The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: CR9108963
Title: Study CR9108963: A 12-month, randomized, double-blind, parallel-group, placebo and active-controlled dose-range finding study of the efficacy and safety of SB-751689 in postmenopausal women with osteoporosis.
Rationale: Orally administered ronacaleret induces transient increases in parathyroid hormone (PTH) in both animal species and humans. Ronacaleret at doses of 75 mg, 175 mg and 475 mg in healthy postmenopausal women showed comparable effects on bone formation biomarkers at the highest dose to that seen previously with teriparatide. Consequently, this study was designed to support investigation of a range of doses of ronacaleret in postmenopausal women with osteoporosis on bone parameters such as bone mineral density (BMD) and longer term safety evaluation
Phase: II
Study Period: 14-May-2007 - 19-Dec-2008
Study Design: A phase II, 12-month, multicentre, randomized, double-blind, double-dummy, parallel-group, placebo and active-controlled dose-range finding study of the efficacy and safety of ronacaleret in 520 postmenopausal women with osteoporosis. An open-label teriparatide (non-randomized) group was included. The study consisted of a maximum 6-week screening period, a 12-month treatment period and a 2-week follow-up visit. Subjects were either treated for 12 months with open-label teriparatide 20 mcg once daily by subcutaneous injection or randomized in a ratio of 1:1:1:1:1:1 to receive ronacaleret 100 mg, 200 mg, 300 mg or 400 mg once daily, alendronate 70 mg once weekly, or placebo. All subjects took calcium (500-660 mg elemental daily) and vitamin D (at least 400 IU daily) supplements once daily in the evening throughout the study. The study was terminated for futility in a phased manner by the sponsor once the results of a 6-month interim analysis were available. The interim analysis showed that 3 of the 4 doses of ronacaleret met the protocol-defined futility criteria. The interim analysis showed that there were no differences between any dose of ronacaleret and placebo in percent change from baseline in LS aBMD at Month 6. However, there were small decreases from baseline in total hip aBMD at Month 6 with all doses of ronacaleret compared with placebo.
Centres: 45 centres in 14 countries: USA 7, Germany 7, Australia 4, Spain 4, Argentina 3, Belgium 3, Norway 3, Poland 3, South Africa 3, Hong Kong 2, Korea 2, Russian federation 2, Denmark 1, and Mexico 1.
Indication: Osteoporosis
Treatment: Subjects took open-label teriparatide 20mcg once daily by subcutaneous injection in the morning for twelve 28-day months or were randomized to receive placebo, alendronate, or ronacaleret 100 mg, 200 mg, 300 mg or 400 mg for 12 months. Randomized subjects took oral study medication as follows: Once daily: ronacaleret 100 mg, 200 mg, 300 mg, 400 mg or matching placebo. Once weekly: alendronate 70 mg or matching placebo.
Objectives: The primary objective was to characterise the dose-response for ronacaleret with respect to safety and efficacy based on BMD and biomarkers of bone turnover to enable dose selection for subsequent studies.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was percent change from baseline in BMD at Month 12 measured by dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine (L1-L4).
Secondary Outcome/Efficacy Variables: The secondary efficacy endpoints were: Change from baseline to month 6 in BMD measured by DXA scans of the lumbar spine (L1-L4).

Change from baseline to months 6 and 12 in BMD measured by DXA scans of the hip (total hip, femoral neck and trochanter).

Change from baseline in parameters of hip structural analysis as measured by DXA-derived data.

Responder rate of subjects who remained the same or had any improvement in DXA BMD (> Baseline) at Months 6 and 12.

Change from baseline to Month 12 in the volumetric integral, cortical, and trabecular density (BMD) at the hip and lumbar spine as measured by QCT scans.

Change from baseline to Month 12 in cortical width and other parameters at the hip and lumbar spine as measured by QCT scans.

Change from baseline to Month 12 in parameters of vertebral and hip strength as measured by QCT-derived finite element analysis.

Responder rate of subjects who remained the same or had any improvement in QCT BMD (> Baseline) at Month 12.

Change from baseline in biochemical markers of bone turnover: CTX1, P1NP and BSAP.

Statistical Methods: The Intent-to-Treat (ITT) and Safety populations consisted of all teriparatide and randomized subjects who received at least one dose of study medication. The primary efficacy comparisons of interest were between each dose of ronacaleret and placebo in percentage change from baseline in mean lumbar spine areal BMD (aBMD) at Month 12. This was analysed by an analysis of covariance (ANCOVA) with the variables ba seline value and fixed effects for treatment and country/region; teriparatide subjects were excluded from the model, since these subjects were not randomized and were disproportionately represented. Each dose of ronacaleret was deemed significantly different from placebo if the Hommel-adjusted p-value was <0.044 at Month 12 or <0.006 at Month 6. Contrasts between each dose of ronacaleret and alendronate were also provided. The percent change in total hip (TH) aBMD at Months 6 and 12, and 12-month percent change in total vertebral body (VBT), volumetric BMD (vBMD), TH vBMD were similarly analysed.

Study Population:

	PBO	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	**TERI**
Number of Subjects:							
Planned, N	80	80	80	80	80	80	40
Entered, N	90	88	83	89	88	90	41
Completed, n (%)	49 (54)	45 (52)	48 (59)	43 (49)	46 (53)	50 (56)	38 (93)
Total Number Subjects Withdrawn, N (%)	41 (46)	42 (48)	34 (41)	45 (51)	41 (47)	39 (44)	3 (7)
Withdrawn due to Adverse Events n (%)	6 (7)	5 (6)	4 (5)	8 (9)	7 (8)	5 (6)	0
Withdrawn due to Lack of Efficacy[1] n (%)	20 (22)	23 (26)	19 (23)	22 (25)	18 (21)	24 (27)	0
Withdrawn for other reasons n (%)	15 (24)	14 (16)	11 (13)	15 (17)	16 (18)	10 (11)	3 (7)
Note 1: equates to Sponsor termination of the study for lack of efficacy of ronacaleret							
Demographics							
N (ITT)	90	87	82	88	87	89	41
Females	100	100	100	100	100	100	100
Mean Age, years (SD)	63.2 (6.75)	64.2 (7.69)	64.2 (7.03)	64.3 (6.57)	65.0 (7.60)	65.1 (7.04)	63.2 (5.92)

Race, n (%)							
White	73 (81)	71 (82)	66 (80)	73 (83)	71 (82)	76 (85)	35 (85)
Primary Efficacy Results:							
Change from baseline at Month 12 in lumbar spine aBMD	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	
n	79	76	74	78	72	75	
Least squares mean (SE)	0.03 (0.38)	0.32 (0.40)	1.39 (0.40)	1.61 (0.39)	1.62 (0.40)	4.54 (0.40)	
95% CI	-0.73, 0.78	-0.46, 1.10	0.60, 2.17	0.84, 2.37	0.83, 2.42	3.76, 5.32	
Placebo contrast							
n		76	74	78	72		
Least squares mean (SE)		0.29 (0.55)	1.36 (0.55)	1.58 (0.54)	1.60 (0.55)		
95% CI		-0.78, 1.37	0.28, 2.44	0.51, 2.65	0.51, 2.69		
p-value		0.590	0.014	0.004	0.004		
Adjusted p-value		0.590	0.028	0.011	0.012		
Alendronate contrast							
n		76	74	78	72		
Least squares mean (SE)		-4.22 (0.56)	-3.15 (0.56)	-2.93 (0.55)	-2.92 (0.56)		
95% CI		-5.31, -3.13	-4.25, -2.06	-4.01, -1.85	-4.02, -1.81		
Secondary Outcome Variables:							
Change from baseline at Month 6 in lumbar spine aBMD	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	
n	79	76	74	77	73	75	
Least squares mean (SE)	0.66 (0.33)	0.21 (0.34)	1.61 (0.35)	0.47 (0.34)	1.01 (0.35)	3.42 (0.34)	
95% CI	0.01, 1.32	-0.46, 0.89	0.93, 2.29	-0.20, 1.13	0.33, 1.70	2.74, 4.09	
Placebo contrast							
n		76	74	77	73		
Least squares mean (SE)		-0.45 (0.47)	0.95 (0.48)	-0.19 (0.47)	0.35 (0.48)		
95% CI		-1.38, 0.48	0.01, 1.89	-1.12, 0.73	-0.59, 1.29		
Alendronate contrast							
n		76	74	77	73		
Least squares mean (SE)		-3.21 (0.48)	-1. 81 (0.48)	-2.95 (0.48)	-2.40 (0.48)		
95% CI		-4.15, -2.26	-2.76, -0.86	-3.89, -2.01	-3.35, -1.45		
Change from baseline at Month 6 in total hip aBMD	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	
n	79	75	74	77	71	74	

Least squares mean (SE)	0.42 (0.23)	-0.26 (0.24)	-0.37 (0.24)	-0.86 (0.23)	-0.88 (0.24)	1.84 (0.24)
95% CI	-0.03, 0.87	-0.73, 0.20	-0.84, 0.10	-1.32, -0.40	-1.35, -0.40	1.37, 2.31
Placebo contrast						
n		75	74	77	71	
Least squares mean (SE)		-0.68 (0.33)	-0.79 (0.33)	-1.28 (0.32)	-1.30 (0.33)	
95% CI		-1.32, -0.04	-1.43, -0.14	-1.92, -0.64	-1.95, -0.65	
Alendronate contrast						
n		75	74	77	71	
Least squares mean (SE)		-2.10 (0.33)	-2.21 (0.33)	-2.70 (0.33)	-2.72 (0.34)	
95% CI		-2.75, -1.45	-2.86, -1.55	-3.35, -2.05	-3.38, -2.06	
Change from baseline at Month 12 in total hip aBMD	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**
n	79	75	74	78	70	74
Least squares mean (SE)	0.27 (0.26)	-0.62 (0.26)	-0.75 (0.27)	-1.07 (0.26)	-1.31 (0.27)	2.70 (0.27)
95% CI	-0.23, 0.77	-1.14, -0.10	-1.28, -0.23	-1.58, -0.56	-1.84, -0.77	2.18, 3.22
Placebo contrast						
n		75	74	78	70	
Least squares mean (SE)		-0.89 (0.36)	-1.02 (0.37)	-1.33 (0.36)	-1.57 (0.37)	
95% CI		-1.61, -0.17	-1.74, -0.30	-2.04, -0.63	-2.30, -0.84	
Alendronate contrast						
n		75	74	78	70	
Least squares mean (SE)		-3.32 (0.37)	-3.45 (0.37)	-3.77 (0.37)	-4.01 (0.38)	
95% CI		-4.05, -2.59	-4.19, -2.72	-4.49, -3.05	-4.75, -3.26	
Change from baseline at Month 12 in integral spinal volumetric BMD	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**
n	42	50	43	43	41	49
Least squares mean (SE)	-1.50 (0.81)	0.49 (0.74)	2.29 (0.81)	2.99 (0.81)	3.90 (0.82)	4.57 (0.74)
95% CI	-3.10, 0.10	-0.95, 1.94	0.69, 3.88	1.39, 4.58	2.28, 5.52	3.11, 6.03
Placebo contrast						
n		50	43	43	41	
Least squares mean (SE)		1.99 (0.92)	3.78 (0.95)	4.48 (0.95)	5.40 (0.96)	
95% CI		0.18, 3.80	1.91, 5.65	2.61, 6.35	3.51, 7.29	
Alendronate contrast						
n		50	43	43	41	

Least squares mean (SE)		-4.08 (0.88)	-2.28 (0.92)	-1.58 (0.92)	-0.67 (0.93)	
95% CI		-5.81, -2.34	-4.09, -0.48	-3.39, 0.22	-2.50, 1.17	
Change from baseline at Month 12 in integral total hip volumetric BMD	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**
n	41	47	40	39	37	45
Least squares mean (SE)	-0.15 (0.47)	-0.28 (0.43)	-1.07 (0.48)	-0.91 (0.48)	-0.52 (0.49)	2.53 (0.44)
95% CI	-1.07, 0.78	-1.12, 0.57	-2.00, -0.13	-1.86, 0.04	-1.49, 0.44	1.68, 3.39
Placebo contrast						
n		47	40	39	37	
Least squares mean (SE)		-0.13 (0.53)	-0.92 (0.55)	-0.76 (0.56)	-0.37 (0.57)	
95% CI		-1.18, 0.92	-2.01, 0.17	-1.86, 0.33	-1.50, 0.75	
Alendronate contrast						
n		47	40	39	37	
Least squares mean (SE)		-2.81 (0.52)	-3.60 (0.54)	-3.44 (0.55)	-3.06 (0.56)	
95% CI		-3.83, -1.79	-4.67, -2.53	-4.52, -2.37	-4.16, -1.95	
Percent change from baseline at Month 12 in spinal QCT parameters						
Total vertebra integral VOI BMD (mg/cm3)						
Baseline	57	60	55	57	55	57	39
Mean (SD)	160.13 (23.53)	159.20 (25.35)	153.81 (24.51)	160.19 (22.59)	155.85 (24.43)	158.53 (28.97)	156.36 (27.21)
% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	-0.98 (3.13)	1.09 (4.01)	3.00 (4.65)	3.91 (4.98)	4.83 (6.56)	5.04 (4.39)	14.80 (8.69)
Mid vertebra integral VOI BMD (mg/cm3)							
Baseline	57	60	55	57	55	57	39
Mean (SD)	131.11 (23.80)	132.03 (27.68)	123.06 (26.01)	131.51 (23.66)	124.91 (25.11)	129.24 (28.42)	130.96 (31.77)
% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	-1.31 (3.54)	1.20 (4.85)	4.65 (5.87)	6.06 (6.48)	7.33 (8.67)	4.85 (5.25)	17.97 (11.27)
Mid cylinder trabecular VOI BMD (mg/cm3)							
Baseline	57	60	55	57	55	57	39
Mean (SD)	83.23 (21.00)	81.53 (24.80)	73.73 (25.29)	79.94 (21.38)	74.79 (21.42)	78.99 (24.23)	81.79 (26.94)

% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	-2.45 (4.39)	1.75 (8.70)	6.17 (10.37)	8.99 (10.52)	13.29 (15.32)	4.88 (7.68)	24.37 (15.92)
Mid osteo trabecular VOI BMD (mg/cm3)							
Baseline	57	60	55	57	55	57	39
Mean (SD)	86.60 (20.47)	84.83 (24.26)	77.01 (24.30)	84.51 (20.62)	78.53 (22.10)	82.72 (25.84)	85.91 (26.88)
% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	-2.21 (4.58)	1.81 (8.26)	7.06 (9.25)	9.54 (9.79)	13.21 (14.68)	5.15 (6.86)	24.21 (15.80)
Total vertebra trabecular VOI BMD (mg/cm3)							
Baseline	57	60	55	57	55	57	39
Mean (SD)	94.80 (19.79)	92.56 (23.03)	87.55 (22.81)	92.78 (20.49)	87.66 (22.51)	91.25 (25.65)	93.82 (24.54)
% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	-2.46 (4.58)	1.67 (7.18)	5.81 (8.31)	8.52 (8.97)	11.40 (12.83)	4.97 (6.43)	23.82 (14.64)
Mid osteo cortical VOI BMD (mg/cm3)							
Baseline	57	60	55	57	55	57	39
Mean (SD)	305.47 (61.63)	315.58 (61.86)	306.31 (65.83)	310.32 (59.43)	312.42 (60.69)	314.38 (69.10)	302.62 (60.92)
% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	-0.30 (4.69)	0.63 (4.80)	2.37 (6.37)	2.57 (5.14)	1.22 (4.39)	4.98 (4.63)	9.25 (7.68)
Total vertebra integral VOI PMMI (g*cm2)							
Baseline	57	60	55	57	55	57	39
Mean (SD)	14.74 (3.95)	14.09 (3.38)	14.39 (3.49)	12.84 (3.18)	14.57 (3.99)	14.66 (4.12)	14.46 (4.24)
% Change from baseline	42	50	43	43	41	49	36
Mean (SD)	0.04 (4.19)	0.85 (4.14)	3.01 (5.18)	3.58 (5.70)	3.54 (5.64)	5.39 (5.87)	12.23 (8.43)
Percent change from baseline at Month 12 in hip QCT parameters							
Femur integral VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	238.79 (35.12)	237.55 (42.03)	227.24 (33.89)	238.01 (39.40)	224.16 (38.44)	232.00 (39.80)	229.40 (37.96)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	0.02 (2.78)	-0.05 (2.67)	-0.81 (2.80)	-0.53 (2.18)	-0.15 (2.98)	2.70 (2.13)	3.92 (2.67)

Femur trabecular VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	85.60 (26.94)	87.07 (31.61)	78.04 (25.79)	81.91 (26.69)	75.92 (26.53)	81.28 (29.61)	80.56 (24.67)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	-0.36 (5.53)	-0.40 (6.81)	-2.16 (7.39)	1.16 (5.06)	2.81 (8.20)	3.05 (5.92)	13.19 (8.96)
Femur cortical VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	503.63 (60.35)	499.08 (66.46)	498.75 (68.17)	503.22 (64.19)	486.27 (64.95)	500.50 (60.24)	486.71 (61.80)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	1.11 (4.04)	-0.32 (2.90)	-1.46 (2.81)	-1.06 (2.53)	-1.79 (3.01)	2.44 (3.13)	0.22 (2.63)
Neck integral VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	277.62 (46.75)	276.51 (54.42)	257.06 (38.08)	270.97 (50.22)	256.35 (42.92)	267.64 (49.48)	263.69 (43.83)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	-0.10 (2.48)	0.16 (2.83)	-0.94 (3.34)	-1.20 (2.99)	-1.45 (3.22)	1.65 (2.72)	2.06 (3.65)
Neck trabecular VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	104.49 (36.77)	105.04 (39.85)	95.28 (31.62)	99.52 (36.51)	93.75 (36.56)	99.67 (36.65)	98.61 (28.83)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	-0.95 (7.44)	-2.19 (7.91)	-2.68 (6.14)	1.35 (9.91)	3.05 (11.18)	2.77 (7.55)	11.27 (10.31)
Neck cortical VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	502.82 (61.79)	500.50 (69.73)	489.31 (65.43)	499.29 (64.71)	482.11 (67.13)	500.27 (65.02)	487.13 (67.81)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	1.23 (4.55)	0.44 (4.16)	-1.67 (3.95)	-1.85 (3.89)	-2.80 (4.55)	1.10 (4.25)	-0.69 (4.49)
Neck cortical VOI thickness (mm)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	2.43 (0.20)	2.42 (0.24)	2.36 (0.21)	2.41 (0.19)	2.41 (0.18)	2.39 (0.23)	2.45 (0.12)
% Change from baseline	41	47	40	39	37	45	26

Mean (SD)	-0.85 (7.09)	-0.13 (5.98)	1.12 (5.75)	-0.88 (4.73)	0.32 (4.93)	-0.13 (5.98)	0.39 (4.36)
Trochanter integral VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	197.21 (26.78)	194.38 (36.80)	188 73 (31.58)	194.59 (33.64)	186.47 (34.03)	190.37 (30.25)	187.40 (30.23)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	-0.58 (3.88)	-0.16 (4.22)	-1.53 (3.92)	-1.16 (3.29)	-0.98 (3.83)	3.15 (3.27)	4.96 (4.74)
Trochanter trabecular VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	69.47 (23.32)	69.99 (30.33)	62.11 (26.32)	65.71 (25.31)	60.68 (21.23)	63.96 (25.61)	62.65 (22.85)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	-1.62 (9.67)	-1.34 (13.50)	-2.54 (11.05)	2.12 (8.82)	2.10 (10.66)	3.55 (7.55)	14.12 (14.51)
Trochanter cortical VOI BMD (mg/cm3)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	409.21 (53.19)	401.78 (58.32)	403.87 (59.93)	403.96 (59.35)	395.26 (60.02)	405.31 (51.38)	394.47 (50.55)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	0.56 (5.29)	-0.70 (4.08)	-1.53 (3.60)	-1.48 (3.53)	-2.59 (4.04)	3.33 (3.57)	1.99 (4.37)
Trochanter cortical VOI thickness (mm)							
Baseline	57	61	54	58	54	58	39
Mean (SD)	2.67 (0.25)	2.65 (0.26)	2.64 (0.28)	2.70 (0.23)	2.68 (0.22)	2.64 (0.27)	2.75 (0.17)
% Change from baseline	41	47	40	39	37	45	26
Mean (SD)	-1.00 (5.85)	0.76 (4.40)	1.01 (5.15)	-0.82 (3.65)	1.60 (3.70)	0.81 (5.39)	0.76 (2.93)
RESPONDERS	**PBO**	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	**TERI**
Month 5							
Vertebra: BMD % change >=0	0	0	1 (100)	0	1 (100)	0	0
Femur: BMD % change >=0	0	0	1 (100)	0	0	0	0
Vertebra+ Femur: BMD % change >=0	0	0	1 (100)	0	0	0	0
Month 6							
Vertebra: BMD % change >=0	0	0	0	0	0	1 (100)	0
Femur: BMD % change >=0	0	0	0	0	0	1 (100)	0

Vertebra+ Femur: BMD % change >=0	0	0	0	0	0	1 (100)	0
Month 12							
Vertebra: BMD % change >=0	16 (38)	29 (58)	32 (74)	35 (81)	31 (76)	44 (90)	34 (94)
Femur: BMD % change >=0	20 (49)	23 (49)	14 (35)	19 (49)	16 (43)	40 (89)	25 (96)
Vertebra+ Femur: BMD % change >=0	10 (26)	19 (40)	12 (30)	17 (44)	16 (43)	35 (83)	24 (96)
Early Withdrawal							
Vertebra: BMD % change >=0	1 (33)	1 (50)	1 (50)	2 (67)	1 (100)	0	1 (100)
Femur: BMD % change >=0	1 (50)	1 (50)	0	1 (33)	1 (100)	0	1 (100)
Vertebra+ Femur: BMD % change >=0	1 (50)	1 (50)	0	1 (33)	1 (100)	0	1 (100)
	PBO	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	**TERI**
BSAP							
Baseline							
n	89	84	81	88	86	89	41
Least squares mean (SE)	14.46 (1.04)	14.96 (1.04)	14.24 (1.04)	15.06 (1.04)	14.12 (1.04)	14.31 (1.04)	14.50 (1.05)
95% CI	13.48, 15.52	13.92, 16.07	13.22, 15.34	14.02, 16.17	13.15, 15.17	13.33, 15.36	13.07, 16.10
Placebo contrast							
n		84	81	88	86	89	41
Least squares mean (SE)		1.03 (1.05)	0.98 (1.05)	1.04 (1.05)	0.98 (1.05)	0.99 (1.05)	1.00 (1.07)
95% CI		0.94, 1.14	0.89, 1.09	0.94, 1.15	0.88, 1.08	0.90, 1.09	0.88, 1.14
Week 4							
n	79	79	76	85	79	83	39
Least squares mean (SE)	14.02 (1.04)	14.72 (1.04)	14.51 (1.04)	15.97 (1.04)	15.72 (1.04)	13.68 (1.04)	16.19 (1.06)
95% CI	13.03, 15.09	13.66, 15.86	13.43, 15.67	14.84, 17.19	14.59, 16.94	12.72, 14.73	14.53, 18.03
Placebo contrast							
n		79	76	85	79	83	39
Least squares mean (SE)		1.05 (1.05)	1.03 (1.06)	1.14 (1.05)	1.12 (1.05)	0.98 (1.05)	1.15 (1.07)
95% CI		0.95, 1.17	0.93, 1.15	1.03, 1.26	1.01, 1.25	0.88, 1.08	1.01, 1.32
Month 3							
n	77	73	71	75	73	78	40
Least squares mean (SE)	12.66 (1.04)	15.23 (1.04)	15.44 (1.04)	18.77 (1.04)	17. 85 (1.04)	9.44 (1.04)	16.53 (1.06)
95% CI	11.73, 13.68	14.08, 16.47	14.25, 16.73	17.37, 20.28	16.51, 19.31	8.74, 10.19	14.8, 18.47
Placebo contrast							
n		73	71	75	73	78	40

Least squares mean (SE)		1.20 (1.06)	1.22 (1.06)	1.48 (1.06)	1.41 (1.06)	0.75 (1.06)	1.31 (1.07)
95% CI		1.08, 1.34	1.09, 1.36	1.33, 1.65	1.26, 1.57	0.67, 0.83	1.14, 1.49
Month 6							
n	69	71	67	73	70	74	37
Least squares mean (SE)	12.81 (1.04)	16.31 (1.04)	17.43 (1.04)	22.18 (1.04)	21.47 (1.04)	8.36 (1.04)	17.63 (1.06)
95% CI	11.87, 13.83	15.10, 17.61	16.11, 18.87	20.56, 23.94	19.87, 23.19	7.75, 9.01	15.81, 19.66
Placebo contrast							
n		71	67	73	70	74	37
Least squares mean (SE)		1.27 (1.06)	1.36 (1.06)	1.73 (1.06)	1.68 (1.06)	0.65 (1.06)	1.38 (1.07)
95% CI		1.14, 1.42	1.22, 1.52	1.55, 1.93	1.50, 1.87	0.59, 0.73	1.20, 1.57
Month 12							
n	50	44	50	40	48	50	37
Least squares mean (SE)	13.25 (1.04)	16.64 (1.04)	18.80 (1.04)	23.36 (1.04)	23.28 (1.04)	8.42 (1.04)	19.08 (1.06)
95% CI	12.24, 14.35	15.34, 18.06	17.33, 20.40	21.52, 25.36	21.47, 25.23	7.78, 9.11	17.12, 21.27
Placebo contrast							
n		44	50	40	48	50	37
Least squares mean (SE)		1.26 (1.06)	1.42 (1.06)	1.76 (1.06)	1.76 (1.06)	0.64 (1.06)	1.44 (1.07)
95% CI		1.12, 1.41	1.27, 1.59	1.57, 1.98	1.57, 1.97	0.57, 0.71	1.26, 1.65
CTX1							
Baseline							
n	88	82	81	87	84	87	41
Least squares mean (SE)	625.2 (1.05)	635.3 (1.05)	632.0 (1.05)	587.9 (1.05)	645.5 (1.05)	630.4 (1.05)	564.0 (1.07)
95% CI	568.4, 687.7	576.0, 700.7	572.1, 698.2	534.1, 647.1	585.7, 711.4	572.8, 693.7	490.2, 648.8
Placebo contrast							
n		82	81	87	84	87	41
Least squares mean (SE)		1.02 (1.07)	1.01 (1.07)	0.94 (1.07)	1.03 (1.07)	1.01 (1.07)	0.90 (1.09)
95% CI		0.89, 1.16	0.88, 1.16	0.82, 1.08	0.90, 1.18	0.88, 1.15	0.76, 1.07
Week 4							
n	76	78	76	83	78	63	38
Least squares mean (SE)	530.7 (1.05)	515.2 (1.05)	525.4 (1.05)	506.1 (1.05)	529.2 (1.05)	288.0 (1.06)	576.1 (1.08)
95% CI	479.3, 587.7	465.1, 570.7	473.2, 583.4	457.9, 559.2	477.7, 586.2	258.6, 320.7	497.5, 667.2
Placebo contrast							
n		78	76	83	78	63	38
Least squares mean (SE)		0.97 (1.08)	0.99 (1.08)	0.95 (1.08)	1.00 (1.08)	0.54 (1.08)	1.09 (1.10)

95% CI		0.84, 1.12	0.86, 1.15	0.83, 1.10	0.86, 1.15	0.47, 0.63	0.91, 1.30
Month 3							
n	76	73	71	75	72	49	40
Least squares mean (SE)	523.5 (1.05)	598.5 (1.06)	688.9 (1.06)	723.2 (1.05)	818.9 (1.06)	257.1 (1.06)	864.1 (1.08)
95% CI	471.9, 580.8	538.5, 665.2	618.5, 767.3	651.8, 802.5	736.6, 910.3	229.1, 288.4	745.7, 1001
Placebo contrast							
n		73	71	75	72	49	40
Least squares mean (SE)		1.14 (1.08)	1.32 (1.08)	1.38 (1.08)	1.56 (1.08)	0.49 (1.08)	1.65 (1.10)
95% CI		0.99, 1.33	1.13, 1.53	1.19, 1.60	1.35, 1.81	0.42, 0.57	1.38, 1.98
Month 6							
n	69	70	66	73	70	34	37
Least squares mean (SE)	517.6 (1.06)	648.2 (1.06)	777.1 (1.06)	859.6 (1.06)	964.3 (1.06)	235.9 (1.07)	1112 (1.08)
95% CI	465.1, 576.0	582.0, 722.0	695.9, 867.8	773.2, 955.6	865.8, 1074	208.1, 267.5	956.3, 1293
Placebo contrast							
n		70	66	73	70	34	37
Least squares mean (SE)		1.25 (1.08)	1.50 (1.08)	1.66 (1.08)	1.86 (1.08)	0.46 (1.09)	2.15 (1.10)
95% CI		1.08, 1.46	1.29, 1.75	1.43, 1.93	1.60, 2.17	0.39, 0.54	1.79, 2.58
Month 12							
n	50	44	49	40	49	50	37
Least squares mean (SE)	525.1 (1.08)	695.2 (1.08)	806.1 (1.08)	852.8 (1.08)	991.9 (1.08)	158.3 (1.08)	1071 (1.10)
95% CI	452.9, 608.8	595.4, 811.6	693.3, 937.3	727.6, 999.6	854.0, 1152	136.5, 183.7	888.0, 1292
Placebo contrast							
n		44	49	10	49	50	37
Least squares mean (SE)		1.32 (1.12)	1.54 (1.11)	1.62 (1.12)	1.89 (1.11)	0.30 (1.11)	2.04 (1.13)
95% CI		1.07, 1.64	1.24, 1.90	1.31, 2.02	1.53, 2.33	0.24, 0.37	1.61, 2.59
P1NP							
Baseline							
n	86	83	81	87	83	88	41
Least squares mean (SE)	47.66 (1.05)	45.59 (1.05)	47.70 (1.05)	46.62 (1.05)	46.19 (1.05)	47.71 (1.05)	48.57 (1.07)
95% CI	43.63, 52.06	41.69, 49.85	43.56, 52.25	42.70, 50.89	42.26, 50.50	43.73, 52.06	42.75, 55.20
Placebo contrast							
n		83	81	87	83	88	41
Least squares mean (SE)		0.96 (1.07)	1.00 (1.07)	0.98 (1.07)	0.97 (1.07)	1.00 (1.07)	1.02 (1.08)
95% CI		0.84, 1.08	0.88, 1.14	0.86, 1.11	0.86, 1.10	0.88, 1.13	0.87, 1.19
Week 4							

n	80	78	75	85	79	81	39
Least squares mean (SE)	45.32 (1.05)	49.67 (1.05)	57.36 (1.05)	60.27 (1.05)	63.46 (1.05)	43.66 (1.05)	92.74 (1.07)
95% CI	41.20, 49.86	45.09, 54.71	51.98, 63.30	54.85, 66.24	57.65, 69.86	39.72, 47.99	80.80, 106.4
Placebo contrast							
n		78	75	85	79	81	39
Least squares mean (SE)		1.10 (1.07)	1.27 (1.07)	1.33 (1.07)	1.40 (1.07)	0.96 (1.07)	2.05 (1.09)
95% CI		0.96, 1.26	1.10, 1.45	1.16, 1.52	1.22, 1.60	0.84, 1.10	1.73, 2.42
Month 3							
n	77	72	72	76	73	79	40
Least squares mean (SE)	39.53 (1.05)	49.99 (1.05)	65.21 (1.05)	73.68 (1.05)	86.84 (1.05)	20.15 (1.05)	99.74 (1.08)
95% CI	35.75, 43.72	45.11, 55.40	58.79, 72.34	66.64, 81.47	78.43, 96.17	18.24, 22.26	86.47, 115.0
Placebo contrast							
n		72	72	76	73	79	40
Least squares mean (SE)		1.26 (1.08)	1.65 (1.08)	1.86 (1.08)	2.20 (1.08)	0.51 (1.07)	2.52 (1.09)
95% CI		1.10, 1.46	1.43, 1.91	1.62, 2.15	1.90, 2.54	0.44, 0.59	2.12, 3.00
Month 6							
n	69	70	67	72	70	74	38
Least squares mean (SE)	38.41 (1.05)	56.37 (1.05)	75.73 (1.06)	90.55 (1.05)	104.6 (1.05)	16.41 (1.05)	117.8 (1.08)
95% CI	34.63, 42.60	50.75, 62.61	68.10, 84.21	81.69, 100.4	94.21, 116.1	14.82, 18.17	101.9, 136.2
Placebo contrast							
n		70	67	72	70	74	38
Least squares mean (SE)		1.47 (1.08)	1.97 (1.08)	2.36 (1.08)	2.72 (1.08)	0.43 (1.08)	3.07 (1.09)
95% CI		1.27, 1.70	1.70, 2.29	2.04, 2.73	2.35, 3.15	0.37, .049	2.57, 3.67
Month 12							
n	50	44	50	40	49	51	37
Least squares mean (SE)	40.74 (1.05)	61.43 (1.05)	82.69 (1.05)	98.04 (1.05)	112.6 (1.05)	16.98 (1.05)	119.0 (1.07)
95% CI	36.81, 45.09	55.32, 68.21	74.56, 91.72	88.33, 108.8	101.6, 124.7	15.37, 18.77	103.7, 136.4
Placebo contrast							
n		44	50	40	49	51	37
Least squares mean (SE)		1.51 (1.08)	2.03 (1.08)	2.41 (1.08)	2.76 (1.08)	0.42 (1.08)	2.92 (1.09)
95% CI		1.30, 1.74	1.76, 2.35	2.08, 2.78	2.39, 3.19	0.36, 0.48	2.46, 3.46

	PBO	RONA 100mg	RONA 200mg	RONA 300mg	RONA 400mg	ALN	TERI
Most Frequent Adverse Events -On-Ther apy	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	67 (74)	75 (86)	66 (80)	75 (85)	70 (80)	71 (80)	37 (90)
Nasopharyngitis	17 (19)	16 (18)	13 (16)	12 (14)	16 (18)	12 (13)	7 (17)
Arthralgia	5 (6)	7 (8)	9 (11)	5 (6)	10 (11)	7 (8)	5 (12)
Diarrhoea	5 (6)	6 (7)	8 (10)	11 (13)	12 (14)	5 (6)	1 (2)
Influenza	7 (8)	6 (7)	5 (6)	6 (7)	9 (10)	7 (8)	4 (10)
Headache	7 (8)	5 (6)	5 (6)	4 (5)	4 (5)	8 (9)	6 (15)
Nausea	4 (4)	1 (1)	6 (7)	9 (10)	11 (13)	6 (7)	2 (5)
Back pain	10 (11)	6 (7)	2 (2)	6 (7)	6 (7)	5 (6)	3 (7)
Dizziness	4 (4)	5 (6)	8 (10)	5 (6)	10 (11)	0	6 (15)
Dyspepsia	4 (4)	6 (7)	3 (4)	6 (7)	3 (3)	4 (4)	3 (7)
URTI	5 (6)	5 (6)	4 (5)	2 (2)	8 (9)	3 (3)	2 (5)
Constipation	2 (2)	5 (6)	4 (5)	9 (10)	5 (6)	2 (2)	0
	PBO	**RONA 100mg**	**RONA 200mg**	**RONA 300mg**	**RONA 400mg**	**ALN**	**TERI**

	n (%) [related]	n (%) [related]	n (%) [related]	n (%) [related]	n (%) [related]	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	0 [0]	2 (2)[0]	5 (6) [0]	7 (8) [0]	3 (3) [0]	6 (7) [0]	4 (10) [1]
Femoral neck fracture	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]
Femur fracture	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]
Nerve injury	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (2) [0]
Radius fracture	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Upper limb fracture	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]
Acute myocardial infarction	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Arrhythmia	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Atrioventricular block	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Myocardial infarction	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]
Metastatic malignant melanoma	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Neuroma	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Non-Hodgkin's lymph oma	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]
Renal neoplasm	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]
Appendicitis	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]
Infection	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]
Pulmonary tuberculosis	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]
Loss of consciousness	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Syncope	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]
Transient ischaemic attack	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (2) [0]
Inguinal hernia	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Upper gastrointestinal haemorrhage	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]
Chest pain	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (2) [1]
Hyperplasia	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (2)[0]
Cystocele	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]	0 [0]

Ovarian cyst	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]
Smear cervix abnormal	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (2) [0]
Nasal septum deviation	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (2) [0]
Salpingo-oophorectomy bilateral	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]
Hypertension	0 [0]	0 [0]	0 [0]	1 (1) [0]	0 [0]	0 [0]	0 [0]
Subjects with fatal SAEs, n (%)	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]

Conclusion: The increases from baseline to month 12 in lumbar spine areal BMD were modest in each of the four ronacaleret groups and were lower than that observed in the alendronate and teriparatide groups. There was a loss from baseline to month 12 in total hip areal BMD with all 4 doses of ronacaleret. The increases from baseline to month 12 in hip areal BMD were similar in the alendronate and teriparatide groups. There was a dose-dependent increase from baseline in vertebral integral volumetric BMD of the lumbar spine after 12 months of treatment with ronacaleret. The increase observed with ronacaleret 400 mg was similar to that attained with alendronate but less than that observed with teriparatide. There were no deaths in this study. There were no SAEs in the placebo group and the SAEs reported were isolated occurrences affecting no more than 1 subject across all remaining treatment groups. Nasopharyngitis was the most frequently reported AE in all treatment groups. AEs that appeared to be dose-related with ronacaleret included nausea and diarrhoea.

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