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Bone mineral density changes following discontinuation of ronacaleret treatment: Off-treatment extension of a randomized, dose-finding phase II trial

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ABSTRACT

Context: Parathyroidectomy in patients with hyperparathyroidism can produce subsequent increases in bone mineral density (BMD). Ronacaleret, a selective calcium-sensing receptor antagonist that stimulates endogenous parathyroid hormone release, induced mild hyperparathyroidism.
Objective: The aim of this study is to evaluate whether BMD changes after cessation of ronacaleret treatment.
Design: Observational, off-treatment, extension of a randomized, placebo-controlled, dose-ranging phase II trial.
Setting: Fifteen academic centers in seven countries.
Patients: Postmenopausal women with low BMD; 171 out of 569 women in the parent study were enrolled in the extension study.
Interventions: Subjects were treated with ronacaleret 100 mg ($n = 16$), 200 mg ($n = 38$), 300 mg ($n = 35$), or 400 mg ($n = 32$) once daily, alendronate 70 mg ($n = 17$) once weekly, or matching placebo ($n = 33$) for 10–12 months; BMD was measured after discontinuation of ronacaleret or alendronate treatment.
Main outcome measure: Mean percent change in lumbar spine areal BMD by dual-energy X-ray absorptiometry at 6–12 months after discontinuing ronacaleret or alendronate compared with the 10- to 12-month BMD measurement of the parent study.
Results: At the lumbar spine, all doses of ronacaleret resulted in gains in BMD while on treatment. These increases in BMD were maintained or increased after discontinuation of ronacaleret. All doses of ronacaleret caused bone loss at the total hip while on active treatment. However, there was an attenuation of this loss in the off-treatment extension study.
Conclusion: The gain in BMD at the lumbar spine was maintained post-treatment and the loss of BMD at the total hip was attenuated. We hypothesize that there may have been some bone remineralization after cessation of ronacaleret.

Introduction

Osteoporosis is a major public health issue that is characterized as a skeletal disorder with compromised bone strength that predisposes to an increased risk of fracture [1]. Fractures of the wrist, hip, and vertebrae are the main clinical manifestations. Hip fractures, in particular, are associated with considerable excess mortality [2]. Parathyroid hormone (PTH) is an anabolic therapy that increases bone mass, quality, and strength in postmenopausal women [3–7]. The release of PTH from the parathyroid gland is regulated by the calcium sensing receptor (CaSR), whereby low serum calcium levels stimulate the release of PTH [8]. Ronacaleret is a CaSR antagonist that mimics the action of low serum calcium at the receptor and stimulates the release of endogenous PTH [9–11].

A phase II dose-ranging clinical trial that compared ronacaleret with alendronate, teriparatide (PTH 1–34) and placebo was performed to evaluate whether ronacaleret would mimic the anabolic action of PTH on bone (NCT00471237; [11]). The trial was phased out for futility reasons because a planned interim analysis demonstrated that none of the ronacaleret doses sufficiently improved total hip bone mineral density (BMD) compared with placebo [11]. At the time of the futility analysis, patients had been enrolled in active treatment for 10 to 12 months.

The interim analysis demonstrated that administration of ronacaleret resulted in prolonged excretion of PTH compared with that previously reported for injectable teriparatide, with mean PTH

Abbreviations: ALN, alendronate; BMD, bone mineral density; BMI, body mass index; CaSR, calcium sensing receptor; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; LSM, least squares means; PBO, placebo; PTH, parathyroid hormone; RONA, ronacaleret; SD, standard deviation; SE, standard error; 25OHD, 25-hydroxyvitamin D.

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levels remaining above the upper limit of normal for at least 4 h at all dose levels and for 8 to 12 h at the two highest dose levels tested (300 mg and 400 mg) [9,11]. Based on these findings, we hypothesized that the pharmacokinetics of PTH release resulted in the induction of mild hyperparathyroidism. Ronacaleret also produced dose-dependent increases in mean levels of pre-dose albumin-adjusted serum calcium and lower total hip BMD reduction in patients receiving ronacaleret compared with patients receiving placebo. There were modest increases in the lumbar spine BMD of between 0.3 and 1.6% with ronacaleret treatment [9,11].

Patients with hyperparathyroidism who undergo a parathyroidectomy experience a subsequent and rapid (within 6 months) increase in BMD [12–15]. On this basis, we proposed that a gain in BMD may occur within the first 6 months after discontinuation of ronacaleret treatment. The study presented here (NCT00891553) was designed to evaluate the potential for increased BMD following cessation of ronacaleret treatment by measuring BMD in subjects after they had discontinued ronacaleret treatment. The primary endpoint was the mean percent change in lumbar spine BMD, as assessed by dual-energy X-ray absorptiometry (DXA) 6 to 12 months after discontinuation of ronacaleret treatment, compared with the final lumbar spine BMD measurement of the parent study at Months 10 to 12.

Materials and methods

The objective of this observational extension study was to evaluate the effect of ronacaleret between 6 and 12 months after discontinuing treatment, as assessed by changes in areal BMD by DXA at the lumbar spine, total hip, femoral neck, and trochanter.

The full methodology of the parent dose-ranging phase II study has been published previously [9,11]. In brief, postmenopausal women with low BMD received either open-label teriparatide 20 μg subcutaneously (once daily) or were randomized in a double-blind manner to ronacaleret 100 mg, 200 mg, 300 mg, or 400 mg once daily, alendronate 70 mg once weekly, or matching placebo. Lumbar spine, total hip, femoral neck, and trochanter BMD were assessed by DXA. The parent study took place in 45 academic centers and the primary endpoint was the percent change from baseline in lumbar spine BMD assessed at Month 12.

Subjects were eligible for the extension study if they had received ronacaleret 200 mg, 300 mg, 400 mg, or placebo for at least 299 days in the parent study and if their final DXA measurement in the parent study had been taken within 4 weeks of the final dose of study medication. Subjects in the ronacaleret 100 mg group were excluded from the extension study because of minimal biomarker changes at the interim analysis. The open-label teriparatide group and the randomized alendronate group were not included as they were not considered relevant to the study hypothesis. However, 16 subjects in the ronacaleret 100 mg group and 17 subjects in the alendronate group were mistakenly enrolled in the extension study and the data for these subjects are included in the analysis. Exclusion criteria for the observational extension study included treatment with strontium or PTH analogs, use of systemic glucocorticoids, or high-dose fluoride since the end of the parent study. BMD was measured on the same machine that the individual subject had used in the parent study [9,11]. All observers were blinded to prior treatment and DXA scans were read by a central reader (Synarc, Inc., San Francisco, CA).

The extension study was conducted in accordance with good clinical practice and the guiding principles of the Declaration of Helsinki; the protocol was approved by the ethical boards at each site, and each subject provided written, informed consent.

One DXA measurement was taken during the extension study, between 6 and 12 months after discontinuing treatment in the parent study. The primary endpoint of the extension study was the percent change in areal BMD at the lumbar spine (L1–L4) compared with the final DXA measurement (taken between Months 10 and 12) of the parent study. Secondary endpoints included change in areal BMD at the total hip, femoral neck, and trochanter in comparison with the final DXA measurement from the active treatment study.

All efficacy and safety analyses were conducted in the safety population, defined as all enrolled subjects who had a DXA assessment during the extension study. The percent change in BMD from the final DXA measurement in the parent study to the extension study DXA measurement was expressed as a least squares means with standard error (SE). The primary comparisons of interest were the differences between each ronacaleret group and the placebo group in lumbar spine BMD change from the final DXA measurement in the parent study. The primary efficacy endpoint was analyzed using parametric analysis of covariance, adjusting for baseline lumbar spine BMD and treatment group, and the results are presented as a point estimate with 95% confidence intervals (CI) for the adjusted mean differences between the treatment groups and the placebo group. Secondary endpoints were analyzed in a similar way. No sample size calculations were performed.

Theory

It has previously been suggested that ronacaleret, a selective CaSR antagonist, can induce mild hyperparathyroidism. We evaluated whether an increase in BMD consistent with remineralization of bone occurs after cessation of ronacaleret treatment.

Results

The follow-up study was conducted in 15 centers from seven countries (Argentina, Australia, Denmark, Hong Kong, Norway, Poland, and the United States) between March and June 2009. Of the 569 subjects enrolled in the parent study, 171 subjects from pre-specified centers were enrolled and were assessed for efficacy and safety in the extension study. All patients completed the study with the exception of one patient from the ronacaleret 400 mg group, who was withdrawn due to a protocol violation and did not have a final DXA measurement.

Baseline demographics and clinical characteristics from this extension study are presented in Table 1. Overall, the demographics of the extension population were representative of the parent study [11]. The mean age in each group was between 63 and 67 years, with menopause occurring between the ages of 47 and 49 years. The lumbar spine BMD T-score ranged between −2.77 and −2.36 (Table 1). On average, the period between the last dose of study medication in the parent study and the DXA measurement in the extension study was 8.5 months (237 days [standard deviation: 39.2; range 177–355]).

The results of lumbar spine BMD are presented in Table 2 and Fig. 1A. With ronacaleret, there was an increase in lumbar spine BMD at 12 months during the parent study (0.3% to 1.6%) [9]. No dose-dependent trends were observed among the ronacaleret groups at the lumbar spine site during the extension study. Compared with the final DXA measurement in the parent study, there was little change in lumbar spine BMD in the ronacaleret 200 mg and 300 mg groups. However, in the ronacaleret 400 mg group, lumbar spine BMD increased by 1.33% (SE 0.66). In contrast, lumbar spine BMD decreased by −1.49% (SE 0.64) in the placebo group, with little change in the alendronate group.

Relative to placebo, significant increases in lumbar spine BMD were observed with ronacaleret 100 mg (2.91% [95% CI 0.72, 5.10]; $p = 0.010$) and 400 mg (2.82% [95% CI 1.00, 4.64]; $p = 0.003$).

BMD results for cortical-rich bone sites are presented in Table 2 (total hip and trochanter) and Fig. 1B (total hip). In the parent study, subjects on ronacaleret had a significant dose-dependent decrease in BMD at the total hip (−0.6% to −1.2%) [9]. In the follow-up study, no dose-dependent trends were observed among the ronacaleret groups for any site and no significant differences were observed relative to the placebo group, in which BMD decreased by −1.22% (SE 0.45) at the total hip and by −1.35% (SE 0.71) at the trochanter. In the ronacaleret groups, there was an attenuation of the bone loss at the

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