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.: CR9108914
Title: A proof-of-concept study of SB-751689 in male and female subjects with a fractured distal radius
Rationale: SB-751689 (ronacaleret) is a potent and selective calcium-sensing receptor antagonist. Blocking the calcium-sensing receptor activity by SB-751689 administration stimulates a transient rise in endogenous parathyroid hormone (PTH) secretion. Increased plasma levels of PTH have been observed following administration of both single and repeated oral doses of SB-751689 in healthy male volunteers and postmenopausal women. The release of PTH resulted in an increase in biochemical markers of bone formation, suggesting an anabolic response to administration of SB-751689. The demonstrated effects of SB-751689 to release PTH and increase bone formation biomarkers have led to the proposed hypothesis that SB 751689 may act as an effective oral anabolic agent to enhance fracture healing.
Phase: IIA
Study Period: The study consisted of three phases: a screening phase of 5 days, a 12 week treatment phase and a follow-up visit (post-treatment) 4 weeks after the last dose of study medication.
Study Design: A randomized, double-blind, placebo-controlled, parallel-group, multicentre, proof-of-concept study
Centres: A total of 18 centers in Argentina (4), Czech Republic (1), Hong Kong (1), Korea (2), Romania (1), Russian Federation (2), South Africa (1), Spain (1), Sweden (3) and Taiwan (2) enrolled subjects for this muticentre study.
Indication: Fracture healing
Treatment: SB-751689 was supplied as oral white to off-white tablets containing 100mg, 200mg, or 400mg of active ingredient or matching placebo tablet. Subjects were to take the morning dose of study medication with a full glass of water followed by a low to medium fat breakfast. The evening dose was to be taken with or without food but not with a high fat meal. All subjects were supplied with calcium (500mg to 660mg elemental daily) and vitamin D (at least 400IU daily) dietary supplements to be taken once daily in the evening.
Objectives: The primary objective of this study was to evaluate the effects of SB-751689 on the time to radiographic healing, defined as the interval in days between the occurrence of the radial fracture and the time of complete bridging and/or disappearance of fracture line at 3 of the following 4 cortices: dorsal, volar, radial, or ulnar.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was time to radiographic fracture healing as defined by the interval in days between the occurrence of the fracture and the time of complete bridging and/or disappearance of the fracture line at 3 of the following 4 cortices: dorsal, volar, radial, or ulnar as assessed by a central reading centre.
Secondary Outcome/Efficacy Variable(s): Secondary endpoints included: presence and/or absence of pain and swelling at visits; range-of-motion over time; time until cast removal; anatomical deformity and displacement direction outcomes for palmar tilt, dorsal shift, radial angle, radial length, and radial displacement; and Serum PTH and calcium concentrations. Exploratory endpoints were: cortical bridging and endosteal healing as assessed by computed tomography (CT) scan at Week 6. Biomarkers of bone turnover endpoints were: change from baseline to Week 6 in 24 hour urine calcium concentrations; and change from baseline to Week 6 and Week 12 in cross-linked C-terminal telopeptide alpha-1 chain of type I collagen (CTX), procollagen type 1 N-propeptide (P1NP), bone-specific alkaline phosphatase (BSAP), and osteocalcin (OC) serum concentrations. Quality of life endpoints were: grip strength at baseline and Weeks 2, 4, 6, 8, 12 and follow-up, Short Form-36 (SF-36) total and sub-scores at baseline and Weeks 4, 8, 12 and follow-up and DASH (Disabilities of the Arm, Shoulder, and Hand) scores and sub-scores at baseline and Weeks 6, 12 and follow-up. Pharmacokinetic/pharmacodynamic (PK/PD) endpoints were: blood concentrations and population PK parameters for SB-751689; and assessment of PK/PD relationship between SB-751689 systemic exposure and efficacy and/or safety outcomes.
Statistical Methods: As a result of the lack of efficacy seen in the osteoporosis study,

CR9108963, an unplanned interim analysis of this study was performed to assess if futility criteria had been reached. The interim analysis assessed whether futility criteria had been reached by evaluating the conditional power of obtaining a statistically significant difference in radiographic healing time between placebo and each SB-751689 arm at the final analysis, given the observed data at the time of the interim analysis. A conditional power of 50% (under the original sample size assumptions for the rest of the data) was used as a guideline for assessing futility. The conditional power to demonstrate a statistically significant difference from placebo in healing time for SB-751689 200mg twice daily and 400mg once daily was 48% and 10%, respectively. Based on the results of the futility analysis GSK concluded that neither dose had sufficient conditional power to continue and made the decision to terminate the study.

Estimation of sample size was based on the following assumptions for the primary efficacy parameter of time to radiographic fracture healing: radiographic healing times are approximately normally distributed; a mean time to radiographic fracture healing in the placebo group of 77 days; 25% reduction in mean time radiographic fracture healing (to 57 days) for SB 751689; common standard deviation for radiographic fracture healing time of 30 days; 20% dropout over 12 weeks; 90% power; family-wise type I error of 5% through use of a Bonferroni adjustment of the 2 treatment comparisons to placebo. Based on these assumptions a total of 219 subjects were to be randomized (73 per arm).

The Intent-to-Treat Population (ITT) consisted of any randomized subjects who received at least one dose of study medication. For efficacy, subjects were assessed according to their randomized treatment. For safety, subjects were assessed according to the treatment they received. The Per-Protocol Population (PP) consisted of any ITT subject who was compliant with protocol-specific criteria, including study medication.

The primary endpoint was analyzed using a parametric analysis of covariance (ANCOVA) and included terms for geographic region, smoking status, and treatment group. The assumptions of normality and homogeneity of variance were assessed by inspection of normal probability plots and residual plots. The primary analysis was performed for the ITT population and repeated on the PP population using the observed case dataset. All other endpoints were confined to the ITT population for the observed case datasets.

Kaplan Meier plots were generated for time until radiographic healing and time until cast removal. Log rank tests were also performed.

Pain and swelling, and range-of-motion over time were summarised by treatment and visit. The percentage of subjects radiographically healed at each visit was summarised. The percentage of subjects with endosteal healing and cortical bridging at 3 of 4 sites as assessed by CT scan at Week 6 were analyzed using logistic regression using the same variables as for the primary data set.

All of the derived SB-751689, PTH(1-84) and PTH(7-84) parameters were listed and summarised. No formal SB-751689 PK/PD testing was undertaken.

Baseline and percentage change from baseline in biomarker data (CTX, P1NP, BSAP, OC) were summarised. Line plots were also generated by treatment group.

DASH scores and grip strength as a proportion to the uninjured hand were summarised by treatment group, visit, and injured hand dominance. In addition, DASH scores and grip strength as a proportion to the uninjured hand were analysed at Week 6 (DASH scores only) and Week 12 using an ANCOVA with treatment, injured hand dominance, smoking status, baseline score and geographic region as variables.

Adverse events (AEs), electrocardiograms (ECGs) and change from baseline in laboratory and vital signs were presented by treatment group. Laboratory and vital sign values outside normal and clinical concern ranges were presented by treatment group. Line charts were generated for pre-dose albumin-adjusted serum calcium, post-dose albumin-adjusted serum calcium, and 24-hr urinary calcium. The incidence of hypercalcemia, withdrawals due to hypercalcemia, incidence of dose reduction due to hypercalcemia, and hypercalcemia management were summarized by treatment group**.**

Study Population: The study recruited ambulatory male and female subjects aged 35 years to <80 years who had sustained a closed, unilateral, extra articular fracture of the distal radius no longer than 5 days prior to randomisation. Arbeitsgemeinschaft für Osteosynthesefragen/Association for the Study of Internal Fixation (AO/ASIF) types 23 A2 and 23-A3 were permissible. Subjects were to be receiving conservative treatment of the distal radial fracture, including closed reduction and immobilization devices (e.g., cast, splint).

	Placebo	**SB-751689 200mg twice daily**	**SB-751689 400mg once daily**
Study Population			
Number of Subjects:	27	28	30
Planned, N	73	73	73
Randomised, N	27	28	30
Completed, n (%)	21 (78)	21 (75)	20 (67)
Total Number Subjects Withdrawn, n (%)	6 (22)	7 (25)	10 (33)
Withdrawn due to Adverse Events n (%)	2 (7)	1 (4)	2 (7)
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for other reasons n (%)	4 (15)	6 (21)	8 (27)
Demographics			
N (ITT)	27	28	30
Females: Males	23:4	24:4	25:5
Mean Age, years (SD)	61.19 (9.12)	57.07 (9.01)	61.83 (8.09)
White, n (%)	19 (70)	18 (64)	20 (67)
Previous Fracture, n (%)	5 (19)	5 (18)	13 (43)
Family history, n (%)			
Osteoporosis related fracture	1 (4)	1 (4)	1 (3)
Hip fracture	2 (7)	3 (11)	0
Osteoporosis	1 (4)	0	1 (3)
Primary Efficacy Results:			
	Placebo	**SB-751689 200mg twice daily**	**SB-751689 400mg once daily**
Time to Radiographic Healing			
N	25	26	25
Time to Radiographic Healing (Days)			
LS mean (SE)	74.02 (5.02)	64.78 (4.72)	67.74 (5.23)
95% CI	64.01, 84.04	55.37, 74.19	57.30, 78.17
SB-751689 vs Placebo			
LS mean (SE)	-	-9.24 (5.93)	-6.29 (5.99)
95% CI	-	-21.1, 2.58	-18.2, 5.66
p-value	-	0.12	0.30
Secondary Outcome Variable(s):			
Time to Cast Removal			

N	23	24	23
Time to Cast Removal (Days)			
LS mean (SE)	43.62 (3.34)	43.63 (3.34)	47.35 (3.53)
95% CI	36.95, 50.29	36.97, 50.30	40.30, 54.40
SB-751689 - Placebo			
LS mean (SE)	-	0.01 (3.91)	3.72 (3.98)
95% CI	-	-7.80, 7.82	-4.24, 11.68
Pain and Swelling (Injured Arm) at Visit, n (%)			
Baseline, N	2	2	5
	2 (100)	2 (100)	5 (100)
Week 2, N	2	3	2
	2 (100)	3 (100)	2 (100)
Week 4, N	6	12	11
	6 (100)	11 (91.7)	8 (72.7)
Week 6, N	19	17	21
	18 (94.7)	12 (70.6)	18 (85.7)
Week 8, N	22	22	23
	18 (81.8)	15 (68.2)	17 (73.9)
Week 12, N	22	21	22
	11 (50.0)	8 (38.1)	12 (54.5)
Range of Motion (Degrees) in Injured Arm at Visit, Mean (SD)			
Baseline, N	27	28	30
Extension	1.30 (5.82)	0	1.97 (6.12)
Flexion	1.48 (6.02)	0	2.10 (6.57)
Pronation	5.93 (21.53)	0	5.23 (16.22)
Radial deviation	0.59 (3.08)	0	1.03 (3.16)
Supination	2.30 (9.81)	0	3.60 (14.26)
Ulnar deviation	1.37 (5.03)	0	1.67 (5.14)
Week 2, N	25	25	24
Extension	0	0.08 (0.40)	3.96 (15.67)
Flexion	0	0.08 (0.40)	1.67 (5.65)
Pronation	0	0.4 (2.00)	5.0 (19.11)
Radial deviation	0	0	1.04 (5.01)
Supination	0	0.40 (2.0)	4.38 (16.24)
Ulnar deviation	0	0.20 (1.00)	1.25 (6.12)
Week 4, N	22	24	24
Extension	5.77 (10.98)	13.54 (20.24)	9.50 (17.65)
Flexion	9.45 (17.30)	13.46 (17.35)	13.38 (19.80)
Pronation	17.27 (31.95)	25.21 (34.27)	21.88 (31.06)
Radial deviation	3.41 (6.25)	7.04 (11.97)	4.38 (6.81)
Supination	13.86 (27.34)	26.25 (35.49)	18.33 (27.09)
Ulnar deviation	4.09 (8.95)	11.04 (16.01)	8.25 (11.76)
Week 6, N	23	22	23
Extension	27.70 (24.99)	27.41 (24.93)	28.87 (20.51)
Flexion	32.91 (23.87)	28.82 (24.55)	36.39 (19.89)
Pronation	51.18 (37.19)	50.00 (40.09)	49.25 (34.95)
Radial deviation	10.00 (8.62)	10.67 (10.99)	11.14 (7.69)
Supination	48.41 (35.94)	49.09 (39.84)	50.50 (35.17)
Ulnar deviation	18.52 (14.66)	18.24 (16.69)	18.55 (10.52)
Week 8, N	23	21	23
Extension	40.78 (18.94)	46.00 (17.89)	39.00 (18.52)
Flexion	42.64 (17.12)	49.09 (18.17)	46.30 (17.88)

Pronation	67.76 (29.79)	71.50 (25.76)	63.36 (27.97)
Radial deviation	14.13 (8.95)	15.57 (6.95)	17.50 (8.95)
Supination	57.95 (30.63)	69.75 (24.36)	63.45 (30.33)
Ulnar deviation	23.09 (14.18)	28.95 (15.78)	24.64 (10.69)
Week 12, N	22	21	22
Extension	43.77 (18.63)	56.76 (21.13)	44.23 (19.08)
Flexion	51.55 (16.63)	62.05 (15.05)	52.36 (16.32)
Pronation	73.25 (25.66)	72.89 (30.38)	66.90 (27.18)
Radial deviation	15.18 (5.91)	18.62 (8.89)	18.41 (6.28)
Supination	66.90 (25.67)	72.63 (29.88)	70.48 (25.49)
Ulnar deviation	27 (12.94)	32.81 (16.16)	27.55 (9.01)
Biomarkers of Bone Turnover at Week 6 and Week 12, Median % change from Baseline (Min-Max)			
6 Weeks, N	23	23	22
BSAP	-2.29 (-34.35, 57.36)	9.63 (-48.11, 50.79)	16.75 (-56.88, 83.95)
OC	-6.59 (-30.00, 224.56)	23.53 (-60.13, 492.59)	43.05 (-29.17, 245.51)
P1NP	6.25 (-20.37, 91.67)	75.00 (-73.47, 156.10)	53.26 (-23.08, 678.13)
CTX1	-12.71 (-64.00, 61.81)	16.98 (-56.61, 142.75)	-6.37 (-48.62, 109.79)
12 Weeks, N	22	21	21
BSAP	-6.87 (-35.88, 31.39)	43.98 (-2.82, 99.22)	18.52 (-24.48, 211.43)
OC	-12.73 (-32.46, 328.07)	67.04 (-43.14, 450.00)	72.85 (-14.58, 240.76)
P1NP	-0.52 (-42.59, 296.77)	114.29 (-4.55, 222.78)	100.00 (-43.59, 434.04)
CTX1	-23.32 (-69.17, 66.74)	-5.58 (-54.99, 161.64)	-0.84 (-73.40, 297.19)
Post-dose Intact Serum PTH at Visit , Mean (SD) Change from Baseline (ng/L)			
Week 2, N	24	25	24
	-4.92 (17.73)	-10.56 (13.17)	59.75 (105.06)
Week 6, N	22	23	23
	-5.59 (22.13)	-4.43 (26.57)	36.65 (55.14)
Week 12, N	21	20	19
	-1.05 (19.26)	-1.75 (19.22)	31.63 (50.23)
Follow-up, N	24	26	23
	-7.63 (18.98)	-3.77 (14.23)	-3.91 (15.53)
Post-dose Whole Serum PTH at Visit , Mean (SD) Change from Baseline (ng/L)			
Week 2, N	25	25	24
	1.05 (5.89)	-3.29 (4.40)	14.90 (30.95)
Week 6, N	23	23	23
	-0.63 (10.39)	-3.94 (3.78)	9.99 (16.31)
Week 12, N	21	20	19
	-0.47 (6.55)	-1.00 (5.55)	6.72 (14.53)
Follow-up, N	25	26	23
	-0.67 (7.41)	-1.47 (4.12)	-1.97 (6.48)

Pre-dose Albumin Adjusted Serum Calcium at Visit, Mean (SD) Change from Baseline (mmol/L)			
Week 1, N	23	26	21
	0.04 (0.08)	0.38(0.15)	0.23 (0.17)
Week 2, N	20	24	19
	0.03 (0.06)	0.40(0.14)	0.24 (0.13)
Week 3, N	20	24	22
	0.04 (0.08)	0.43 (0.17)	0.24 (0.13)
Week 4, N	20	20	22
	0.03 (0.07)	0.37(0.16)	0.25 (0.13)
Week 5, N	19	23	18
	0.05 (0.08)	0.37(0.16)	0.23 (0.10)
Week 6, N	20	20	19
	0.04 (0.09)	0.48(0.27)	0.25 (0.14)
Week 8, N	20	22	21
	0.03 (0.09)	0.41 (0.12)	0.23 (0.14)
Week 12, N	19	19	18
	0.02 (0.08)	0.35 (0.18)	0.23 (0.15)
Follow-up, N	23	24	21
	0.01 (0.08)	0 (0.04)	0.04 (0.06)

24 Hour Urine Calcium Excretion Values at week 6, n (%)			
Baseline, N	26	28	29
10 mmol/24 hr	1 (4)	0	0
>7.5 to <10 mmol/24 hr	4 (15)	2 (7)	0
1.25 to 7.5mmol/24hr	18 (69)	23 (82)	25 (86)
1.25 mmol/24 hr	2 (8)	2 (7)	4 (14)
Week 6, N	23	23	23
10 mmol/24 hr	2 (9)	3 (13)	1 (4)
>7.5 to <10 mmol/24 hr	4 (17)	8 (35)	3 (13)
1.25 to 7.5mmol/24hr	15 (65)	10 (43)	18 (78)
1.25 mmol/24 hr	2 (9)	1 (4)	0
Number and Percent of Subjects with Hypercalcemia, n (%)			
Baseline, N	27	28	30
pre > 2.74 mmol/l	0	15 (54%)	0
post > 2.99 mmol/l	0	1 (4%)	0

Safety Results: An on therapy adverse event (AE) and Serious Adverse Event (SAE) was defined as an AE with onset on or after the start date of study medication and up to 14 days after the last dose of medication.

	Placebo N=27	**SB-751689 200mg twice daily N=28**	**SB-751689 400mg once daily N=30**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	16 (59)	15 (54)	14 (47)
Abdominal pain upper	1 (4)	2 (7)	4 (13)
Headache	4 (15)	1 (4)	1 (3)
Hypercalcemia	0	6 (21)	0
Diarrhoea	0	3 (11)	2 (7)
Nausea	2 (7)	1 (4)	1 (3)
Dyspepsia	1 (4)	0	2 (7)
Musculoskeletal pain	0	1 (4)	3 (10)
Dizziness	0	0	3 (10)
Cough	0	0	3 (10)
Nasopharyngitis	0	2 (7)	1 (3)
Arthralgia	2 (7)	0	0
Anxiety	0	0	2 (7)

Serious Adverse Events - On-Therapy, n (%) [n considered by the investigator to be related to study medication]

	Placebo N=27	**SB-751689 200mg twice daily N=28**	**SB-751689 400mg once daily N=30**
Subjects with non-fatal SAEs, n	1 (4) [0]	0	0
Unstable wrist fracture	1 (4) [0]	0	0
Subjects with fatal SAEs, n (%)	0	0	0

Conclusion:
There was no significant decrease in time to radiographic fracture healing (primary endpoint) in subjects treated with SB-751689 as compared to placebo. Similarly, there were no notable differences between placebo and SB-751689 for the secondary endpoints; time to cast removal; range of motion over time; and pain and swelling over time. However, treatment with SB-751689 resulted in an increase in the serum levels of a number of biomarkers associated with bone

turnover (BSAP, P1NP and OC) and relatively little change in the bone resorption biomarker CTX. There were no deaths or SAEs in either SB-751689 group. AE withdrawals were low and similar between treatment groups. Hypercalcemia as an AE was only reported by subjects in the SB 751689 200mg twice daily group and was the most frequently occurring AE suspected by the investigators to be related to the study medication. Administration of SB 751689 was associated with increases in intact PTH, whole PTH, and albumin adjusted serum calcium. Fifteen (54%) subjects in the SB-751689 200mg twice daily group recorded albumin adjusted serum calcium values requiring the management of hypercalcemia. No subject in the placebo or SB-751689 400mg once daily group recorded pre-or post-dose albumin adjusted serum calcium values requiring the management of hypercalcemia. There were no clinically relevant trends in any other laboratory parameter or any vital sign or ECG results.