.3)	0 (0.0)	2 (33.3)
1,25-OH vitamin D analog, n (%)	3 (75.0)	5 (83.3)	2 (40.0)	4 (66.7)

*Subjects could be receiving multiple types of binders.

Table 3. Mean Baseline Biomarker, Volumetric BMD, and Agatston Scores of Subjects With Paired QCT Measurements

	Placebo n=4	Sotatercept 0.3 mg/kg n=6	Sotatercept 0.5 mg/kg n=5	Sotatercept 0.7 mg/kg n=6
Whole PTH, pg/mL	209.2	104.8	135.5	100.4
BSAP*, µg/L	24.0	18.0	13.2	15.5
P1NP†, ng/mL	548.3	376.2	468.4	437.5
CTX‡, pg/mL	3,152.3	2,062.5	2,266.8	2,246.5
Total hip integral BMD, mg/cm^3	276.8	286.6	280.0	281.0
Femoral neck cortical BMD, mg/cm^3	640.5	667.0	593.1	594.8
Spine (L1, L2) BMD, mg/cm^3	140.1	125.6	149.1	118.7
VC total Agatston score§	6,498.8	9,472.7	3,618.5	1,862.1

Note: The n reflects the number of randomized subjects with paired QCT assessments; actual number of subjects available for each parameter may vary. PTH=parathyroid hormone.
*Bone-specific alkaline phosphatase (BSAP) reference range: males, 6-30; females (premenopausal), 3-19; females (postmenopausal), 6-26.
†Procollagen type 1 N-propeptide (P1NP) reference range: males, 30-110; females, 20-108.
‡C-terminal telopeptide (CTX) reference range: males, 0-854; females (premenopausal), 26-573; females (postmenopausal), 104-1,008.
§Lower Agatston scores indicate lower levels of VC.

Safety Assessments

- The safety findings from this study are described in detail elsewhere.[14]
- 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.
- AEs were mostly mild or moderate in severity, unrelated to the study drug, relatively similar between treatment groups, and generally consistent with subjects' medical histories.
- In the first 28-day dose cycle and during the 225-day treatment phase, home blood pressure measurements showed no consistent or dose-dependent changes from baseline among subjects in any of the treatment groups.

QCT VC Measurements

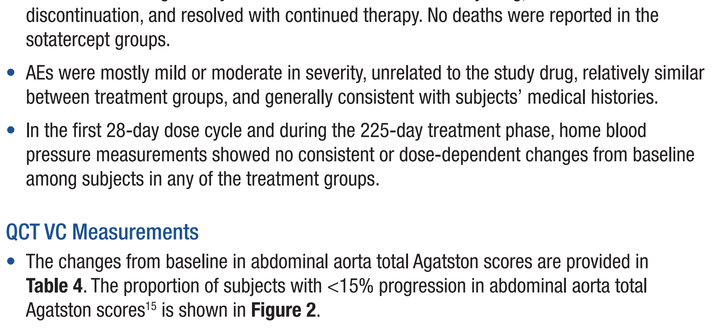
- The changes from baseline in abdominal aorta total Agatston scores are provided in **Table 4**. The proportion of subjects with <15% progression in abdominal aorta total Agatston scores[15] is shown in **Figure 2**.

Table 4. Change From Baseline at Day 225 in Abdominal Aorta Total Agatston Score and Square Root Transformed Total Volume Score*

	Placebo n=4	Sotatercept 0.3 mg/kg n=6	Sotatercept 0.5 mg/kg n=5	Sotatercept 0.7 mg/kg n=6
Abdominal aorta total Agatston score				
Change from baseline total Agatston score	787.8	8,578.9	225.7	171.0
% change from baseline total Agatston score	58.4	29.9	17.3	7.4
Square root transformed total volume score				
Baseline square root of total volume, mm^3	39.0	46.2	33.1	27.4
Change from baseline square root of total volume, mm^3	3.4	11.1	1.2	1.3

Note: The n reflects the number of randomized subjects with paired QCT assessments; actual number of subjects available for each parameter may vary.
*Lower total Agatston and square root transformed total volume scores indicate lower levels of VC.

Figure 2. Proportions of Subjects With <15% Progression in Their Abdominal Aorta Total Agatston Score



QCT Volumetric BMD Measurements

- **Table 5** provides the percent change from baseline in femoral neck cortical and lumbar spine trabecular volumetric BMD measurements.

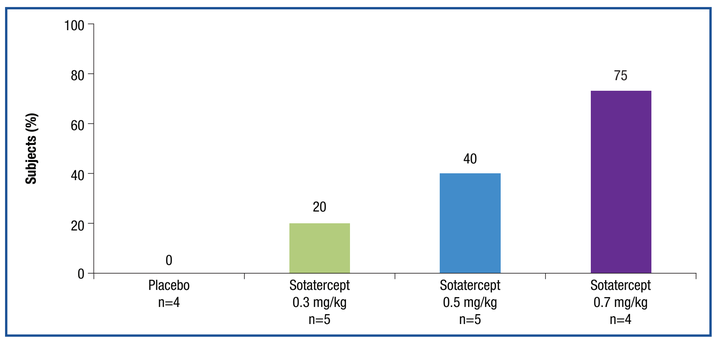
Table 5. Percent Change From Baseline at Day 225 in Femoral Neck Cortical and Lumbar Spine (L1, L2) Trabecular BMD

	Placebo n=4	Sotatercept 0.3 mg/kg n=6	Sotatercept 0.5 mg/kg n=5	Sotatercept 0.7 mg/kg n=6
Femoral neck cortical				
% change from baseline BMD (n)	–1.4 (4)	–1.4 (5)	1.6 (5)	–0.1 (4)
Lumbar spine (L1, L2) trabecular				
% change from baseline BMD (n)	10.9 (4)	8.0 (6)	0.5 (5)	4.5 (6)

Note: The n reflects the number of randomized subjects with paired QCT assessments; actual number of subjects available for each parameter may vary.

- Proportions of subjects with >2% gain in femoral neck cortical BMD were determined[16]; sotatercept treatment is associated with increases in the proportion of subjects with a >2% increase in femoral neck cortical bone (**Table 5** and **Figure 3**).
- In high-turnover ROD, trabecular bone mass increases, as measured by lumbar spine trabecular BMD, without a reduction in vertebral fracture rates in ESKD compared with the general population.[12,17] In this setting, the increased trabecular bone mass is of poor quality.[18] Sotatercept appears to slow the increase in trabecular bone mass in the lumbar spine, compared with placebo (**Table 5**).

Figure 3. Proportions of Subjects With >2% Increase in Femoral Neck Cortical BMD



CONCLUSIONS

- Based on baseline biomarker data, subjects in this study tended to have high-turnover ROD. The placebo group had changes as expected for high-turnover ROD: decreased cortical bone mass, increased trabecular bone mass, and increased VC that occurred at a rate similar to other large studies in ESKD.[15]
- In this small interim dataset evaluating exploratory QCT data measured at baseline and Day 225 (after up to eight 28-day dose cycles), there is an apparent effect of sotatercept on multiple parameters of CKD-MBD, including slowing progression of VC, increasing femoral neck cortical bone mass, and slowing the increase in trabecular bone mass in the lumbar spine. Bone histomorphometry data are required to better characterize the effects on lumbar spine BMD.
- The clinical findings of less VC and increase in bone mass are consistent with the histologic findings in the mouse model of *ldlr*-/- high-fat fed, ablative CKD-3 (5/6 nephrectomy) for VC.[8]
- Important differences in baseline characteristics may influence these results; for example, the placebo group had the longest length of time on dialysis, the highest bone turnover biomarkers, and higher baseline Agatston scores. Conversely, the placebo group had the lowest use of calcium-based phosphate binders, and their PTH decreased through the study to levels more similar to the other groups.
- Sotatercept may be able to address significant unmet needs for the treatment of CKD-MBD in ESKD, while also increasing Hb.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2009; S1-S130.
2. Pearsall RS, Canalis E, Cornwall-Brady M, et al. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. *Proc Natl Acad Sci U S A.* 2008;105:7082-7087.
3. Fuller K, Bayley KE, Chambers TJ. Activin A is an essential cofactor for osteoclast induction. *Biochem Biophys Res Commun.* 2000;268:2-7.
4. Sakai R, Eto Y, Ohtsuka M, Hirafuji M, et al. Activin enhances osteoclast-like cell formation in vitro. *Biochem Biophys Res Commun.* 1993;195:39-46.
5. Perrien DS, Akel NS, Edwards PK, et al. Inhibin A is an endocrine stimulator of bone mass and strength. *Endocrinology.* 2007;148:1654-1665.
6. 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 its murine analog (RAP-011) on anemia and in preventing bone loss in C57BL/6 mice with 5/6 nephrectomy [oral presentation SA-OR087]. Presented at: the American Society of Nephrology (ASN) Kidney Week 2012; October 30-November 4, 2012; San Diego, CA.
7. Chantry AD, Heath D, Mulivor AW, et al. Inhibiting activin-A signaling stimulates bone formation and prevents cancer-induced bone destruction in vivo. *J Bone Miner Res.* 2010;25:2633-2646.
8. Fang Y, Agapova O, Sugatani T, et al. Treatment of the CKD-MBD with a ligand trap for the activin receptor type 2A [abstract]. Presented at: the American Society of Nephrology (ASN) Kidney Week 2014; November 11-16, 2014; Philadelphia, PA.
9. Agapova O, Fang Y, Sugatani T, et al. Chronic kidney disease (CKD) stimulates aortic endothelial to mesenchymal transition (EnMT) which causes vascular calcification and is inhibited by an activin ligand trap [abstract]. Presented at: the American Society of Nephrology (ASN) Kidney Week 2014; November 11-16, 2014; Philadelphia, PA.
10. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15:827-832.
11. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. *AJR Am J Roentgenol.* 2004;182:1327-1332.
12. Leonard MB. A structural approach to skeletal fragility in chronic kidney disease. *Semin Nephrol.* 2009;29:133-143.
13. Malluche HH, Hruska K, Singh HM, et al. Sotatercept: initial signal-seeking quantitative computed tomography results for bone mass and vascular calcification in hemodialysis subjects treated with escalating doses: interim analysis of ACE-011-REN-001 [poster TH PO602]. Presented at: the American Society of Nephrology (ASN) Kidney Week 2014; November 11-16, 2014; Philadelphia, PA.
14. Smith WT, Havil J, Kopyt N, et al. Long-term effects of 3 dose levels of sotatercept compared with placebo for correction of anemia in hemodialysis subjects: Interim analysis of ACE-011-REN-001 [poster FP661]. Presented at: the 52nd ERA-EDTA Congress; May 28-31, 2015; London, UK.
15. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant.* 2011;26:1327-1339.
16. Malluche HH, Davenport D, Cantor T, et al. Bone mineral density and serum biochemical predictors of bone loss in patients with CKD on dialysis. *Clin J Am Soc Nephrol.* 2014;9:1254-1262.
17. Duan Y, De Luca V, Seeman E. Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone. *J Clin Endocrinol Metab.* 1999;84:718-722.
18. Malluche HH, Porter DS, Moniere-Faugere MC, et al. Differences in bone quality in low- and high-turnover renal osteodystrophy. *J Am Soc Nephrol.* 2012;23:525-532.

This study was sponsored by Celgene Corporation.

Presented at: the 52nd ERA-EDTA Congress; May 28–31, 2015; London, UK

Scan this QR code to receive the PDF of the poster