The effect of PTH(1–84) or strontium ranelate on bone formation markers in postmenopausal women with primary osteoporosis: results of a randomized, open-label clinical trial

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Abstract
Summary We explored the effects of PTH(1–84) compared with strontium ranelate on bone remodeling as measured by bone remodeling markers in postmenopausal women with osteoporosis. Biochemical markers of bone formation were significantly increased after treatment with PTH(1–84) but not strontium ranelate, indicating a different mechanism of action between these agents.

Introduction
PTH(1–84) and strontium ranelate (SR) are both known to reduce fracture risk in osteoporosis. Measuring changes in biochemical markers of bone turnover induced by these agents can help in characterizing the action of PTH(1–84) and SR on bone remodeling.

Methods
A 24-week, randomized, open-label, parallel group, phase IV trial was conducted in 81 postmenopausal women with primary osteoporosis (≥50 years of age, lumbar spine, or total hip T-score ≤−2.5 SD) to assess the effect of SR as compared to PTH(1–84) on bone formation markers P1NP and BSAP. The bone resorption marker CTX was also measured. Subjects were randomly assigned to receive daily either 100 μg PTH(1–84) (n=41) (subcutaneous injection) or oral 2 g SR (n=40) for 24 weeks with daily supplements of 800 IU vitamin D3 and 1,000 mg calcium. Patient-reported outcomes were collected to investigate the effect of treatment on quality of life (QoL).

Results
Percentage changes from baseline in P1NP and BSAP were significantly increased for PTH(1–84) by week 24 compared with SR (p<0.0001). Significant changes from baseline in P1NP and BSAP were noted for PTH(1–84) from week 4 onwards; no significant changes were noted for SR. A trend towards a positive impact on QoL was seen with PTH(1–84) treatment. Safety profiles concur with previous analyses.

Conclusions
PTH(1–84) had a more rapid and higher effect on bone formation markers compared to SR, indicating that SR has a different mode of action on bone remodeling than the bone building agent PTH(1–84) in postmenopausal women with osteoporosis.

Keywords
Osteoporosis · Parathyroid hormone · Quality of life · Strontium ranelate

Introduction
Postmenopausal osteoporosis is characterized by an imbalance between bone resorption and formation, which leads to an...
increase in bone fragility and increased susceptibility to fracture [1]. Anticatabolic (antiresorptive) agents are currently the most widely used drugs in osteoporosis therapy, exerting their antifracture efficacy through a significant reduction of bone resorption. Bone-forming (anabolic) therapies act to reverse the deterioration of bone architecture by stimulating bone remodeling and provide an important advancement for the treatment of osteoporosis.

Biochemical markers of bone remodeling have been suggested to be of value for the assessment of fracture risk, and in the future, they may be useful for monitoring the efficacy of antiresorptive or anabolic therapy [2]. The level of these markers may identify changes in bone remodeling within a relatively short time interval (several days to months) before changes in bone mineral density (BMD) can be detected [3]. Such bone turnover markers include markers of bone formation such as bone-specific alkaline phosphatase (BSAP), which reflects the cellular activity of osteoblasts, and N-terminal propeptide of procollagen type I (P1NP), considered to be a quantitative measure of newly formed type I collagen. C-telopeptide of type I collagen (CTX), a degradation product of bone collagen, is a marker of bone resorption [4]. Bone marker measurements reflect the whole-body rates of bone resorption and bone formation and, although they offer little information on BMD changes in individual women, they nevertheless may provide a more representative index of overall skeletal bone loss/formation than otherwise obtained by measuring the rates of change in BMD at specified skeletal sites [4].

Parathyroid hormone (PTH) is an anabolic agent that has been shown to increase both bone formation and resorption markers as a result of increased bone remodeling, acting to increase bone mass and improve microarchitecture leading to a reduction in fractures. This has been demonstrated for both of the PTH preparations currently licensed for the treatment of osteoporosis: full-length PTH [PTH(1–84)] [5–8] and teriparatide [PTH(1–34)] [9]. Of the analyzed bone markers, P1NP has been suggested to be the most sensitive predictor of BMD response to PTH treatment in postmenopausal women with osteoporosis [10]. Strontium ranelate (SR) is an anti-osteoporotic drug which reduces fracture incidence and, in contrast to other available treatments for osteoporosis, has been suggested to have a dual mode of action (MOA) by increasing bone formation and reducing bone resorption [11, 12].

In this trial, we explore the effects of PTH(1–84) compared with SR on bone formation in postmenopausal women with osteoporosis as measured by changes in bone turnover markers over a 24-week treatment period. Osteoporosis can have a drastic impact on QoL; therefore, the resulting effect of such treatment on QoL is also evaluated.

Methods

Study design and interventions

This was a 24-week, international, multi-center, randomized, open-label, parallel group, phase IV trial. Patients were recruited from study centers in Austria (four sites) and Spain (five sites). Following a screening period of 2–6 weeks, patients were randomized to receive either full-length PTH(1–84) or SR (week 0–24). PTH(1–84) was supplied in dual-chamber cartridges suited for the Preotact® pen (Nycomed, Denmark). Each cartridge contained 1.61 mg recombinant full-length PTH(1–84) as lyophilized powder in one chamber and 1 mL sterile solvent for reconstitution in the other chamber. The recommended daily dose of 71.4 μL contained 100 μg PTH(1–84) and was administered as one daily subcutaneous (sc) injection in the abdomen by self-administration. The daily dose of 2 g (one sachet) SR was an oral suspension in water taken immediately after mixing at bedtime at least 2 h before or after intake of calcium, any food or drinks, other than water. Throughout the study, patients were supplemented with 800 IU of daily vitamin D3 and 1,000 mg calcium. Randomization took place at baseline visit by contacting an electronic randomization system via the internet. The randomization was based on blocks and stratified by site.

Patients

Postmenopausal (≥5 years) women with primary osteoporosis (lumbar spine or total hip T-score ≤−2.5 standard deviation [SD]), ≥50 years of age, were included in this study. Patients were excluded if they had been treated with selective estrogen-receptor modulators or calcitonin in the month prior to study entry, if they had been treated with any bisphosphonate for >3 years or within the previous 6 months, or if they had ever been treated with intravenous bisphosphonate. Patients were also excluded if they had been treated with fluoride for >3 months in the previous 10 years, if they had ever been treated with SR, PTH(1–34) or PTH(1–84), or had any other medical condition or medication use known to affect bone metabolism.

Additionally, after blood sampling (performed within the screening period and after at least 14 days of supplemental calcium/vitamin D3 intake), patients were excluded if they had a serum 25-hydroxycholecalciferol [s-25(OH)D] level <20 ng/mL, serum PTH >65 pg/mL plus serum calcium (s-calcium) >2.49 mmol/L, if the patient had elevated s-calcium (>2.55 mmol/L), elevated serum alkaline phosphatase (defined as 3× upper limit of normal), if kidney function was impaired with creatinine clearance <30 mL/min, or if the

\[ \text{PTH} \]
patient had severe impaired liver function. All participants gave written informed consent before enrollment.

Outcome measures

Blood analyses

Bone markers (primary endpoints: P1NP and BSAP and secondary endpoint: CTX) were measured at baseline (week 0) and after 4, 12, and 24 weeks of treatment via batch analyses (Synarc laboratories). S-calcium measurements were taken during the screening period at baseline and after 4, 12, and 24 weeks of treatment. S-calcium was also measured at any unscheduled visits in order to monitor for elevated s-calcium (>2.67 mmol/L). Patients fasted for 12 h prior to all planned blood samplings; in order to reduce circadian variation, sampling was standardized, being performed between 8 and 10 am.

Quality of life analyses

Patients completed questionnaires assessing physical disability and pain in order to investigate the effect of treatment on QoL. The Oswestry Disability Questionnaire (ODI; version 2.1) was completed by patients at baseline and after 12 and 24 weeks of treatment. The Numerical Rating Scale (NRS), an 11-point scale assessment of the intensity of current back pain, was completed at baseline and after 4, 12, and 24 weeks of treatment (0=no pain and 10=the worst imaginable pain).

Safety evaluation

The safety analysis data set was defined as all patients that were randomized and received at least one treatment dose. Safety was monitored at each contact/visit by the use of a non-leading question: “Have you experienced any health problems since the last visit?” Vital signs (systolic blood pressure [BP], diastolic BP, pulse, and respiratory rates) and s-calcium levels were also assessed at all visits. Additional safety variables including clinical laboratory results (hematology, serum chemistry) were monitored during the trial. Number and nature of adverse events (AEs) and serious adverse events (SAEs) observed by the investigator or reported by the patient at all visits were recorded.

Statistical analysis

The trial was designed to have 95% power for detecting a difference of 0.39 (increase of 60% in PTH and 8% in SR), assuming a SD of 0.40, both taking log-transformed data into account. Based on a two-sided t test, n=29 subjects per group were required, i.e., a total of 58 subjects. The Hochberg adjustment for multiplicity was not taken into account since the two primary variables were expected to be positively correlated. Allowing for a drop-out rate of 15%, a total of 70 subjects was therefore planned to be randomized.

The intention-to-treat (ITT) data set used in the efficacy analyses was defined as all randomized subjects. All statistical tests were two-sided. A significance level of 5% was used throughout to establish statistical significance. All statistical tests were pre-planned, except for the QoL analyses.

The changes in bone markers were analyzed using an analysis of covariance (ANCOVA) with treatment and center as fixed effects and the baseline bone marker value as a covariate. An F test was used to test the effect of treatment on the endpoint. P values corresponding to the tests of treatment effect for the primary endpoints were adjusted using the Hochberg procedure. As the bone marker data was log-normally distributed, the values of the endpoints were In-transformed for the ANCOVA analyses. The estimated least square mean difference between treatments was presented with 95% confidence intervals (CIs). Mean relative changes from baseline were estimated by the least squares mean and presented as percentage changes from baseline by transforming back from the In-scale.

The percentage change from baseline to each visit was displayed by descriptive statistics for each treatment. A comparison was made for each visit evaluating the least square mean percentage change from baseline in order to determine a significant difference from baseline by the primary ANCOVA model for each treatment group. A Wilcoxon Rank Sum test was applied to examine any difference between treatment groups on the QoL analyses.

The trial was approved by the relevant IEC/IRB/competent authorities. Registration number: NCT00479037 (http://www.clinicaltrials.gov).

Results

Patient disposition

The treatment groups were similar with regard to demographic and baseline characteristics (Table 1). The first patient's first visit was on 26 April 2007, and the last patient's final visit took place on 26 January 2009. The trial ended when the last patient had completed the study regimen. In total, 160 patients were screened, and 82 patients were randomized during the study (Fig. 1). One patient withdrew consent during the screening period but was randomized in error; however, the patient did not receive any treatment and was not included in the ITT population. Therefore, the ITT data set consisted of 41
## Table 1 Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>PTH(1–84) n=41</th>
<th>Strontium ranelate n=40</th>
<th>All (ITT) n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at screening, years</td>
<td>64.0 (8.6)</td>
<td>64.9 (8.5)</td>
<td>64.4 (8.5)</td>
</tr>
<tr>
<td>Family history of osteoporosis, n (%)</td>
<td>10 (24.4%)</td>
<td>7 (17.5%)</td>
<td>17 (21.0%)</td>
</tr>
<tr>
<td>Mean (SD) age at onset of menopause, years</td>
<td>46.8 (3.8)</td>
<td>47.9 (6.4)</td>
<td>47.3 (5.3)</td>
</tr>
<tr>
<td>Lumbar spine L1–L4, standardized BMD, mean (SD), g/cm²</td>
<td>0.75 (0.08)</td>
<td>0.77 (0.07)</td>
<td>0.76 (0.07)</td>
</tr>
<tr>
<td>Lumbar spine T-score ≤−2.5, n (%)</td>
<td>39 (97.5%)</td>
<td>37 (92.5%)</td>
<td>76 (95.0%)</td>
</tr>
<tr>
<td>Total hip, standardized BMD, mean (SD), g/cm²</td>
<td>0.76 (0.12)</td>
<td>0.75 (0.13)</td>
<td>0.75 (0.12)</td>
</tr>
<tr>
<td>Total hip T-score ≤−2.5, n (%)</td>
<td>9 (22.0%)</td>
<td>9 (23.1%)</td>
<td>18 (22.5%)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, n (%)</td>
<td>37 (90.2%)</td>
<td>33 (82.5%)</td>
<td>70 (86.4%)</td>
</tr>
<tr>
<td>None</td>
<td>4 (9.8%)</td>
<td>5 (12.5%)</td>
<td>9 (11.1%)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;2</td>
<td></td>
<td>2 (5.0%)</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>Prevalent hip fractures, n (%)</td>
<td>3 (7.3%)</td>
<td>2 (5.0%)</td>
<td>5 (6.2%)</td>
</tr>
</tbody>
</table>

*BMD* bone mineral density, *ITT* intention-to-treat, *n* number of patients, *PTH*(1–84) full-length parathyroid hormone, *SD* standard deviation

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**Fig. 1** Patient flow during trial period. *PTH*(1–84) full-length parathyroid hormone, *SAE* serious adverse event, *AE* adverse event.
patients randomized to the PTH(1–84) group and 40 to SR. Nine patients discontinued the trial, three patients in the PTH(1–84) group and six patients in the SR group. Primary reasons for discontinuation were AEs in four patients (two patients in each treatment group), withdrawal of consent in three patients (one patient in the PTH(1–84) group and two patients in the SR group), and two patients discontinued in the SR group for other reasons.

Overall, 70 patients had no prevalent vertebral fractures at screening, while nine patients (four patients in the PTH(1–84) group and five patients in the SR group) reported one prevalent vertebral fracture, and two patients in the SR group reported more than two prevalent vertebral fractures (Table 1). Seventy-two patients completed the trial, 38/41 patients in the PTH(1–84) group and 34/40 patients in the SR group. The family history of osteoporosis and incidence of prevalent fractures were similar between groups.

Efficacy

Primary endpoint: changes in bone formation markers

\( \text{P1NP and BSAP} \)

\( \text{P1NP} \) At 24 weeks of treatment, the primary analysis showed that the percentage change from baseline for P1NP was significantly higher in the PTH(1–84)-treated group compared with SR \((p<0.0001)\). The least square estimated mean difference (95% CI) between the two groups was 360.3% (256.5%; 494.3%). There was a significant mean increase from baseline in P1NP levels throughout the study for the PTH(1–84) treatment group; a significant treatment difference was also seen at all visits (Fig. 2).

For PTH(1–84), the raw mean percentage change (±standard deviation [SD]) at week 4 was 112.9±101.2, at week 12 this was 302.5±280.3, and at week 24, this was 446.1±355.3. In the SR group, the raw mean percentage change at week 4 was −0.3±23.9, at week 12, this was −4.8±24.4, and at week 24, this was −6.2±36.9. It should be noted that the high variability in both treatment groups is a result of a variable range of values in the study population; therefore, a reliable estimate comes from the pre-planned primary model with log-transformed measurements. This showed that an increase was apparent by week 4 with least square estimates of the mean percentage change (95% CI) from baseline of 87.7% (65.9%; 112.4%) in the PTH(1–84)-treated group. At week 12, this was 225.6% (172.3%; 289.2%), and at 24 weeks, this was 307.7% (238.6%; 390.9%). Changes compared to baseline were significant \((p<0.0001)\) for all visits. A significant least square mean percentage change from baseline was not observed for SR: at week 4, there was a change of −4.0% (−15.4%; 8.9%) \((p=0.518)\), by week 12, this was −6.3% (−22.4%; 13%);

\( \text{BSAP} \) The percentage change from baseline for BSAP, the other primary analysis, was similar to that of P1NP in that the change was significantly higher in the PTH(1–84)-treated group compared with SR \((p<0.0001)\). The estimated mean difference (95% CI) between the two groups was 92.9% (63.8%; 127.1%).

For the PTH(1–84) treatment group, the raw mean percentage change (±SD) at week 4 was 18.8±29.7. At weeks 12 and 24, BSAP levels had increased to 73.5±76.5 and 129.6±100.3, respectively. In the SR group, the raw mean change from baseline was 9.8±32.4 at week 4, 2.5±17.1 at week 12, and 4.9±22.9 at week 24. There was a significant least square mean percentage increase from baseline in BSAP levels throughout the study for PTH(1–84) (Fig. 3). A significant treatment difference was seen from week 12 onwards. The least square mean percentage change (±SD) at week 4 was 11.9% (±3.4%; 21.0%) \((p=0.005)\) in the PTH(1–84)-treated group; at weeks 12 and 24, BSAP levels had increased by 57.8% (41.3%; 76.1%) and 98.9% (76.4%; 124.2%), respectively \((p<0.0001)\).

Modest, non-significant changes were observed in the SR treatment group throughout the study period. The least square mean percentage change from baseline was 5.6% (−2.4%; 14.3%) \((p=0.174)\) at week 4, 1.7% (−9.3%;

\[ \text{Fig. 2} \quad \text{P1NP: mean relative changes from baseline estimated by the least squares means from the linear model and presented as percentage changes from baseline by time on treatment (95% CI) *p<0.0001 vs. baseline.} \]

\( \text{P1NP N-terminal propeptide of pro-collagen type I, PTH(1–84) full-length parathyroid hormone, CI confidence interval} \)
14.1% (p=0.766) at week 12, and 3.1% (−8.5%; 16.2%) (p=0.611) at week 24.

Secondary endpoint: changes in bone resorption marker CTX

The least square mean percentage change in CTX levels from baseline for PTH(1–84)-treated patients increased throughout the study (Fig. 4). The levels (95% CI) were 6.9% (−5.6%; 21.1%) at week 4 (p=0.286), 94.6% (70.9%; 121.5%) at week 12 (p<0.0001); 112.8% (83.8%; 146.5%) at week 24 (p<0.0001). Modest, non-significant changes were noted for SR from baseline throughout the study, with a mean change of −6.0% (−17.3%; 6.8%) at week 4 (p=0.334), −6.8% (−18.7%; 6.9%) at week 12 (p=0.308), and −10.7% (−23.0%; 3.5%) at week 24 (p=0.131).

At 24 weeks of treatment, the difference between the two treatment groups was 138.5% (94.8%; 191.8%) (p<0.0001) in the least square mean estimate of the percentage change from baseline.

Quality of life

Oswestry disability index

In the ITT dataset, the absolute change from baseline to 24 weeks of treatment in ODI score (the higher the ODI score, the higher the patient’s disability) was a mean decrease of 4.88 score points for the PTH(1–84) group and a mean increase of 1.39 points for the SR group (p=0.058 between treatment groups). The mean percentage ODI score (±SD) at baseline in the PTH(1–84) group was 19.71% (±18.45); after 24 weeks of treatment, this was 15.23% (±14.27). In the SR group, the mean value was 19.80% (±18.19) at baseline and 18.09% (±17.82) after 24 weeks of treatment.

Mean percentage changes from baseline to 24 weeks of treatment were a decrease of 22.43% in the PTH(1–84) group and an increase of 5.14% in the SR group (p=0.20).

Numerical rating scale

In the ITT dataset, there was a decrease in mean NRS score (±SD) for the PTH(1–84) group from 3.68±3.09 points at baseline to 2.61±2.27 points at 24 weeks of treatment, while in the SR group, the mean value was 3.78±2.91 points at baseline and 2.83±2.64 points at 24 weeks of treatment. The mean absolute change from baseline to 24 weeks of treatment in NRS score for the PTH(1–84) group was −1.24 points and was −0.89 points for the SR group (p=0.60).

Safety and tolerability

Most AEs considered probably or possibly related to trial drug by the investigator (adverse drug reactions [ADRs])
were of moderate (eight and six patients in the PTH(1–84) and SR group, respectively) or mild (15 and six patients in the PTH(1–84) and SR group, respectively) severity. The most frequently reported moderate ADR was nausea with three patients in each treatment group. The most frequently reported mild ADRs were nausea, headache, and hypercalcemia. Nausea was reported in five patients in the PTH(1–84) group and in one patient in the SR group. Headache was reported by three patients in the PTH(1–84) group and two patients in the SR group.

In the PTH(1–84) group, mean values for s-calcium concentration at randomization were 2.36 mmol/L; this had increased after 4 weeks of treatment (2.47 mmol/L) remaining at this level throughout treatment (Fig. 5). For the SR-treated group, s-calcium levels were 2.37 mmol/L at randomization and decreased to 2.29 mmol/L after 24 weeks of treatment.

In the PTH(1–84) group, four patients had elevated s-calcium (>2.67 mmol/L) after 4 weeks of treatment. The incidence was similar in subsequent visits (three patients after 12 weeks of treatment and five patients after 24 weeks). The majority of these incidents were mild (eight mild, three moderate) and had resolved at the following visit after discontinuing calcium/D₃ supplemental treatment. For two patients, elevated s-calcium was resolved by reducing the daily PTH(1–84) treatment to every second day.

There were no serious AEs of hypercalcemia during the study. No AE of hypercalcemia was observed in the SR group. One AE involving hypertensive crisis was considered serious and possibly/probably related to PTH(1–84) by the investigator; this occurred in a patient with a previous medical history of hypertensive crises. There were no safety concerns regarding vital signs, physical findings, and body measurements and fractures during the treatment period. No deaths occurred in this trial.

Discussion

Predominant osteoporosis treatment strategies utilize anti-resorptive therapies, maintaining bone structure by inhibiting bone loss rather than stimulating new bone growth at trabecular or cortical sites. In contrast, PTH, a known anabolic agent, has been shown to increase bone turnover by rapidly stimulating both bone resorption and formation, resulting in a net anabolic effect when levels are transiently elevated on a daily basis [6, 8]. SR is a bone remodeling agent thought to affect both bone resorption and formation, having been shown both in vitro and in different animal species in vivo and, to a certain extent, in clinical trials to inhibit bone resorption and promote bone formation [11–16]. Despite these findings, the precise MOA of SR (the inhibition of bone resorption and presumed promotion of bone formation) still remains unclear. In a study in primates, SR decreased the indices of bone resorption while maintaining bone formation in alveolar bone. Notably, however, the amount of trabecular bone remained unchanged [15]. Moreover, in a study in postmenopausal women with osteoporosis, SR increased bone formation markers and decreased bone resorption markers [11]. As yet, however, there is little evidence that SR has an effect on bone remodeling in humans, since it is not clear whether SR significantly increases the levels of biochemical bone markers from baseline.

This clinical trial investigated whether PTH(1–84) was superior to SR in increasing bone formation markers over a 24-week treatment period in postmenopausal women with osteoporosis.

By measuring changes in levels of biochemical markers of bone formation (P1NP and BSAP) and bone resorption (CTX), it was possible to gain an insight into the effect of the different pharmacological treatments on bone turnover throughout the treatment period. The results showed that at 24 weeks of treatment, the percentage change from baseline in all measured bone formation markers was significantly higher in the PTH(1–84) treatment group as compared with the SR group. The PTH(1–84) group had a rapid, large, and sustained increase in the levels of bone formation markers. Supported by previous data from several clinical trials on PTH treatment, and in accordance with the notion of the “anabolic window”, the anticipated increase in the concentration of the bone resorption marker CTX was somewhat delayed in comparison with the change in the concentration of the bone formation markers [5, 8, 17]. There was a wide variability of P1NP response to both PTH(1–84) and SR treatment in this study, which was adjusted for using the log-transformed measurements. It should however be noted that this biological response of P1NP is in line with previous analyses that utilized either PTH(1–84) [5] or PTH(1–34) [18]. Notably, the results from this study are

![Fig. 5 Total serum calcium levels—safety data set, PTH(1–84) full-length parathyroid hormone](image-url)
supported by the findings of a similar analysis performed by Recker et al. [18] that compared the effects of teriparatide [PTH(1–34)] with that of SR on biochemical markers over a period of 6 months. No significant change in P1NP levels occurred in the SR group; however, a small decrease in concentration was observed rather than an increase. This observation is in line with the results of Recker et al. [18], who observed a small, but statistically significant reduction in P1NP levels from baseline after 3 and 6 months of SR treatment. In our analysis, although P1NP levels decreased, a minor increase in BSAP levels was noted perhaps suggestive of a slight effect of SR on bone formation; however, this was non-significant. CTX concentration also did not significantly alter from baseline in the SR treatment group. These changes in BSAP and CTX levels were in the same range as those observed in other studies and so were not unexpected [11, 19]. Recker et al. reported a small but statistically significant reduction from baseline in CTX at 1 and 3 months, while BSAP levels remained unchanged. Therefore, although some similarities in bone microarchitecture between PTH(1–34) and SR have been observed [18, 20], these findings in biochemical markers of bone formation suggest that SR and PTH have different MOA, with antifracture effects of SR possibly mediated through direct physical mechanisms independent of bone remodeling [21].

PTH(1–84) and SR have each been shown to be effective anti-osteoporotic treatment strategies [5, 6, 11]. Using different QoL questionnaires to measure the impact of treatments on health-related QoL (HR-QoL) is a useful means of collating data on the impact of different anti-osteoporotic agents on the HR-QoL in patients with osteoporosis. The ODI, a validated questionnaire, evaluates the extent to which a patient's functional activity is restricted by pain. For patients with lower back pain, Ostelo et al. [22] report a percentage change from baseline in the range of 20% to 30% as the minimally important change that is of clinical relevance and suggest a range of 10.0 to 12.0 points as the minimally important absolute change from baseline. In this trial, the patient-reported outcome measures (ODI score) showed changes suggestive of benefit in PTH(1–84)-treated patients, although these were not clinically significant. It is however interesting to consider that the changes seen in this trial, in which patients had a relatively good score at baseline, may reach clinically significant proportions in patients with a more severe disability.

Patients were also asked to assess the intensity of their back pain using the NRS questionnaire. It is known that as back pain intensity fluctuates daily, assessments by NRS provide a "snapshot" of the degree of discomfort experienced by the individual. The magnitude of the decrease in NRS scores deemed to be clinically relevant has been discussed elsewhere [22] (the lower the NRS score the better the patient is feeling) and has been reported to be in the range of 1.0 to 2.0 points; however, Ostelo et al. [22] have proposed a cut-off value of 2.0 points as a guide to clinical improvement. The results from this analysis suggest a clinically relevant trend towards an improvement in NRS scores in favor of patients treated with PTH(1–84); again, a consideration of this finding being the relatively good baseline scores of the patient group in this study.

When considering the results of this trial, it should be noted that the majority of patients did not have any prevalent vertebral fractures at screening, the study population was relatively young with a mean age of 64 years, while the limitations associated with the open-label design of the trial, in which one of the drugs was administered subcutaneously, should also be taken into account. The possible contribution of calcium supplementation to the effects on bone marker levels should also be considered [23]. It is important that further investigation is performed in this field in order to gain a fuller appreciation of the benefits of such treatment strategies.

The safety data are in line with the existing safety profile for both PTH(1–84) and SR, and no new safety concerns were identified for the treatment of osteoporosis in postmenopausal women with these therapeutic agents. The incidence of the most common AEs (nausea, headache, and elevated s-calcium) was higher in the PTH(1–84) group compared with the SR group. However, for the majority of patients, the elevated s-calcium resolved quickly and no serious AE of hypercalcemia was reported during the study.

The results of this trial demonstrate that PTH(1–84) has a more rapid and higher effect on bone formation markers compared to SR, indicating that SR has a different action on bone remodeling as compared to the bone building agent PTH(1–84) in postmenopausal women with osteoporosis. Patient-reported outcomes suggest that PTH(1–84) treatment has a trend towards a positive impact on QoL when compared with SR, and further studies could contribute to increased understanding of the impact of these anti-osteoporotic treatments on QoL.

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