The Effects of Ronacaleret, a Calcium-Sensing Receptor Antagonist, on Bone Mineral Density and Biochemical Markers of Bone Turnover in Postmenopausal Women with Low Bone Mineral Density

Lorraine A. Fitzpatrick, Christine E. Dabrowski, Gregory Ciconetti, David N. Gordon, Socrates Papapoulos, Henry G. Bone III, and John P. Bilezikian

GlaxoSmithKline (L.A.F., C.E.D., G.C., D.N.G.), King of Prussia, Pennsylvania 19406; Leiden University Medical Center (S.P.), 2333 ZA Leiden, The Netherlands; Michigan Bone and Mineral Clinic (H.G.B.), Detroit, Michigan 48236; and Columbia University College of Physicians and Surgeons (J.P.B.), New York, New York 10032

Context: Ronacaleret, a calcium-sensing receptor antagonist that stimulates PTH release from the parathyroid glands, was evaluated as an oral osteoanabolic agent for the treatment of osteoporosis.

Objective: Our objective was to compare the effects of ronacaleret, teriparatide, and alendronate on bone mineral density (BMD) and markers of bone turnover.

Design and Setting: In this randomized, placebo-controlled, dose-ranging trial, spine and hip BMD were assessed by dual-energy x-ray absorptiometry and bone turnover markers were measured.

Patients: Patients included 569 postmenopausal women with low BMD.

Interventions: Subjects were offered open-label 20 μg teriparatide sc once daily or were randomized to 100, 200, 300, or 400 mg oral ronacaleret once daily, 70 mg alendronate once weekly, or placebo and were followed for up to 12 months.

Main Outcome Measure: Percentage change from baseline in lumbar spine BMD was assessed at month 12.

Results: With ronacaleret, the increases in lumbar spine BMD at 12 months (0.3–1.6%) were significantly lower than those attained with teriparatide (9.1%) or alendronate (4.5%). There were small decreases in total hip, femoral neck, and trochanter BMD at month 12 with ronacaleret compared with increases in the teriparatide and alendronate arms. Bone turnover markers increased in the ronacaleret and teriparatide arms and decreased in the alendronate arm. PTH elevations with ronacaleret were prolonged relative to those previously reported with teriparatide.

Conclusion: The densitometric findings in the context of prolonged PTH elevation and increased bone turnover suggest ronacaleret induces mild hyperparathyroidism. Ronacaleret only modestly increased lumbar spine BMD and decreased BMD at hip sites. (J Clin Endocrinol Metab 96: 0000–0000, 2011)
plexus. In contrast, pulsatile administration of teriparatide increased osteoblast number and bone formation.

These findings have been substantiated in humans. When the skeleton is exposed to continuous PTH, as seen in primary hyperparathyroidism, bone loss occurs at pre-dominantly cortical sites with relative preservation of cancellous architecture (2, 3). Intermittent, pulsatile secretion of PTH, as administered for the treatment of postmeno-pausal osteoporosis as a daily sc injection, increases bone mineral density (BMD) and bone strength, and prevents vertebral and nonvertebral fractures (4–7). Theoretically, pulsatile PTH could be achieved by acutely stimulating the release of endogenous PTH by inhibiting the calcium-sensing receptor (CaSR). Short-term antagonism of the CaSR with ronacaleret, an orally available selective calcilytic, results in the release of endogenous PTH (8). Ronacaleret was considered as a therapeutic option for the treatment of osteoporosis.

Previously published data indicate that a calcium receptor antagonist induced transient increases in PTH in murine species and in humans (8). Administration of a calcilytic to ovariectomized Sprague Dawley rats transiently increased PTH plasma concentrations, increased trabecular and cortical BMD, and improved bone strength. Administration of a calcilytic agent to human subjects increased PTH (1-84) concentrations and raised serum calcium levels. Furthermore, 475 mg ronacaleret administered to healthy postmenopausal women for 4 wk showed effects on bone formation biomarkers comparable to those previously reported with teriparatide (9). This study was undertaken to characterize the dose response for ronacaleret with respect to safety and efficacy based on BMD and biomarkers of bone turnover to enable dose selection for further development as an oral treatment for postmenopausal osteoporosis.

Subjects and Methods

Study design

This was a randomized, placebo-controlled, dose-ranging trial augmented with an open-label arm conducted in 569 women who had been postmenopausal for at least 5 yr. Subjects were recruited from 45 centers in 14 countries. Women were enrolled if they had a T-score less than or equal to −2.5 (if no prevalent vertebral fracture) or less than or equal to −2.0 (if one prevalent vertebral fracture) at the femoral neck, total hip, trochanter, or lumbar spine and more than −4.0 at all sites. Women with more than one prevalent vertebral fracture or with any previous nonvertebral osteoporosis-related fragility fracture after the age of 40 were excluded. Women deficient in vitamin D defined as 25-hydroxyvitamin D below 50 nmol/dl, with metabolic bone disease, with contraindications to alendronate or teriparatide, or with clinically significant abnormal baseline chemistry values were also excluded. Previous treatment with osteoporosis medications was prohibited unless sufficient time to wash out the medication had occurred (for details, see Supplemental Appendix, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).

Subjects were offered open-label teriparatide or were randomly assigned in equal proportions to one of six treatment regimens and were to be followed for 12 months. The primary endpoint was percent change from baseline in lumbar spine BMD at month 12. Other endpoints were percent change from baseline in hip BMD and in markers of bone turnover. Investigators and all participants were blinded to randomized treatment group assignments, serum calcium, albumin-adjusted serum calcium, urinary calcium, PTH (whole and intact), alkaline phosphatase, serum phosphate, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D results.

An independent safety review committee consisting of sponsor personnel who were not involved in the conduct of the study provided ongoing unblinded review of the albumin-adjusted serum calcium levels. The Institutional Review Board for each center approved the study protocol, and all women provided written informed consent before participation in this study. The study was phased out for futility based on the results of a preplanned interim analysis on data obtained through the 6-month visit. At the time of study phase-out, subjects completed one final visit, which occurred between months 10 and 12. At this time, the majority of randomized subjects with study termination as the primary reason for early withdrawal were scheduled for a visit at month 10 (Fig. 1) and underwent all procedures usually performed at month 12 including dual-energy x-ray absorptiometry (DXA). For the purposes of this report, study participants who had their final study visit at month 10 are included with those who completed the study at month 12. This is referred throughout as month 10–12 in the Results and Discussion.

Treatment assignments

Women who qualified according to local regulatory approvals were offered open-label teriparatide at 20 μg sc once daily. Subjects who declined teriparatide sc injections or were screened after the teriparatide cohort was fully enrolled were randomly assigned in equal proportions to oral ronacaleret at 100, 200, 300, or 400 mg once daily, alendronate at 70 mg once weekly, or placebo, for 12 months. The ratio of open-label teriparatide subjects to randomized subjects within each treatment group was 1:2. The women self-injected teriparatide [PTH (1-34); Forteo/Forsteo, Eli Lilly and Co., Indianapolis, IN]. Alendronate or matching placebo was taken once weekly, and ronacaleret or matching placebo was taken once daily. All women took calcium (500–660 mg elemental) and vitamin D (at least 400 IU) dietary supplements once daily. Compliance was defined as taking more than 75% and less than 120% of assigned medication.

Efficacy measures

Areal BMD (aBMD) (grams per square centimeter) assessments, measured by DXA and analyzed at a central reading facility (Synarc, San Francisco, CA), were planned at baseline, month 6, and month 12. Serum was assayed by Quest Diagnostics (Van Nuys, CA, and Middlesex, UK) for markers of bone formation [procollagen type I N propeptide (P1NP) and bone-specific alkaline phosphatase (BSAP)] and bone resorption [C-terminal telopeptide α1 chain of type I collagen (CTX1)] at baseline, wk 4, and months 3, 6, 10,
Safety assessments

Albumin-adjusted serum calcium concentrations were measured before and after dose at estimated peak concentrations for teriparatide (4–6 h) and randomized subjects (8–12 h) at wk 2 and 4 and months 6 and 12. Twenty-four-hour urinary excretion of calcium and creatinine was measured at baseline and months 1, 6, and 12. Specific ordered algorithms were used if albumin-adjusted serum calcium levels became elevated.

Subjects were questioned at each visit about adverse events, which were classified by system organ class and preferred term. Subjects with confirmed significant BMD loss of more than 6% at the lumbar spine or total hip or more than 7% at the femoral neck were notified.

Due to the nature of this study with a placebo-control arm, the chance of being randomized to the placebo arm and the attendant risks involved. BMD was monitored for bone loss at 6 months, and the investigators were notified if bone loss exceeded 6% at the lumbar spine or total hip or 7% at the femoral neck from baseline. All subjects were vitamin D replete before entry, and all were provided calcium (at least 500–660 mg elemental daily) and vitamin D (at least 400 IU daily) supplements.

Statistical analyses

It was hypothesized that the 12-month mean percent change from baseline in lumbar spine aBMD would be 6.5% in the ronacaleret arms and 1% in the placebo arm (6), with SD of 7 and 6% in the ronacaleret and placebo arms, respectively. The 6-month mean percent change from baseline in lumbar spine aBMD was assumed to be 4.5 and 0.5% for the ronacaleret and placebo arms, respectively, with a common SD of 5%.

Sample size considerations were adjusted for multiplicity by first allocating 0.006 and 0.044 type I error to the interim and final analysis, respectively. Furthermore, within each analysis, a Bonferroni correction was considered to address the testing of placebo vs each ronacaleret dose. Under these assumptions, 68 evaluable subjects provided more than 90% power to compare placebo with each dose of ronacaleret at the lumbar spine at the interim and final analyses, while controlling family-wise type I error at the 5% significance level. Although a Bonferroni correction was used in sample size calculations, use of Hommel-adjusted P values for the actual analysis was prespecified. To compensate for a 15% rate of nonevaluable subjects, enrollment of 80 subjects in each of the four ronacaleret arms and the placebo arm was planned.

Percent change from baseline in least-squares aBMD was analyzed using an analysis of covariance model that adjusted for treatment, baseline aBMD, and region. Teriparatide subjects
were excluded from the model because they were not randomized and were disproportionately represented. For this reason, only summary statistics have been provided in Supplemental Table 1.

For measures of aBMD at the lumbar spine, each dose of ronacaleret was deemed significantly different from placebo if the Hommel-adjusted P value for the placebo-contrast was less than 0.044 at 12 months or less than 0.006 at 6 months. Because multiplicity adjustments did not extend beyond tests for the lumbar spine, unadjusted 95% confidence intervals were used to compare total hip aBMD; summary statistics were reported for other hip locations.

For biomarkers of bone turnover, a repeated-measures model was used on log-transformed data and adjusted for treatment, visit, and treatment by visit interaction. Least-squares means, SE, and 95% confidence intervals (without multiplicity adjustments) were back transformed to the original scale.

Analyses were performed on the intention-to-treat (ITT) population, which consisted of all teriparatide and randomized subjects who received at least one dose of investigational product, unless indicated otherwise. The number of ITT subjects is listed in Fig. 1. The absolute change from baseline in each marker of bone turnover was presented for the per-protocol population, which consisted of ITT subjects who were compliant with the protocol. Per-protocol observations were used as the primary population for biomarkers to decrease any noise introduced by noncompliers.

Results
Disposition, baseline characteristics, and compliance
Data were collected from May 2007 to December 2008. There were 41 women who elected to receive open-label teriparatide therapy, and another 528 women were randomly assigned to one of four ronacaleret doses, alendronate, or placebo (Fig. 1). Of these, 564 subjects were eligible for ITT analysis; five subjects did not receive investigational product. The ages of the women ranged from 45–79 yr. Baseline demography and clinical characteristics were balanced among the treatment groups (Table 1). Compliance was assessed, and all subjects in the teriparatide arm except two were compliant, having taken more than 75% of the allotted injections; the two noncompliant subjects took less than 75% of the allotted teriparatide injections. The majority of randomized subjects (>90%) were compliant with both the daily and weekly study medication, having taken more than 75% of the allotted medication. One subject on placebo took twice the number of daily tablets, and one subject on 100 mg ronacaleret took 1.3 times the number of weekly tablets. One subject who was randomized to 300 mg ronacaleret took 1.25 times the number of daily tablets.

Bone mineral density
The study was terminated in a phased manner after the results of a preplanned interim analysis at 6 months showed that no dose of ronacaleret significantly improved BMD of the lumbar spine over that attained with placebo. Therefore, the results from subjects who completed a final visit at either month 10 or 12 are pooled. Lumbar spine BMD increased significantly from baseline to month 10–12 in the teriparatide, alendronate, and ronacaleret arms above 200 mg (Fig. 2A). The modest increases in lumbar spine BMD of 1.4–1.6% attained with ronacaleret 200–400 mg, although statistically significant, were considerably lower than the increase in BMD with teriparatide (9.1%) or alendronate (4.6%). Total hip BMD increased significantly from baseline to month 10–12 in the teriparatide (2.7%) and alendronate groups (2.7%) as compared with significant losses in all ronacaleret arms (−0.6 to −1.2%) (Fig. 2B). There were also losses in BMD at the femoral neck and trochanter after 12 months of

### Table 1. Baseline demographic and clinical characteristics of study groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>100 mg (n = 87)</th>
<th>200 mg (n = 82)</th>
<th>300 mg (n = 88)</th>
<th>400 mg (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.2 ± 7.69</td>
<td>64.2 ± 7.03</td>
<td>64.3 ± 6.57</td>
<td>65.0 ± 7.60</td>
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<tr>
<td>Age at menopause (yr)</td>
<td>46.7 ± 5.43</td>
<td>48.2 ± 5.99</td>
<td>47.8 ± 6.28</td>
<td>47.2 ± 5.76</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.81</td>
<td>25.0 ± 4.24</td>
<td>25.4 ± 3.80</td>
<td>25.1 ± 3.65</td>
</tr>
<tr>
<td>Fractures [n (%)]</td>
<td>33 (38 %)</td>
<td>32 (39)</td>
<td>38 (43)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Lumbar spine BMD, T-score</td>
<td>−2.69 ± 0.65</td>
<td>−2.51 ± 0.84</td>
<td>−2.59 ± 0.84</td>
<td>−2.57 ± 0.84</td>
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<tr>
<td>Hip BMD, T-score</td>
<td>−1.53 ± 0.72</td>
<td>−1.79 ± 0.70</td>
<td>−1.55 ± 0.66</td>
<td>−1.79 ± 0.76</td>
</tr>
<tr>
<td>Serum 25-OH/D (nmol/liter)</td>
<td>97.0 ± 97.85</td>
<td>91.6 ± 66.77</td>
<td>106.4 ± 116.64</td>
<td>95.1 ± 72.74</td>
</tr>
<tr>
<td>Serum 1,25(OH)₂D (pmol/liter)</td>
<td>142.2 ± 46.96</td>
<td>141.0 ± 53.11</td>
<td>134.9 ± 35.34</td>
<td>133.5 ± 42.20</td>
</tr>
<tr>
<td>PTH (ng/liter)</td>
<td>37.26 ± 13.09</td>
<td>37.68 ± 14.26</td>
<td>37.40 ± 11.89</td>
<td>37.28 ± 12.81</td>
</tr>
<tr>
<td>Albumin-adjusted serum Ca (mmol/liter)</td>
<td>2.29 ± 0.07</td>
<td>2.29 ± 0.08</td>
<td>2.28 ± 0.07</td>
<td>2.28 ± 0.08</td>
</tr>
</tbody>
</table>

Data are expressed as means ± sd except where indicated otherwise. The T-score is the number of sd above or below the mean plateau value of BMD in young adults. ALN, Alendronate; 25-OHD, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; PBO, placebo; RONA, ronacaleret; TER, teriparatide.
treatment with ronacaleret compared with little or no gain in the placebo arm (Supplemental Table 1). This contrasts with increases observed in these hip sites in both the teriparatide and alendronate arms.

**Biochemical markers of bone turnover**

The teriparatide group had a rapid and large increase in the level of P1NP, a marker of bone formation (Fig. 3A). The increase with teriparatide was apparent at wk 4 (103 μg/liter), reaching maximal concentrations (121 μg/liter) at month 6 that were sustained to month 10–12 (Fig. 3A). Although ronacaleret also increased P1NP in a dose-dependent manner, the increase was somewhat delayed in comparison with teriparatide. Increases in BSAP, a marker of bone formation, were apparent at month 6 in the 200- to 400-mg ronacaleret and teriparatide arms, although the maximal increases observed at month 10 were 2-fold higher with 400 mg ronacaleret as compared with teriparatide (Fig. 3B).

Teriparatide therapy was also associated with an increase in the level of CTX1, a marker of bone resorption, although this increase lagged behind the increase in comparison with the change in P1NP (Fig. 3C). Increases in CTX1 with teriparatide were apparent at month 3, reaching maximal concentrations at month 10. Increases in CTX1 with ronacaleret were delayed in comparison with teriparatide; mean increases from baseline were apparent at month 6 with 200–400 mg ronacaleret compared with month 3 for teriparatide. As expected, alendronate decreased markers of bone turnover (Fig. 3, A–C); decreases in CTX1 were apparent earlier (at wk 4) than the decreases in P1NP and BSAP (at month 3).

**Parathyroid hormone**

In a subset of subjects at month 10–12, concentrations of intact PTH increased rapidly
with all doses of ronacaleret, reaching maximal concentrations by 1 h after dose and remaining above the upper limit of normal (reference range, 10–65 ng/liter) until 4 h after dose before declining slowly thereafter (Fig. 4A). A similar intact PTH profile was observed after 6 months of therapy with ronacaleret (data not shown). Neither alendronate nor placebo administration had any effect on intact PTH levels. A similar profile for whole PTH was observed (data not shown).

Serum and urinary calcium

Baseline values for albumin-adjusted serum calcium concentrations were similar among the treatment groups, ranging from 2.28–2.29 mmol/liter. Compared with placebo, there were dose-dependent increases in trough (before dose) albumin-adjusted serum calcium concentrations with ronacaleret throughout the study (Fig. 4B). Pre-dose concentrations of serum calcium remained elevated above baseline values at all assessments from wk 1 onward in the ronacaleret groups compared with more modest pre-dose elevations in the teriparatide arm or slight decreases in the alendronate arm (Fig. 4B). Mean pre-dose albumin-adjusted serum calcium levels remained below 2.5 mmol/liter in the ronacaleret arms at all assessments.

A predefined algorithm was used to monitor subjects and intervene if a subject had hypercalcemia. One subject in the 300-mg ronacaleret arm was withdrawn from the study due to increased serum calcium reported as an adverse event. Two subjects in the 400-mg ronacaleret arm had confirmed pre-dose elevations of serum calcium higher than 2.74 mmol/liter and had their calcium supplements discontinued. Initial (unconfirmed) levels of albumin-adjusted serum calcium higher than 2.74 mmol/liter occurred in one subject in each of the 100- and 200-mg ronacaleret and teriparatide arms, four subjects in the 300-mg ronacaleret arm, and 11 subjects in the 400-mg ronacaleret arm. No subject in any treatment group had pre- or postdose elevations in serum calcium of 3.74 mmol/liter or higher at any point during the study.
Approximately 75% of subjects had 24-h urine calcium excretion values within the normal range at baseline and throughout the study. However, more subjects in the 200- to 400-mg ronacaleret arms had elevated urine calcium excretion rates of at least 10 mmol/24 h compared with all other treatment groups (Supplemental Table 2).

**Safety**

Forty subjects withdrew from the study due to adverse events, which were evenly distributed across the ronacaleret, alendronate, and placebo groups (Table 2). The most common adverse event in all treatment groups was nasopharyngitis (Table 2). Adverse events that appeared to be dose related to ronacaleret included nausea, diarrhea, and arthralgia. Subjects with confirmed bone loss over 6% at the lumbar spine or total hip or over 7% at the femoral neck were informed about their bone loss. The number of subjects with any confirmed BMD loss above the protocol prespecified thresholds was infrequent in the ronacaleret arms and similar to that observed in the placebo arm (Table 2). No subject in the alendronate or teriparatide arms experienced confirmed bone loss above the predefined thresholds. Cell frequencies were too small to justify the use of a $\chi^2$ goodness-of-fit test for testing differences among the proportion of subjects with bone loss.

Although this phase II trial was not designed or powered to assess fracture incidence, four fractures were reported as serious adverse events. These were one femoral neck and one femur fracture, both in the alendronate group; one radius fracture in the 100-mg ronacaleret arm; and one upper limb fracture in the 400-mg ronacaleret arm.

**Discussion**

This is the first placebo-controlled, randomized, clinical trial in which an oral CaSR antagonist has been used to stimulate endogenous PTH secretion in a population of postmenopausal women with low bone mass. We compared the effects of ronacaleret with alendronate, a potent inhibitor of bone resorption and teriparatide, a bone formation agent, on BMD and markers of bone metabolism. Ronacaleret increased BMD at the lumbar spine at 10–12 months, although the magnitudes of these changes were substantially smaller than that attained with either alendronate or teriparatide. The increases in BMD of the spine attained with teriparatide and alendronate are consistent with previous studies with these agents (4, 10–12). With all doses of ronacaleret, there were small decrements in BMD at the total hip, femoral neck, and trochanter compared with increases with teriparatide and alendronate or little or no gain with placebo.

Both ronacaleret and teriparatide rapidly increased biochemical markers of both bone formation (P1NP and BSAP) and bone resorption (CTX1). Whereas the increments in P1NP occurred within 28 d of initiating teriparatide therapy, the P1NP responses to all ronacaleret doses were more modest and delayed by comparison; there were progressive increases in P1NP with 200–400 mg ronacaleret, and maximal levels were achieved later (month 10) compared with teriparatide (maximal at month 6). The increments in biochemical markers of bone turnover with teriparatide seen in this study were very similar to those observed in previous studies (5, 10, 13). This earlier and more rapid increase in bone formation markers than in those reflecting bone resorption may reflect the PTH anabolic window, where, initially, bone formation occurs followed by increased bone resorption (2). In contrast, a similar anabolic window was not observed with ronacaleret administration, and the resultant changes in BMD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100 mg (n = 87)</th>
<th>200 mg (n = 82)</th>
<th>300 mg (n = 88)</th>
<th>400 mg (n = 87)</th>
<th>TER (n = 41)</th>
<th>ALN (n = 89)</th>
<th>PBO (n = 90)</th>
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<td>1 (1)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
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<tr>
<td>Any AE</td>
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<td>66 (80)</td>
<td>75 (85)</td>
<td>70 (80)</td>
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<td>7 (17)</td>
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<td>5 (6)</td>
<td>10 (11)</td>
<td>5 (12)</td>
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<td>11 (13)</td>
<td>12 (14)</td>
<td>1 (2)</td>
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<td>11 (13)</td>
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<td>4 (10)</td>
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<td>6 (7)</td>
<td>6 (7)</td>
<td>3 (7)</td>
<td>5 (6)</td>
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<td>9 (10)</td>
<td>5 (6)</td>
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</table>

Data are expressed as number (percentage) of subjects. AE, Adverse event; ALN, alendronate; BMD, bone mineral density; PBO, placebo; RONA, ronacaleret; TER, teriparatide; URTI, upper respiratory tract infection.

$^a$ BMD loss of 6% or more at the lumbar spine or total hip or loss of 7% or more at the femoral neck.
were similar to those observed with chronic, continuous PTH secretion (3, 14).

The action of PTH either to increase or decrease bone density is related to the duration of exposure. Intermittent exposure to PTH is associated with an anabolic effect on bone, whereas continuous exposure to PTH (i.e. primary hyperparathyroidism) is associated with net bone resorption. Short-lived antagonism of the parathyroid gland CaSR could cause an immediate spike in PTH secretion, mimicking the effect of exogenously administered PTH (8). In this study, ronacaleret administration led to a rapid, dose-dependent, prolonged release of endogenous PTH, presumably through inhibition of the parathyroid cell CaSR (9). This profile of PTH secretion after ronacaleret is distinct from the pharmacokinetic profile of teriparatide when administered sc. Teriparatide administration is associated with a faster uptake, a higher peak level, and a more rapid offset to baseline or below baseline levels (15).

Both ronacaleret and teriparatide consistently increased serum calcium. In addition, there were dose-dependent increases in trough (pre-dose) serum calcium concentrations with ronacaleret throughout the study. Serum calcium concentrations returned to pretreatment levels at the follow-up visit after discontinuation of dosing.

The effects of ronacaleret on intact PTH, serum calcium, and bone turnover markers, along with the densitometric effects, suggest that ronacaleret may induce a mild hyperparathyroid state. The elevated serum calcium concentrations are the hallmark of diagnosis of this disorder (16). The results from the bone turnover markers suggest that the anabolic window was too narrow to create an osteoanabolic effect. Treatment with ronacaleret had different effects on a site containing primarily cancellous bone (lumbar spine) and sites that contain more cortical bone (femur). The actions of PTH as a therapy for osteoporosis as well as in primary hyperparathyroidism include these differential effects at predominantly trabecular and cortical sites (4, 14, 17, 18). In mild primary hyperparathyroidism, trabecular bone is relatively preserved, whereas the cortical compartment may experience bone loss (19). The disparate effects of ronacaleret on trabecular and cortical bone are also consistent with this hypothesis.

A limitation of this study was the inability to randomize subjects to blinded treatment with teriparatide due to the differing modes of administration, which may have confounded comparisons of efficacy and tolerability. However, the DXA scans were analyzed in a blinded fashion, and the effect of teriparatide on BMD of the lumbar spine and total hip are similar to those observed in other controlled studies (4, 6, 10, 17, 18). Furthermore, investigators were blinded to the serum calcium and urinary calcium results, and the effects of teriparatide on serum calcium and urinary calcium excretion mirrored those of other controlled studies (4).

In conclusion, the elevated serum calcium levels, the lack of an anabolic window on bone turnover markers, and the minimal benefit on BMD despite relative preservation of trabecular bone compared with the loss at cortical sites all suggest that ronacaleret induced mild hyperparathyroidism. This study provides insights into the importance of the profile of PTH pulsatility and the subsequent anabolic window that both appear to be required for the osteoanabolic action of PTH.

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Address all correspondence and requests for reprints to: Lorraine A. Fitzpatrick, M.D., GlaxoSmithKline, Biopharm Devel-
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