Influence of Renal Function on Pharmacokinetics, Pharmacodynamics, and Safety of a Single Dose of Romosozumab

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Abstract

We evaluated the pharmacokinetics, pharmacodynamics, and safety of a single subcutaneous dose of romosozumab 210 mg, a monoclonal antibody against sclerostin, in an open-label, parallel-group study in participants with severe (stage 4) renal impairment (RI; n = 8) or end-stage renal disease requiring hemodialysis (ESRD-RH; n = 8), or healthy participants with normal renal function (n = 8). Compared with the group with normal renal function, the mean romosozumab exposure was 31% and 43% higher as measured by maximum observed serum concentration and area under the concentration-time curve, respectively, in the severe RI group and similar to those in the ESRD-RH group. For all 3 groups, the maximum mean percent increase in procollagen type 1 N terminal propeptide and decrease in serum C-telopeptide levels from baseline were observed on day 15. Changes in procollagen type 1 N terminal propeptide and serum C-telopeptide were of similar patterns in all 3 groups. The single dose of romosozumab 210 mg was well tolerated. Adverse events (AEs) were reported for 13 patients (7 patients with severe RI and 6 with ESRD-RH), with no deaths, AEs, or serious AEs leading to withdrawal. The incidence of subjects with postbaseline transient decreases in serum calcium (severe RI, n = 1; ESRD-RH, n = 5) and increases in intact parathyroid hormone (severe RI, n = 7; ESRD-RH, n = 7; healthy, n = 3) were greater in severe RI and ESRD-RH groups than in the healthy group. All reported events of hypocalcemia (severe RI, n = 1; ESRD-RH, n = 4) were asymptomatic. These results support the use of romosozumab without dose adjustment in patients with severe RI or ESRD-RH.

Chronic kidney disease (CKD) is common among older adults and is a risk factor for bone loss and subsequent increased risk of fractures when compared with age-matched individuals with normal renal function.[1,2] The age-adjusted incidence of fractures was ≈4-fold higher in patients with end-stage renal disease (ESRD) compared with that in the general population for both men and women.[1] In the United States, ≈1 in 2 women and up to 1 in 4 men aged ≥50 years are at risk of an osteoporotic fracture.[3] As CKD and osteoporosis often occur as comorbidities in older individuals, it is important to evaluate the safety and efficacy of osteoporosis treatments in patients with renal impairment (RI).

Sclerostin is an osteocyte-secreted glycoprotein that regulates bone formation by inhibiting the Wnt and bone morphogenetic protein signaling pathways.[4,5] Romosozumab (EVENITY [romosozumab-aqqg in the United States]) is a monoclonal antibody that binds and inhibits sclerostin, with the dual effect of increasing bone formation and decreasing bone resorption.[6] As of January 7, 2021, a romosozumab 210 mg once monthly dose has been approved in 46 countries around the world for the treatment of osteoporosis (United States) or severe osteoporosis (European Union) in postmenopausal women at high risk for fracture.[7,8]

In the phase 3 FRAME (NCT01575834) and ARCH (NCT01631214) studies, treatment with romosozumab 210 mg once monthly for 12 months significantly increased bone mineral density (BMD) and reduced fracture risk compared with placebo or alendronate in women with postmenopausal osteoporosis.[9,10] In the phase 3 BRIDGE study (NCT02186171) in men with osteoporosis aged 55 to 90 years, treatment with romosozumab 210 mg once monthly for 12 months resulted in a significant increase in the spine and hip BMD compared with placebo.[11]

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[Correction added on 11 May 2022, after first online publication: The corresponding author's email address and reference 23 are updated.]

In healthy men and postmenopausal women, a single dose of romosozumab exhibited a greater-than-dose-proportional increase in the serum concentrations across the subcutaneous (SC) and intravenous dose ranges examined, with clearance decreasing as the dose increased.[12] The nonlinear pharmacokinetics (PK) was associated with target-mediated (sclerostin) elimination and was most pronounced between the 1- and 3-mg/kg SC dose groups, while a linear PK was observed with ≥3-mg/kg dose. CKD was found to be associated with disturbances in the Wnt pathway, and an elevated level of serum sclerostin was reported in patients with CKD.[13–15] An inverse relationship was observed between serum sclerostin and the estimated glomerular filtration rate (eGFR) in patients with CKD.[16,17] Thus, it is important to examine the impact of severe RI or ESRD on the PK, pharmacodynamics (PD), and safety of romosozumab.

Methods

Study Design and Participants

This open-label, single-dose, parallel-group, phase 1 study was conducted at 5 centers in the United States on an outpatient basis in healthy participants, patients with stage 4 RI, and patients with ESRD requiring hemodialysis (ESRD-RH) (NCT01833754). The study was conducted in accordance with the US Food and Drug Administration and International Conference on Harmonisation Good Clinical Practice regulations/guidelines and was approved by the appropriate institutional review board, ethical review committee, or equivalent at each study site. Informed consent was obtained from each participant.

Men and women aged at least 50 years with a body weight of ≥45 and ≤110 kg at screening were included. Participants were enrolled in the following 3 groups based on renal function: healthy participants with normal renal function (eGFR ≥80 mL/min/1.73 m^2), patients with ESRD-RH, and patients with stage 4 RI with eGFR 15 to 29 mL/min/1.73 m^2 who were not anticipated to require hemodialysis or renal transplantation within 6 months of enrollment and were anticipated to have appropriate renal function for the duration of the study. Renal function was assessed on the basis of the GFR calculated using the abbreviated Modification of Diet in Renal Disease Study equation.[18] The eGFR, in mL/min/1.73 m^2, was calculated as follows:

Estimated GFR (mL/min/1.73 m^2) = 175 × [serum creatinine (mg/dL)] –1.154 × [age] –0.203 × [0.742 if participant is a woman] × [1.212 if participant is Black].

All participants received a single SC dose of romosozumab 210 mg (Amgen Inc., Thousand Oaks, California) on day 1 of the study and were required to take daily calcium and vitamin D supplements. All participants received an oral loading dose of vitamin D (50 000 IU) at enrollment. For patients with stage 4 RI and ESRD-RH, the actual dose of daily calcium and vitamin D was determined on the basis of the patient's albumin-adjusted serum calcium level at screening; healthy participants were required to take supplements containing ≥500 mg calcium and ≥400 IU vitamin D daily.

Outcome Measures

In this study, we measured the following PK parameters for romosozumab: area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC$_{last}$), AUC from time 0 to infinity (AUC$_{inf}$), maximum observed serum concentration (C$_{max}$), and time to reach C$_{max}$ (t$_{max}$).

Other end points included evaluation of PD parameters, such as the bone formation markers procollagen type 1 N terminal propeptide (P1NP) and bone-specific alkaline phosphatase (BSAP) and the bone resorption markers serum C-telopeptide (sCTX) and tartrate-resistant acid phosphatase-5b (TRAP-5b).

Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs), clinically relevant changes in vital signs and clinical laboratory parameters, physical examinations, electrocardiograms, and subject incidence of anti-romosozumab antibodies.

The Medical Dictionary for Regulatory Activities version 16.1 was used to code and report all adverse events (AEs). The severity of AEs was determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The hypocalcemia toxicity grade was calculated as follows: grade 1, less than lower limit of normal to 8.0 mg/dL (2.0 mmol/L); grade 2, <8.0 to 7.0 mg/dL (<2.0-1.75 mmol/L); grade 3, <7.0 to 6.0 mg/dL (<1.75-1.5 mmol/L); and grade 4, <6.0 mg/dL (<1.5 mmol/L).

Blood samples for bone turnover markers (P1NP, sCTX, BSAP, TRAP-5b) and intact parathyroid hormone (iPTH), serum phosphorus, and serum calcium were taken at baseline (day –1) and on days 8, 15, 22, 29, 43, 57, and 85. Romosozumab concentrations were measured at baseline (day –1) and on days 2, 3, 4, 6, 8, 11, 15, 18, 22, 29, 36, 43, 57, and 85. All samples were analyzed centrally. Serum concentrations of romosozumab were measured by a validated enzyme-linked immunosorbent assay by Clinigene International Ltd (Bangalore, India). Serum concentrations of P1NP and sCTX were analyzed using enzyme-linked immunosorbent assay and radioimmunoassay, respectively. Serum concentrations of BSAP, TRAP-5b, total calcium, and iPTH were measured using standard laboratory procedures. Serum concentrations of bone turnover markers were measured by Quintiles

Table 1. Baseline Participant Characteristics by Baseline Renal Function

	Patients With Stage 4 RI (N = 8)	Patients With ESRD-RH (N = 8)	Healthy Participants (N = 8)	Total Participants (N = 24)	Reference Range
Male	4 (50.0)	5 (62.5)	1 (12.5)	10 (41.7)	NA
Race					NA
American Indian or Alaska Native	1 (12.5)	0 (0.0)	0 (0.0)	1 (4.2)	
Black or African American	1 (12.5)	3 (37.5)	1 (12.5)	5 (20.8)	
White	6 (75.0)	5 (62.5)	7 (87.5)	18 (75.0)	
Age, y	66.5 ± 8.4	65.1 ± 6.7	63.0 ± 8.8	64.9 ± 7.8	NA
Age group					NA
<65 y	3 (37.5)	2 (25.0)	5 (62.5)	10 (41.7)	
≥65 y	5 (62.5)	6 (75.0)	3 (37.5)	14 (58.3)	
≥75 y	1 (12.5)	0 (0.0)	2 (25.0)	3 (12.5)	
eGFR, mL/min/1.73 m^2	24.3 ± 4.7	…	85.3 ± 11.5	…	NA
Weight, kg	76.5 ± 10.2	79.2 ± 13.7	77.2 ± 5.4	77.6 ± 9.9	NA
BMI, kg/m^2	28.5 ± 4.8	27.7 ± 5.9	29.3 ± 2.3	28.5 ± 4.4	NA
PINP, μg/L	96.1 ± 66.7	358.7 ± 237.4	54.8 ± 25.5	161.7 ± 187.2	16.5-101.1
sCTX, ng/L	552.1 ± 358.1	1609.9 ± 556.1	390.9 ± 269.1	818.0 ± 663.1	0.0-1008.0
BSAP, U/L	16.4 ± 8.7	27.0 ± 14.3	21.8 ± 7.6	21.5 ± 10.9	14.0-43.0
TRAP-5b, U/L	4.3 ± 1.1	5.6 ± 2.3	4.3 ± 1.8	4.7 ± 1.8	1.2-7.6[26]
Albumin-adjusted serum calcium, mmol/L	2.5 ± 0.2	2.4 ± 0.1	2.3 ± 0.1	2.4 ± 0.2	2.1-2.8
iPTH, pmol/L	5.0 ± 1.6	11.8 ± 12.0	4.7 ± 3.4	7.2 ± 7.7	1.1-6.9
25 Hydroxyvitamin D,[a] nmol/L	108.6 ± 24.7	132.0 ± 52.9	117.9 ± 24.6	119.5 ± 36.3	74.9-249.6

BMI, body mass index; BSAP, bone-specific alkaline phosphatase; eGFR, estimated glomerular filtration rate; ESRD-RH, end-stage renal disease requiring hemodialysis; iPTH, intact parathyroid hormone; NA, not applicable; PINP, procollagen type 1 N terminal propeptide; RI, renal impairment; sCTX, serum C-telopeptide; SD, standard deviation; TRAP-5b, tartrate-resistant acid phosphatase-5b.

Values are n (%) or mean ± SD. Planned total dose of romosozumab for all 3 groups is 210 mg. Patients with stage 4 RI: eGFR 15-29 mL/min/1.73 m^2. Patients with ESRD-RH: eGFR not determined. Healthy participants: eGFR ≥80 mL/min/1.73 m^2.

[a] All participants received an oral loading dose of vitamin D (50,000 IU) at enrollment.

Laboratories Ltd (Marietta, Georgia), while screening for anti-romosozumab antibodies was conducted at Pharmaceutical Product Development (Richmond, Virginia) using validated immunoassays and bioassays.

Statistical Analysis

This was an estimation study, and sample size was determined using practical considerations. Noncompartmental analysis using Phoenix WinNonlin version 8.1 (Certara, Princeton, New Jersey) was performed on individual romosozumab concentrations to estimate AUC_{last}, AUC_{inf}, C_{max}, and t_{max}.

For PK estimation, 2-sided 90%CIs were provided for describing the precision of the geometric least squares mean (GLSM) ratio of AUC values and of C_{max} values for the stage 4 RI group vs the healthy participants group comparison and the ESRD-RH group vs the healthy participants group comparison.

For all parameters, percent changes from baseline were summarized for all postbaseline scheduled visits. Descriptive summaries over time and/or changes from baseline over time were reported by treatment group.

Results

Baseline Characteristics

A total of 24 participants were enrolled, including 8 in each group: stage 4 RI group, ESRD-RH group, and healthy participants group. All enrolled participants completed the study. Table 1 summarizes the baseline characteristics for each group. In this study, 42% of participants were men, 75% were White, and the mean ± standard deviation (SD) age of participants at baseline was 64.9 ± 7.8 years. Overall, 14 participants (58%) were aged ≥65 years, of whom 3 participants (13%) were aged ≥75 years; 10 participants (42%) were aged <65 years.

The average body weight and body mass index were comparable across treatment groups. Mean ± SD values for all bone turnover markers at baseline were higher in patients with ESRD-RH than in patients with stage 4 RI and healthy participants. The mean albumin-adjusted serum calcium levels at baseline were within the normal range for all 3 treatment groups. The mean ± SD iPTH levels at baseline were higher for patients with ESRD-RH (11.8 ± 12.0 pmol/L) compared with patients with stage 4 RI (5.0 ± 1.6 pmol/L) and healthy participants (4.7 ± 3.4 pmol/L).
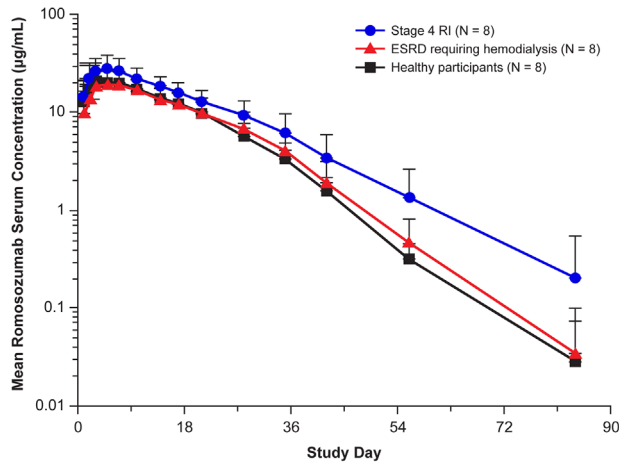
Figure 1. Mean ± standard deviation serum concentration-time profiles of romosozumab. Mean ± standard deviation serum concentration-time profiles of romosozumab from participants with normal renal function, stage 4 RI, or ESRD-RH after a single subcutaneous dose of romosozumab 210 mg, depicted as a log-linear plot. The lower limit of quantification was 50 ng/mL. ESRD-RH, end-stage renal disease requiring hemodialysis; RI, renal impairment.

Table 2. Serum Romosozumab Pharmacokinetic Parameter Estimates for a Single Subcutaneous Dose of Romosozumab 210 mg

PK Parameter	Patients With Stage 4 RI (N = 8)	Patients With ESRD-RH (N = 8)	Healthy Participants (N = 8)
t_{max}, day	5.0 (3.0-7.0)	5.0 (3.0-7.0)	5.0 (3.0-7.0)
C_{max}, μg/mL	28.9 (10.8)	19.8 (7.3)	22.4 (10.3)
	[14.8-51.5]	[9.39-31.9]	[13.5-45.2]
AUC_{last}, μg · day/mL	637 (218)	444 (154)	443 (143)
	[323-983]	[216-643]	[264-700]
AUC_{inf}, μg · day/mL	642 (221)	447 (154)	445 (143)
	[326-987]	[218-647]	[265-703]

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed serum concentration; eGFR, estimated glomerular filtration rate; ESRD-RH, end-stage renal disease requiring hemodialysis; PK, pharmacokinetics; RI, renal impairment; SD, standard deviation; t_{max}, time to reach C_{max}.
t_{max} is reported as median (range) and other parameters are reported as mean (SD) [range]. Patients with stage 4 RI: eGFR 15-29 mL/min/1.73 m^2. Patients with ESRD-RH: eGFR not determined. Healthy participants: eGFR $\geq$80 mL/min/1.73 m^2.

Pharmacokinetics of Romosozumab

Mean ± SD serum concentration-time profiles of romosozumab by renal function group are presented in Figure 1. Table 2 summarizes all PK parameters by renal function group. Romosozumab was rapidly absorbed in all groups, with a median t_{max} of 5 days after a single SC dose of 210 mg (Table 2). The GLSM point estimates and 90%CIs for the ratio of PK parameters in patients with stage 4 RI or ESRD-RH compared with healthy participants are presented in Table 3. The mean ± SD C_{max} values for patients with stage 4 RI, patients with ESRD-RH, and healthy participants were 28.9 ± 10.8, 19.8 ± 7.3, and 22.4 ± 10.3 μg/mL, respectively. The GLSM point estimates (90%CI) for the ratio of C_{max} in patients with stage 4 RI and patients with ESRD-RH compared with healthy participants were 1.313 (0.945-1.824) and 0.895 (0.638-1.256), respectively. Additionally, the mean ± SD AUC_{inf} values for patients with stage 4 RI, patients with ESRD-RH, and healthy participants were 642 ± 221, 447 ± 154, 445 ± 143 μg · day/mL, respectively. The GLSM point estimates (90%CI) for the ratio of AUC_{inf} in patients with stage 4 RI and patients with ESRD-RH compared with healthy participants were 1.425 (1.048-1.937) and 0.989 (0.723-1.354), respectively. Values for AUC_{last} were nearly identical to those for AUC_{inf} for all groups. The GLSM point estimates (90%CI) for the ratio of AUC_{last} in patients with stage 4 RI and patients with ESRD-RH compared with healthy participants were 1.422 (1.046-1.933) and 0.988 (0.721-1.354), respectively. Individual values for C_{max}, AUC_{last}, and AUC_{inf} are plotted in Figure 2. The mean romosozumab exposure, as measured by C_{max} and AUC values, was higher in patients with stage 4 RI than in healthy participants. The mean romosozumab exposure was similar between patients with ESRD-RH and healthy participants.

Pharmacodynamics of Bone Turnover Markers

The mean concentrations for all bone turnover markers measured in this study were higher in patients with ESRD-RH than in patients with stage 4 RI or healthy participants at baseline and throughout the study.

The maximum mean percent change from baseline in P1NP levels occurred on day 15 for all groups and was 110.1% for patients with stage 4 RI, 89.0% for patients with ESRD-RH, and 125.0% for healthy participants (Figure 3A). After reaching the peak levels, the mean P1NP concentrations decreased and reached near to the baseline levels by day 57 in all 3 groups. In all 3 groups, the mean sCTX concentrations decreased and reached the nadir by day 15, with the mean percent change from baseline of –17.0%, –30.1%, and –45.4% for patients with stage 4 RI, patients with ESRD-RH, and healthy participants, respectively (Figure 3B). After day 15, sCTX concentrations started to return to baseline levels in all groups.

The maximum mean percent change from baseline to day 22 in BSAP levels was 79.2%, 68.6%, and 52.6% for patients with stage 4 RI, patients with ESRD-RH, and healthy participants, respectively (Figure 3C). The maximum mean percent change from baseline in TRAP-5b level was –27.3% (day 15), –31.8% (day 43), and –34.7% (days 22 and 29) for patients with stage 4 RI, patients with ESRD-RH, and healthy participants, respectively (Figure 3D). The maximum mean percent increase in BSAP levels was observed on day 22 for

Table 3. Statistical Analysis of Unbound Romosozumab Pharmacokinetic Parameters After a Single Subcutaneous Dose of Romosozumab 210 mg by Renal Function Group

Parameter	Renal Function Group	N	Geometric LS Mean	Geometric LS Mean Ratio,[a] % (90%CI)
C_{max}, μg/mL	Healthy participants	8	20.795	
	ESRD-RH	8	18.613	0.895 (0.638-1.256)
	Stage 4 RI	8	27.300	1.313 (0.945-1.824)
AUC_{inf}, μg • day/mL	Healthy participants	8	425.208	
	ESRD-RH	8	420.521	0.989 (0.723-1.354)
	Stage 4 RI	8	605.879	1.425 (1.048-1.937)
AUC_{last}, μg • day/mL	Healthy participants	8	423.247	
	ESRD-RH	8	418.157	0.988 (0.721-1.354)
	Stage 4 RI	8	601.695	1.422 (1.046-1.933)

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed serum concentration; eGFR, estimated glomerular filtration rate; ESRD-RH, end-stage renal disease requiring hemodialysis; LS, least squares; RI, renal impairment.
Patients with stage 4 RI: eGFR 15-29 mL/min/1.73 m^2. Patients with ESRD-RH: eGFR not determined. Healthy participants: eGFR $\geq$80 mL/min/1.73 m^2.
[a] Ratios are relative to the healthy participants group.

Table 4. Subject Incidence of Treatment-Emergent Adverse Events

	Patients With Stage 4 RI (N = 8)	Patients With ESRD-RH (N = 8)	Healthy Participants (N = 8)	Total Participants (N = 24)
All treatment-emergent adverse events	7 (87.5)	6 (75.0)	0 (0.0)	13 (54.2)
Serious adverse events	1 (12.5)	1 (12.5)	0 (0.0)	2 (8.3)
Leading to discontinuation of romosozumab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common treatment-emergent adverse events (>5%)				
Hypocalcemia	1 (12.5)	4 (50.0)	0 (0.0)	5 (20.8)
Hyperparathyroidism secondary	4 (50.0)	0 (0.0)	0 (0.0)	4 (16.7)
Arthralgia	1 (12.5)	1 (12.5)	0 (0.0)	2 (8.3)
Constipation	0 (0.0)	2 (25.0)	0 (0.0)	2 (8.3)
Vomiting	1 (12.5)	1 (12.5)	0 (0.0)	2 (8.3)

eGFR, estimated glomerular filtration rate; ESRD-RH, end-stage renal disease requiring hemodialysis; RI, renal impairment.
Values are n (%). Planned total dose of romosozumab for all 3 groups is 210 mg. Patients with stage 4 RI: eGFR 15–29 mL/min/1.73 m^2. Patients with ESRD-RH: eGFR not determined. Healthy participants: eGFR $\geq$80 mL/min/1.73 m^2.

all groups, while the mean TRAP-5b concentrations reached the nadir between days 15 and 29 for all 3 groups.

The maximum mean percent increases from baseline in P1NP and BSAP and the maximum mean percent decreases from baseline in sCTX and TRAP-5b were observed within 2 to 3 weeks in all treatment groups. Mostly, all bone turnover markers returned to near baseline levels by the end of study.

Safety
TEAEs were reported for 13 patients (54.2%): 7 of 8 patients (87.5%) with stage 4 RI and 6 of 8 patients (75.0%) with ESRD-RH; no TEAE was reported for any of the healthy participants (Table 4). Serious AEs were reported for 2 patients: 1 patient each with stage 4 RI and ESRD-RH. Of the 2 serious AEs, one was

CTCAE grade 3 anemia (history of iron deficiency anemia) on study day 67, and the other was hospitalization for repair of preexisting mitral valve regurgitation on study day 37, CTCAE grade 4; neither were considered related to romosozumab by the investigator. There were no deaths or AEs leading to withdrawal.

The most common AEs (subject incidence >5%) were hypocalcemia (5 patients [1 patient with stage 4 RI; 4 patients with ESRD-RH]), secondary hyperparathyroidism (4 patients, all with stage 4 RI), arthralgia (2 patients [1 patient with stage 4 RI; 1 patient with ESRD-RH]), constipation (2 patients, both with ESRD-RH), and vomiting (2 patients [1 patient with stage 4 RI; 1 patient with ESRD-RH]) (Table 4). All AEs of hypocalcemia and secondary hyperparathyroidism were considered related to romosozumab by the
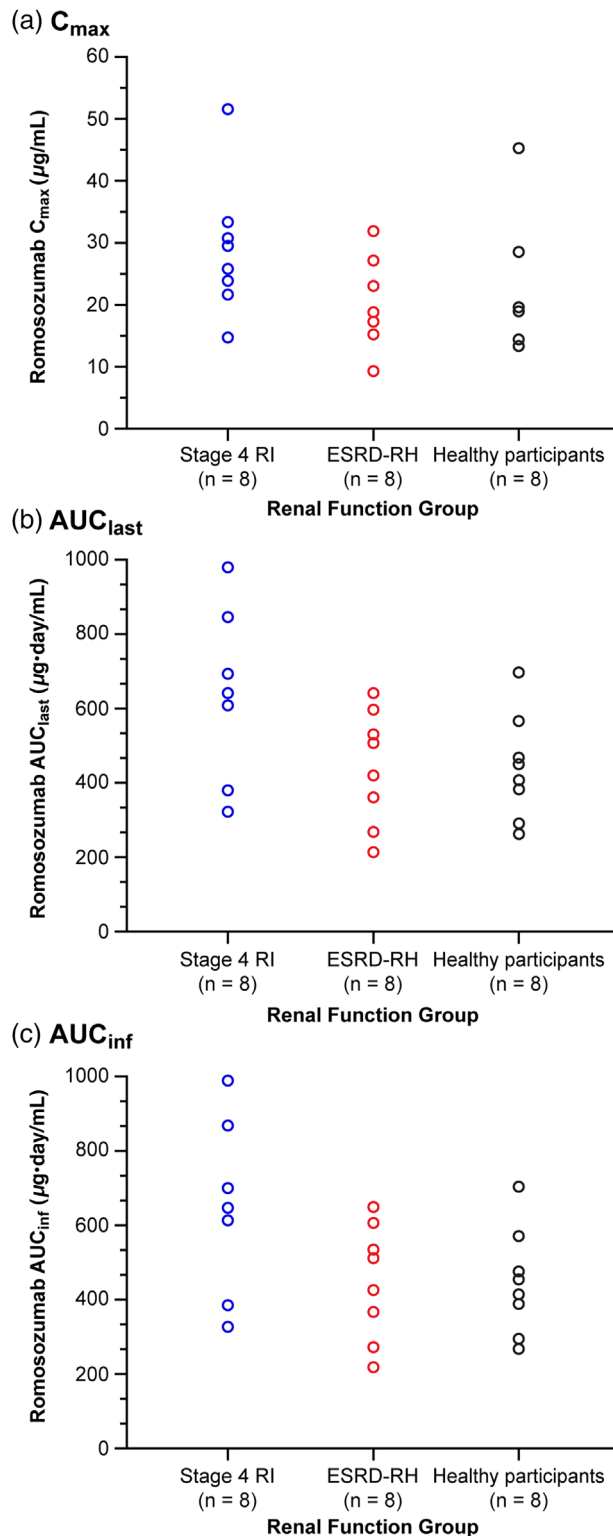
(a) Cmax

(b) AUClast

(c) AUCinf

Figure 2. Scatterplots of individual values for romosozumab pharmacokinetics parameters. Scatterplots of individual values for (A) C_{max}, (B) AUC_{last}, and (C) AUC_{inf}. AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed serum concentration; ESRD-RH, end-stage renal disease requiring hemodialysis; RI, renal impairment.

investigator. All reported AEs of hypocalcemia were asymptomatic.

The AEs of interest during this study included hypocalcemia (20.8% of total participants; 1 patient with stage 4 RI [12.5%] and 4 patients with ESRD [50.0%]), AEs potentially associated with hypersensitivity: urticaria and rash (1 patient each [4.2%] with ESRD-RH), and injection-site reactions (1 patient [4.2%] with ESRD-RH). The CTCAE toxicity grades for hypocalcemia were grade 3 for 1 patient with ESRD-RH, grade 2 for 2 patients with ESRD-RH, and grade 1 for 1 patient each with stage 4 RI and ESRD-RH.

The mean percent change from baseline for albumin-adjusted serum calcium reached the nadir on day 15 for healthy participants (–1.9%) and by day 22 for patients with stage 4 RI (–4.8%) and patients with ESRD-RH (–12.9%), after which the levels returned to near baseline levels by the end of study (Figure 4A). Overall, 6 patients had a decrease in albumin-adjusted serum calcium concentrations of CTCAE grade ≥1 during the study (1 patient with stage 4 RI had a grade 1 decrease, 4 patients with ESRD-RH had a grade 2 decrease, and 1 patient with ESRD-RH had a grade 3 decrease). Of these, 5 patients reported asymptomatic hypocalcemia as an AE as described earlier.

After administration of romosozumab, serum iPTH levels increased in all treatment groups. Overall, 17 participants (7 patients with stage 4 RI, 7 patients with ESRD-RH, and 3 healthy participants) had an iPTH value above the normal upper limit (>6.897 pmol/L) at any time point after screening or baseline. Greater mean iPTH values and the mean percent increase from baseline in iPTH were observed in patients with ESRD-RH or stage 4 RI vs healthy participants. At day 29, the mean percent increases from baseline in iPTH were 150% in patients with stage 4 RI, 287% in patients with ESRD-RH, and 94% in healthy participants, after which the iPTH levels returned to near baseline levels (Figure 4B).

No clinically relevant changes occurred in serum chemistry, hematology, or urinalyses except decreases from baseline in serum concentrations of calcium and phosphorus after receiving romosozumab. No clinically important changes in vital sign parameters or electrocardiogram measurements relative to baseline were observed in any participant during this study.

The administration of romosozumab resulted in a greater decrease in serum calcium level and a greater compensatory physiological increase in iPTH in patients with stage 4 RI and ESRD-RH than in healthy participants. Most of these changes were transient and returned to baseline level by the end of study (day 85; Figure 3).

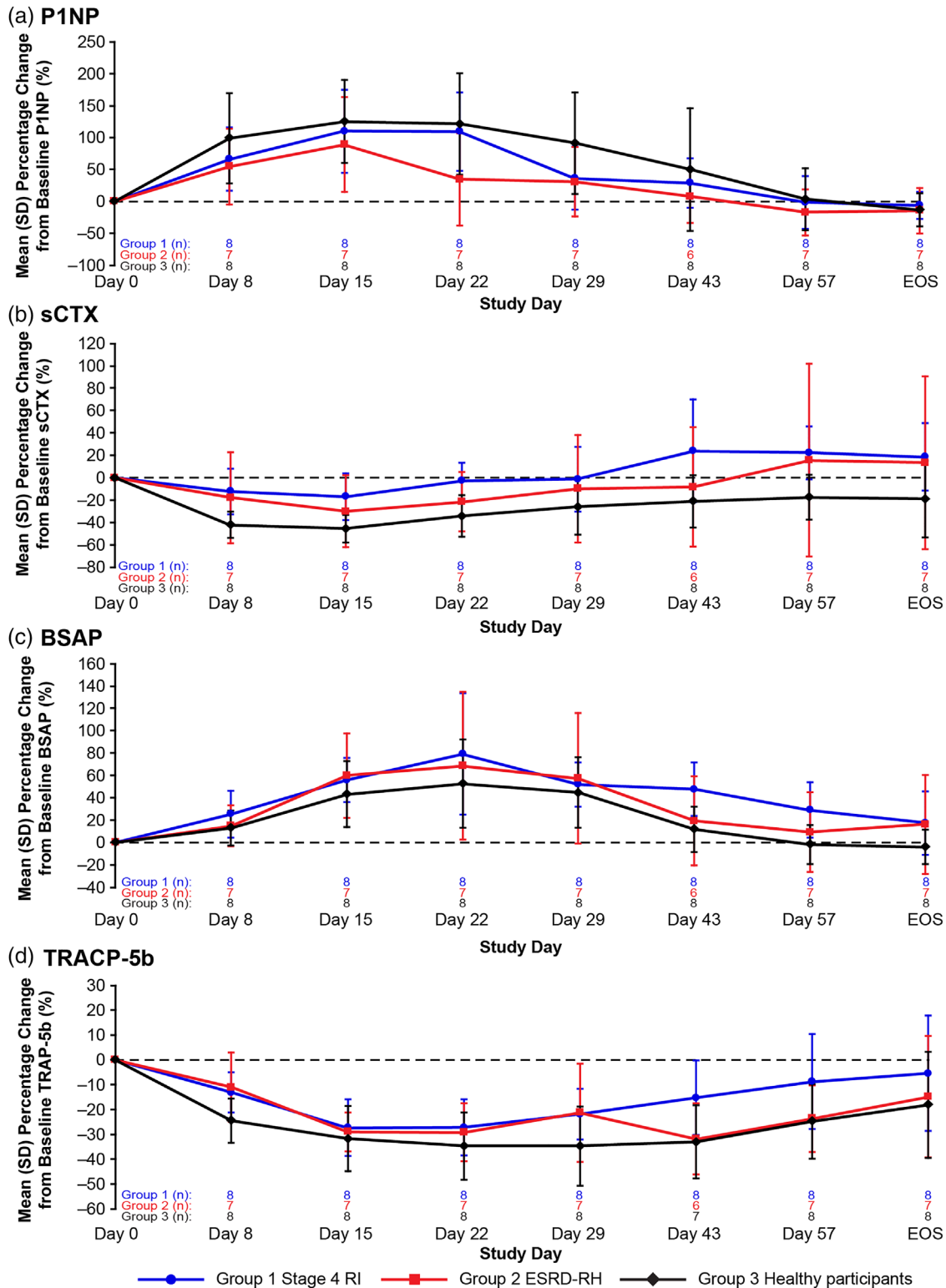One healthy participant who was administered romosozumab tested positive for anti-romosozumab

Figure 3. Mean (SD) percent change from baseline in bone turnover markers following a single subcutaneous dose of romosozumab 210 mg. BSAP, bone-specific alkaline phosphatase; EOS, end of study; ESRD-RH, end-stage renal disease requiring hemodialysis; P1NP, procollagen type 1 N terminal propeptide; RI, renal impairment; sCTX, serum C-telopeptide; SD, standard deviation; TRAP-5b, tartrate-resistant acid phosphatase-5b.
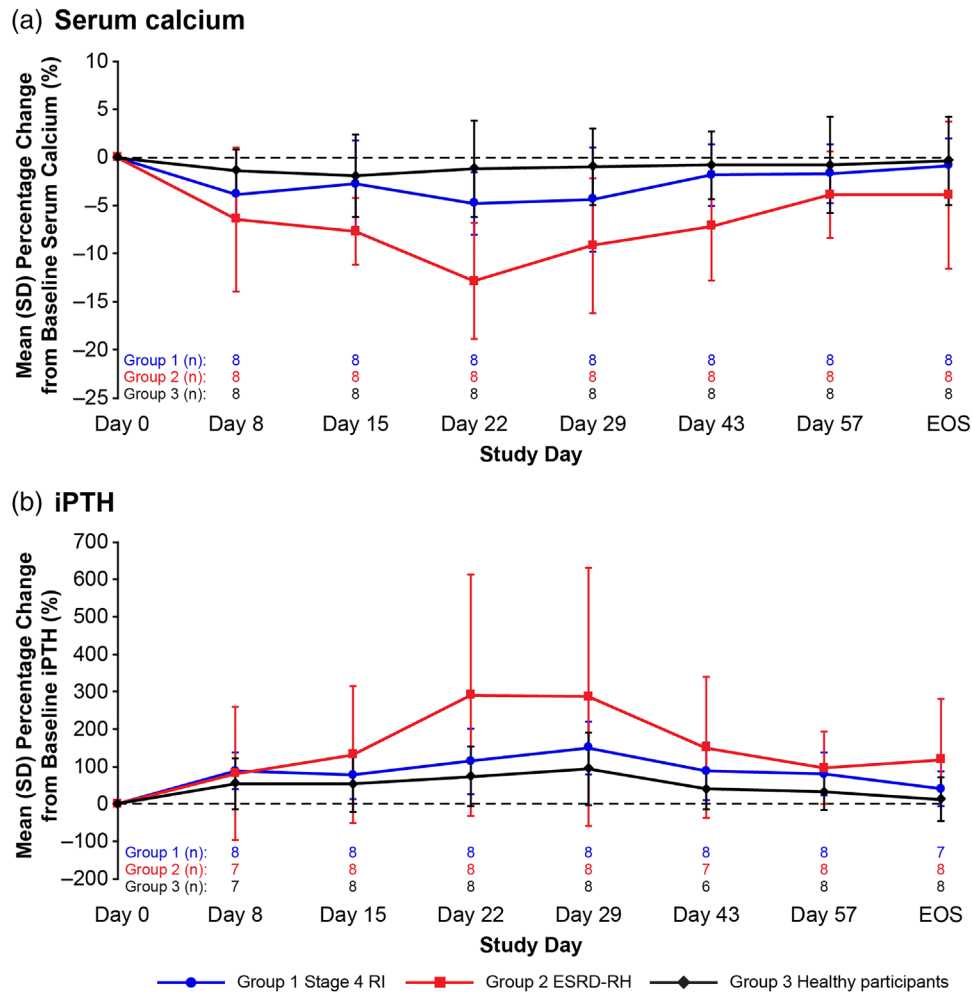
Figure 4. Mean (SD) percent change from baseline in albumin-adjusted serum calcium and iPTH following a single subcutaneous dose of romosozumab 210 mg. EOS, end of study; ESRD-RH, end-stage renal disease requiring hemodialysis; iPTH, intact parathyroid hormone; RI, renal impairment; SD, standard deviation.

binding antibodies on day 85. This participant tested negative for anti-romosozumab neutralizing antibodies. The participant's serum romosozumab concentrations were similar to those from other healthy participants.

Discussion

Per the current US Food and Drug Administration guidelines, an RI study may not be necessary for monoclonal antibody therapeutics if no other clinical concerns are present.[19] The monoclonal antibodies are often too large (≥ 150 kDa) for glomerular filtration and are typically eliminated through proteolytic degradation or target-mediated disposition.[20]

Compared with the healthy controls, 76 adult patients with CKD undergoing dialysis had significantly higher serum sclerostin levels, and sclerostin was inversely associated with iPTH.[21] In addition, Graciolli et al[22] reported higher bone sclerostin levels in patients of

all CKD stages than in healthy participants. As elevated serum sclerostin levels have been previously reported in patients with CKD, it was expected that treatment with romosozumab in patients with both CKD and osteoporosis would result in a lower systemic exposure due to higher target-mediated elimination, and a higher dose of romosozumab may be required to achieve optimal osteoanabolic treatment effects. However, in this study, renal function impairment in patients with stage 4 RI showed greater romosozumab exposure compared with healthy participants after a single 210-mg SC dose as assessed by the C_{max} and AUC values. Although the serum sclerostin levels at baseline were not measured in this study, the results of the PK and PD analysis suggest that baseline sclerostin levels may not be predictive of the PK of romosozumab in patients with CKD.

The population PK analysis of data from 11 studies including ≈1500 subjects at various stages of RI with eGFR values ranging from 7 to 144 mL/min/1.73 m[2]

showed an increase in romosozumab AUC with increasing severity of RI (data on file). Similar to the findings of the population PK analysis, we observed a higher romosozumab exposure in patients with stage 4 RI in this study. The higher romosozumab exposures in patients with stage 4 RI observed in the current study were lower than the values observed with 5 and 10 mg/kg SC doses in the first-in-human (FIH) study.[12] In the single-dose FIH study in healthy participants, romosozumab was generally well tolerated across all evaluated doses. The number of AEs in subjects receiving 5 or 10 mg/kg was 6 of 9 and 5 of 6 subjects, respectively, with only 1 serious AE of hepatitis reported in the 10-mg/kg group, which resolved during the study. In addition, mild, transient decreases in mean serum ionized calcium concentrations of ≈4% from baseline occurred after a single SC or intravenous dose of romosozumab in the FIH study, with levels returning to baseline over the course of the study or over the follow-up period; these findings were not associated with any reported AEs.[12] The 210-mg SC dose administered in this study was comparable to the 3 mg/kg SC dose in the FIH study, which was well tolerated by participants in the FIH study.

As this was a phase 1 study, no efficacy measurements were performed. In the post hoc analyses of 2 pivotal phase 3 clinical trials assessing romosozumab, namely, ARCH and FRAME, similar efficacy and safety of romosozumab was observed in women with postmenopausal osteoporosis with normal renal function and in those with mild to moderate CKD.[23] Additionally, in a recent study, improvement in bone density was reported after 6 months of romosozumab treatment in patients with osteoporosis requiring hemodialysis.[24] Thus, increase in BMD after romosozumab treatment does not seem to be dependent on the stage of RI in the patient.

Compared with the healthy participants, the baseline P1NP and sCTX levels were higher in patients with CKD (stage 4 RI and ESRD-RH) in this study. The baseline values of BSAP and TRAP-5b were slightly higher in patients with ESRD-RH and were similar between patients with stage 4 RI and healthy participants. However, the general pattern and profile of all 4 bone turnover markers were similar among the 3 groups. For the bone formation markers (P1NP and BSAP), the levels increased within 2 to 3 weeks after romosozumab administration and returned to the baseline levels at the end of the study. For the bone resorption markers (sCTX and TRAP-5b), the levels decreased within 2 to 3 weeks after romosozumab administration and returned to the baseline levels by day 85. The observed trends in these markers were similar to the trends observed in the FIH study.[12] A similar trend is also observed in women with postmenopausal osteoporosis, wherein

compared with placebo, treatment with romosozumab 210 mg resulted in a peak increase from baseline of ≈145% in serum P1NP levels and a maximal reduction from baseline of ≈55% in sCTX levels 2 weeks after initiating treatment.[7]

Patients with stage 4 RI or ESRD-RH rely more heavily on bone to provide a source of calcium due to their impaired ability to excrete calcium from urine and to absorb calcium in the gastrointestinal tract.[25] The low calcium levels often result in increased iPTH levels in patients with CKD. This was evident from the greater decreases from baseline in albumin-adjusted serum calcium for patients with ESRD-RH and stage 4 RI than for healthy participants after romosozumab treatment. To avoid the risk of hypocalcemia due to the transient changes in serum calcium levels, all participants in this study were required to take daily calcium and vitamin D supplementation. However, these changes were transient and returned to baseline levels by the end of study. These changes did not translate into any serious clinical outcomes; none of the AEs of hypocalcemia in this study were symptomatic, and no patient reported calcium levels of <1.5 mmol/L during the study period. Secondary hyperparathyroidism is considered a hallmark of CKD and higher iPTH levels at baseline were observed in patients with stage 4 RI and ESRD-RH than in healthy participants. After administration of the single SC dose of romosozumab on day 1, serum iPTH levels increased across all treatment groups. However, due to the greater reductions in serum calcium levels in patients with stage 4 RI and ESRD-RH, a greater compensatory physiological increase in iPTH was observed compared with healthy participants, and iPTH levels remained above baseline at the end of study in these patients.

In the post hoc analysis of phase 3 trials, FRAME and ARCH, of 9770 women with postmenopausal osteoporosis and mild to moderate CKD, only 2 women with mild CKD and treated with romosozumab reported AEs of mild to moderate hypocalcemia.[23]

Conclusion

In conclusion, compared with the healthy participants, after a single SC dose of romosozumab 210 mg, a higher PK and similar patterns of change in bone turnover markers were observed in patients with CKD. Based on the results from the phase 3 studies and postmarket observations, BMD change after treatment with romosozumab was not significantly affected in patients with CKD.[23,24] Therefore, dose adjustments are not required for romosozumab administration in these patients. A single dose of romosozumab of 210 mg SC was found to be safe in patients with CKD (stage 4 RI and ESRD-RH). However, due to higher

risk of hypocalcemia in patients with impaired renal function who receive romosozumab, monitoring calcium levels and adequate supplementation with calcium and vitamin D during romosozumab treatment is recommended.

Conflicts of Interest

C.-P.H., J.M., and Z.Y. are employees of and have stock/stock options in Amgen. Y.B. is a former employee of Amgen. G.B. is an employee of US Renal Care, Inc.

Data Sharing

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/

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