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Authors

Black, DM
Bilezikian, JP
Greenspan, SL
et al.

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Improved adherence with PTH(1–84) in an extension trial for 24 months results in enhanced BMD gains in the treatment of postmenopausal women with osteoporosis

D. M. Black,

Department of Epidemiology and Biostatistics, University of California, San Fransisco, Suite 5700, 185 Berry Street, San Francisco, CA 94107, USA

J. P. Bilezikian,

Division of Endocrinology, Metabolic Bone Diseases Unit, College of Physicians and Surgeons, Columbia University, New York, NY, USA

S. L. Greenspan,

Divisions of Endocrinology and Metabolism and Geriatrics, University of Pittsburgh, Pittsburgh, PA, USA

C. Wüster,

Clinic for Endocrinology and Osteology, Mainz, Germany

M. Muñoz-Torres,

Unidad de Metabolismo Óseo, Servicio de Endocrinologia y Nutrición, Hospital Universitario San Cecilio, Granada, Spain

H. G. Bone,

Michigan Bone and Mineral Clinic, Detroit, MI, USA

C. J. Rosen,

Maine Medical Center Research Institute, 81 Research Drive, Scarborough, Maine 04074, USA

H. S. Andersen, and

Nycomed: a Takeda company, Roskilde, Denmark

D. A. Hanley

Division of Endocrinology and Metabolism, University of Calgary Faculty of Medicine, Calgary, AB, Canada

D. M. Black: dblack@psg.ucsf.edu

Abstract

Correspondence to: D. M. Black, dblack@psg.ucsf.edu.

Conflicts of interest

Funding and trial support was provided by NPS Pharmaceuticals. DM Black has received grant support from Novartis, Merck, Roche and Amgen; and consulting or advisory board fees from Eli Lilly, Amgen, Zosano, Radius and Nycomed: a Takeda Company. JP Bilezikian has received grant support from NPS Pharmaceuticals for unrelated research. DA Hanley has received grant support from NPS Pharmaceuticals for unrelated research, and has received honoraria from NPS Pharmaceuticals and from Nycomed Canada for participation on advisory boards. HS Andersen is an employee of Nycomed: a Takeda Company. HG Bone has received grant support from NPS Pharmaceuticals for this and other unrelated studies.

Summary—The purpose of this study is to examine the effect of PTH(1–84) treatment over 24 months followed by 12 months discontinuation on BMD, bone turnover markers, fractures and the impact of adherence on efficacy.

Introduction—There is limited information about the effect of PTH(1-84) after 18 months and limited data about the impact of compliance on response to anabolic therapy.

Methods—Seven hundred and eighty-one subjects who received active PTH(1–84) in the Treatment of Osteoporosis with Parathyroid hormone trial for approximately 18 months were entered into a 6-month open-label extension. Thereafter, they were followed for 12 additional months after discontinuation of treatment. Endpoints examined included changes in BMD and biochemical markers.

Results—PTH(1–84) treatment over 24 months increased BMD at the lumbar spine by 6.8 % above baseline ($p < 0.05$). The total corresponding BMD increases at the hip and femoral neck were 1.1 and 2.2% above baseline. Larger increases in spine BMD were observed in participants with ≥80 % adherence to daily injections of PTH(1–84) (8.3% in adherent vs 4.9 % in poorly adherent patients). Total hip BMD gains were 1.7 % in adherent vs 0.6 % in poorly adherent participants. Markers of bone turnover (BSAP and NTx) peaked 6 months after starting PTH(1–84) treatment and declined slowly but remained above baseline at 24 months. After discontinuation of PTH(1–84) treatment (at 24 months), bone turnover markers returned to near baseline levels by 30 months. The adherent group sustained significantly fewer fractures than the poorly adherent group.

Conclusions—PTH(1–84) treatment over 24 months results in continued increases in lumbar spine BMD. Adherence to treatment with PTH(1–84) for up to 24 months is also associated with greater efficacy.

Keywords

Adherence Lumbar spine BMD Postmenopausal osteoporosis PTH(1–84) Vertebral fracture

Introduction

Two forms of parathyroid hormone (PTH) have been registered as anabolic therapies for postmenopausal osteoporosis: teriparatide PTH(1–34) and full-length parathyroid hormone PTH(1–84). The safety and efficacy of both forms of PTH have been demonstrated in large phase III randomized, placebo-controlled trials [1, 2]. A daily dose of 20 μg PTH(1–34) over a median time of 21 months reduced vertebral and non-vertebral fractures significantly by 65 and 36%, respectively. Patients in this study were postmenopausal women with established osteoporosis who had an average of 2.3 vertebral fractures at study entry [2]. In a group of low-risk women, only 18 % of whom had vertebral fractures, a daily subcutaneous dose of 100μg PTH(1–84) for 18 months reduced the risk of a new vertebral fracture by 61 % ($p = 0.001$) [1]. This included a reduction in the risk of a first vertebral fracture of 68 % ($p = 0.006$) in those without a prevalent fracture. The effect of PTH(1–84) over periods longer than 18 months has not been assessed.

Antiresorptives, which act mainly by reducing bone resorption and overall turnover, have been studied for longer periods. Several antiresorptives including estrogens, bisphosphonates, calcitonin, raloxifene and most recently denosumab have been tested in randomized studies for up to 10 years [3–5]. In contrast to antiresorptives, PTH increases bone turnover while stimulating bone formation at a greater rate and to a greater degree than bone resorption. The net effect is bone accrual, particularly at cancellous sites such as the lumbar spine, with significant improvements in microstructural properties [6]. Several studies have suggested that bone turnover markers begin to fall as early as 12 months after PTH treatment, although they remain above baseline levels for the typical 18–24-month treatment course [1, 7]. However, the optimal duration of PTH therapy is unknown.

Adherence and persistence to therapy are major barriers to successful treatment of osteoporosis [8]. Poor adherence has been reported in at least 50 % of subjects within the first year, with this figure increasing thereafter [9–11]. As many as 50–75% of women discontinue their medication after 12 months [12, 13]. Poor adherence has an impact on efficacy. Analysis of over 35,000 women taking alendronate or risedronate showed that fracture rates in subjects with low adherence were 20–30 % higher than those who adhered to medication for 24 months [11]. On the other hand, high rates of persistence with daily anabolic therapy are reported in a real-world setting with values as high as 87 % [14], a percentage that is comparable to clinical trials [2, 15–18]. There have been, however, no studies of the effect of adherence to PTH treatment on BMD, bone markers and fractures.

In the Open Label Extension Study (OLES) to the Treatment of Osteoporosis with PTH (TOP) trial, we investigated the effects of PTH(1–84) treatment over 24 months in subjects with postmenopausal osteoporosis and their course after discontinuation of PTH(1–84) treatment for another 12 months. We also evaluated the effect of adherence to therapy during the treatment period on BMD, biochemical marker responses and fracture incidence during and after the 24-month treatment period.

Methods

The TOP clinical trial

The TOP clinical trial was an 18-month, randomized, double-blind, placebo-controlled trial that assessed the effect of PTH(1–84) on vertebral fracture incidence and safety in postmenopausal osteoporotic women [1]. A previous phase II trial had established the efficacy and safety of the dose used in TOP (100 μg per day) [17]. The broad entry criteria included postmenopausal women (>55 years of age) with a BMD T-score ≤ −2.5 and no vertebral fractures, or a BMD T-score ≤ −2.0 and one to four vertebral fractures and younger postmenopausal women (45–54 years of age) if their BMD T-score was ≤ −3.0 at the lumbar spine, femoral neck, or total hip with no prevalent vertebral fracture; women with a BMD T-score ≤ −2.5 and one to four vertebral fractures. Participants were followed for safety at 1, 3, 6, 9, 12, 15 and 18 months from randomization. Other details of study design are provided in reference [1].

Open-Label Extension Study

The OLES was designed as a continuation of the TOP study to examine the longer-term effects of PTH(1–84). Subjects randomized to PTH(1–84) in TOP were followed for an additional 6 months of PTH(1–84) treatment in an open-label design. Eligible subjects included those who completed the TOP protocol or those prematurely discontinued in TOP due protocol-defined events (e.g. fracture or excessive bone loss, etc). Subjects who had been assigned alternative protocol-defined dosing regimens including injections every other day or once per week were eligible. Exclusions from entry into the OLES extension included use of prohibited medications (PTH or its analogs, bisphosphonates, HRT, systemic corticosteroids, etc,), poor compliance in the TOP protocol, contraindications for PTH such as elevated serum or urinary calcium at OLES baseline or significant concurrent illnesses. Subjects who received PTH(1–84) for less than 18 months during TOP were administered PTH(1–84) in the OLES so that their total exposure time to PTH(1–84) was 24 months. Subjects were then monitored for 12 months without further PTH(1–84) treatment or any anti-osteoporosis therapy, but calcium and vitamin D supplementation were continued. Participant visits occurred at 6 and 18 months after start of the extension study. For the extended treatment period of 6 months and the follow-up period of 12 months, without further treatment, there was no parallel placebo group. The study was conducted with IRB/ethical committee approval at each investigative site, and written informed consent was obtained from each participant prior to study activities.

Treatment

All participants in the OLES received 100μg PTH(1–84) (supplied by NPS Pharmaceuticals), which was administered once daily by self-injection. All OLES participants were provided with calcium (700 mg/day) and vitamin D_3 (400 IU/day) for the duration of the study. Calcium supplementation was discontinued if a patient developed hypercalcemia or hypercalciuria; if the condition continued, the dosing frequency of the study drug, but not the dose, was reduced to every other day, twice weekly or once weekly until controlled.

Endpoints

Efficacy

The effects of PTH(1–84) over 24 months of treatment with a subsequent 12 months discontinuation (months 24–36 of the study) were determined as changes from baseline in BMD by DXA at the spine (primary outcome variable), total hip and femoral neck and one third radius. Measurements of BMD were made on either Hologic (Holigic Inc, Bedford, MA, USA) or Lunar (GE Medical Systems, Madison, WI, USA) densitometers and reported as percent change. Further details of methods have been previously reported [1, 17]. In addition to total hip and femoral neck BMD, other secondary outcomes included biochemical markers of bone turnover (serum levels of bone-specific alkaline phosphatase, BSAP; and urinary N-telopeptide cross-links of type I collagen, NTx). Details of assays used have been previously reported [1]. Blood and urine samples were obtained from participants at baseline and throughout the 36-month study period. Vertebral fracture incidence, another secondary outcome, was assessed by semi-quantitative comparison of lateral and anterior/

posterior radiographs of the thoracic and lumbar spine (T4–L4) at baseline and from lateral thoracic and lumbar radiographs at months 24 and 36. Other secondary endpoints included non-vertebral fractures (reported as adverse events and not formally adjudicated). Fractures due to malignant disease, infection, excessive trauma and those involving the face and skull were excluded.

Safety

For this analysis, we reported only adverse events (AEs) recorded during the OLES phase of the study that included the six additional months of PTH(1–84) treatment and the follow-up period of 12 months. The safety profile over 18 months has been described previously [1]. Treatment-emergent AEs were defined as any event that occurred, became more severe or increased in intensity after onset of receiving the study medication. Serum and urinary calcium levels were recorded throughout the study.

Statistical analysis

In this analysis, we included only women randomized to PTH(1–84) in the TOP trial who continued in the protocol up to 24 months (n = 781). Thus, for many analyses there was no comparison group, with the main evaluations being historical ‘within group’ comparisons. The densitometric efficacy endpoints were analyzed by determining the percentage change from baseline within a treatment group. The population analysed in the OLES included all subjects who received at least one dose of PTH(1–84) during the OLES study. All primary and secondary endpoints used this population.

The significance of percentage changes in BMD during OLES was assessed by one-way ANOVA (with the treatment group as a covariate) to obtain an estimate of the least squares means to compare values to initial baseline values. Significance on a 5 % level was determined if t values provided sufficient evidence to reject the null hypothesis of the estimated least squares mean being zero. The statistical tests were not adjusted for multiplicity. For bone markers, median values of the percentage change from baseline in the levels of each marker are shown along with interquartile ranges. At each time point all available data are used. There is no imputation for missing data.

Results for spine BMD and bone turnover markers were defined relative to the baseline. In order to assess the biological effect of daily PTH(1–84) treatment, we performed subgroup analyses of BMD in which we stratified participants according to their adherence to 24 months of PTH(1–84).

Participants were requested to return both used and unused carpules, and the number of injections actually used was calculated from these returns. This information, together with dispensing records from the previous visit, was used to estimate the number of injections used and then adherence. We defined the high adherence group as subjects continuing in the study for at least 19 months (TOP + OLES, total 24 months of treatment) and within this time period, administering at least 80 % of daily injections of PTH(1–84). The number of daily injections of PTH (1–84) out of the total number of days enrolled in the study was used to calculate the adherence for each subject.

These subjects were compared to the remaining OLES participants who used less than 80 % of their daily injections or remained in follow-up for less than 19 months. A gap without PTH(1–84) of more than 90 days between TOP and OLES led to a categorization of low adherence.

Reported safety data included AEs occurring with an incidence of at least 3 % during the OLES. Additional information on safety included elevated serum calcium and/or urinary calcium. Elevated serum calcium was defined as a level greater than 10.7 mg/dl. Increased urinary calcium was defined by a fasting morning urine calcium/creatinine spot ratio ≥1.0 mmol/mmol and/or 24-h urine calcium ≥360 mg/day.

Results

Study population in OLES

Figure 1 describes the subjects enrolled in this study. This population was analysed for efficacy and safety of PTH(1–84) and included all women who received at least one dose during the open-label extension.

Patient characteristics

Of the 790 subjects intended to receive PTH(1–84) in OLES, 781 received at least one dose of PTH(1–84). The interruption of PTH(1–84) treatment during the transition between TOP and OLES was not more than 21 days and pertained only to 13 % of the OLES study population.

Baseline characteristics

The enrollment characteristics for subjects of the OLES population are summarized in Table 1. At baseline, the average age of the population in OLES was 63.8 years; 83 % were Caucasian and 94% postmenopausal for at least 5 years. Most subjects were recruited from the USA (39%), Argentina (19 %) or Canada (13 %). In the 12 months prior to entering the TOP trial, 32 % had taken osteoporosis therapy, mostly hormone replacement therapy (70 %) and bisphosphonate treatment (36.8 %). The mean duration of bisphosphonate exposure was 46 days, and the mean time from the last bisphosphonate dose to OLES baseline was 924 days. For subjects in the OLES, 18 % of the population had a prevalent vertebral fracture at the TOP baseline. The table shows adherence to the treatment schedule. Of the study subjects, 43.3 % were not adherent. In every category, however, they did not otherwise differ from the population that did adhere to the study medication.

BMD changes from baseline at lumbar spine, femoral neck, total hip and one third radius

Figure 2 shows the changes in BMD over the 24 months of PTH(1–84) treatment and in the follow-up period of 12 months without treatment. Mean lumbar spine BMD increased from baseline up to 24 months of treatment. After 24 months of PTH(1–84) treatment, lumbar spine BMD had increased by 6.8 % from baseline ($p < 0.05$). There were increases in BMD at the spine and hip between 18 and 24 months, although these did not achieve statistical significance. After treatment cessation, lumbar spine BMD fell promptly but still remained 4.6 % above baseline after 6 months and 3.9 % above baseline after 12 months. At the hip

regions, increases in BMD at 24 months of PTH(1–84) treatment were 1.1 % (total hip) and 2.2 % (femoral neck). Similar to lumbar spine BMD, when PTH(1–84) was stopped at 24 months, BMD promptly fell. At 36 months, the percentage change from baseline for the total hip and the femoral neck was 0.2 and 1.1 %, respectively. Data are available at the one third radius site for 79 subjects. As expected, this site experienced a decline in BMD during the 24 months of exposure to PTH(1–84). The decline from baseline over 24 months reached 5.2 %. Over the next 12 months, there was a further small decrease of 1.2%.

The impact of adherence on BMD changes

The adherent population constituted 57% of the study group. Significantly larger overall changes in lumbar spine BMD were observed in subjects with high adherence to the study medication throughout the study. Figure 3 illustrates these results. Among the group with high adherence, the increases over 24 months were significantly larger (8.3%) than those who were not as adherent (4.9 %, $p < 0.001$). Increases in femoral neck BMD over 24 months were larger at 2.6 % in the adherence group than in the poorly adherent group (1.9 %, $p = 0.155$). At the total hip, those subjects who adhered to PTH(1–84) treatment experienced a significantly greater increase in BMD (1.7 %) than those who did not adhere (0.6 %, $p = 0.002$). There was no significant difference in changes at the one third radius site between adherent and less adherent subjects (−5.8 vs −5.1 %, $p = 0.54$).

Bone turnover markers

The bone formation marker, BSAP, reached a maximum at 6 months, remained at this level up to 12 months and then began to fall, despite continuing PTH(1–84) therapy. The median percentage change reached a maximum level of 87 % above baseline, following which BSAP levels fell so that at 24 months the BSAP levels were only 27% above baseline values. With treatment discontinuation, further declines in BSAP were seen such that, by the end of 36 months BSAP, values were not different from baseline (Fig. 4a). There was no notable difference between the adherent and poorly adherent group in the BSAP change and the medians for both groups for all visits were similar (data not shown). The bone resorption marker, NTx, expressed as urinary NTx/creatinine, followed a similar course to that seen with BSAP (Fig. 4b). After 6 months of treatment, NTx reached a maximum with a median value 97 % above baseline. Thereafter, NTx levels started to decline but, like BSAP, at month 24 the NTx still remained 24 % above baseline level. With discontinuation of PTH(1–84) treatment, a further decline in NTx levels occurred, and by month 36, NTx levels were not different from baseline values. The same pattern was seen for the NTx as for the BSAP in that there was no difference between the adherent and poorly adherent groups.

Fractures

During the 18 months of the TOP trial, subjects on active PTH treatment had a 1.3 % risk of vertebral fractures compared with 3.4 % for the placebo. During the OLES phase, in a population of 771 subjects who had not received bisphosphonate therapy after PTH treatment, there was only one new vertebral fracture during months 18–24. During the 12-month follow-up period, without further treatment with PTH(1–84), only two additional vertebral fractures were seen, leading to a similar annualized incidence of new vertebral

fractures of 0.28 %. There was a difference in vertebr al fracture incidence during the first 18 months, which was not materially altered during the extension (Table 2).

TOP and OLES were not powered to assess the incidence of non-vertebral fractures. There were no additional hip or wrist fractures during the 6-month extension period, and there were no differences between adherent and poorly adherent subjects in the overall incidence of non-vertebral fractures. However, over the 12-month discontinuation phase, a further three hip fractures were seen, and all occurred in subjects with <80 % adherence to treatment. For wrist fractures, a further four fractures were seen during the discontinuation phase (two wrist fractures each in the adherent group and poorly adherent group)

Safety associated with OLES

The most frequently reported AEs during the OLES treatment phase were increased urinary calcium levels (6.4 %), arthralgia (6.1 %), increased serum calcium levels (5.1 %), headache (4.6 %) and nausea (4.4 %).

Mean pre-dose serum total calcium values were within the normal range during PTH(1–84) treatment, although there was an increase of 3.6 % from baseline levels (9.67 mg/dl), reaching a maximum at month 3 (10.02 mg/dl). Levels decreased after month 3 and remained slightly above baseline at month 24 of treatment (9.79 mg/dl). Total serum calcium levels declined further towards baseline, reaching a level of 9.71 mg/dl at the end of the 12-month follow-up period with no treatment.

Discussion

The results from the OLES provide evidence for continued efficacy of PTH(1–84) during a 24-month treatment period. BMD at the lumbar spine continued to increase during the 24 months of treatment with PTH(1–84), reaching 6.8 % above baseline. At the hip and the femoral neck, the corresponding gains in BMD at month 24 with PTH(1–84) were 1.1 and 2.2 %, respectively. The changes suggest further increments to month 24 above those seen during the TOP clinical trial (month 18) and point to the continued anabolic effects, particularly at hip sites over time. Following discontinuation of PTH(1–84) therapy after 24 months, the BMD declines at the lumbar spine and hip were consistent with the Parathyroid Hormone and Alendronate (PaTH) study, which included PTH(1–84) therapy for only 1 year [15]. In this study, one treatment arm did not receive alendronate after PTH(1–84) therapy and showed rapid declines in BMD, similar to the results reported in our study. In the PaTH study, BMD gains were maximized in the group that received alendronate following PTH therapy compared to placebo. In our study, none of our patients were treated with bisphosphonates following PTH therapy. The bone turnover markers peaked at 6 months before declining gradually during the last 12 months of therapy and then during the 12 months without therapy.

Although not designed as a fracture-prevention study, the 6-month open-label extension period suggests maintenance of the reduced vertebral fracture risk seen during TOP, with a similar low rate of vertebral fracture. Furthermore, despite a decline in BMD during the discontinuation period, the low rate of vertebral fractures persisted during the 12 months

after PTH(1–84) treatment was stopped. A previous observational follow-up study showed a similar continued reduction in vertebral fracture incidence 18 months after the discontinuation of teriparatide therapy, but in that study, approximately 47 % of women reported the use of antiresorptives, which complicated interpretation of the data [19]. In our study, the incidence of fractures remained low over the 12-month follow-up phase without any further anti-osteoporotic treatment such as antiresorptive therapy. It should be noted, however, that the number of vertebral fractures remained low despite a decrease in lumbar spine BMD and bone turnover markers that remained close to the baseline value over the 12-month follow-up phase. While no randomized studies have compared the effects of using antiresorptives following PTH versus no antiresorptive therapy on fractures, results from PaTH (for BMD and markers) suggest that antiresorptive therapy, particularly bisphosphonates, may be a better clinical option than full cessation of therapy [15].

This study demonstrates for the first time the importance of adherence to daily anabolic therapy in postmenopausal women with osteoporosis. The changes in lumbar spine BMD over 24 months were greatest in subjects showing high levels of adherence to daily treatment with PTH(1–84). At all points during the study, the increases in BMD were greatest in the population of subjects showing high adherence. At month 24, the difference (from baseline) between the high adherence and low adherence (8.3 versus 4.9 %, respectively) populations was 3.3 %. In the OLES population, the fracture incidence rates were significantly lower in adherent subjects when compared with those who were less adherent. Adherence to PTH therapy was associated with a lower number of vertebral fractures during the treatment period, and this persisted into the post-treatment period.

There are no other studies evaluating the safety and efficacy of PTH(1–84) treatment beyond 18 months. One study of PTH(1–34) in patients treated for glucocorticoid-induced osteoporosis continued for 36 months [20]. In postmenopausal osteoporosis, longer-term studies are more limited. For PTH(1–34), lumbar spine BMD continued to increase for up to 24 months, with increases of 10–13 % in postmenopausal women with established osteoporosis [21, 22]. This increase was dependent on pretreatment with bisphosphonates. Similarly to the results reported here, Finkelstein et al. showed that in a group of postmenopausal women treated with 40 μg PTH(1–34) for 24 months, bone turnover markers started to decline at 12 months [7].

The incidence of AEs in OLES was lower than that observed in the TOP clinical trial. This may be explained by the previous exposure to medication in TOP or due to the fact that the subjects enrolled in OLES were a selected group of subjects.

There are some significant limitations to the OLES trial. For the last 6 months of PTH(1–84) treatment and the 12 months of untreated follow-up, the study was open label, and there was no placebo comparison. Furthermore, the women who continued into OLES were a self-selected sample of subjects treated with PTH(1–84) in TOP. This group was highly selected since those with adverse reactions to the drug, or those who had high levels of serum or urinary calcium, would be less likely to have participated further in the continuation study.

Conclusions

The results presented here support the efficacy of PTH(1–84) over 2 years in the treatment of postmenopausal osteoporosis. We observed significant increases in BMD at the lumbar spine, total hip and femoral neck, as well as continued low vertebral fracture rates to 24 months. Although more exhaustive fracture prevention data are needed to determine optimal duration of PTH treatment, these data suggest that BMD accrual over a period of 24 months is accompanied by continued benefit with a low number of vertebral fractures. The larger gains in lumbar spine BMD and lower vertebral fracture incidence seen in adherent subjects point to the importance of achieving effective patient adherence.

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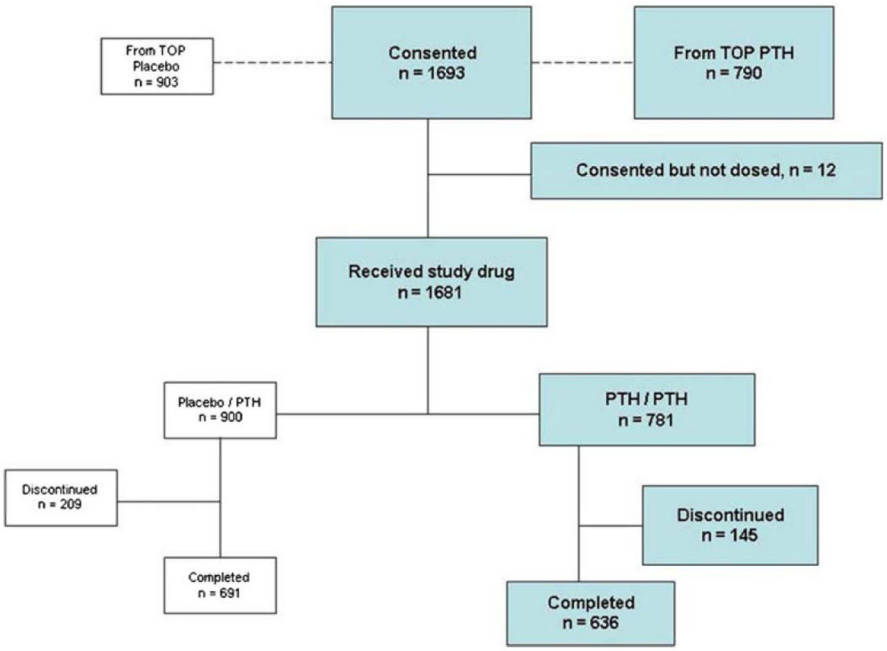

Fig. 1.

Study flow diagram. The study subjects are represented by the *shaded boxes*. The modified intention-to-treat population was analysed for efficacy and safety and included all women who received at least one dose of PTH(1–84). There was no corresponding placebo group. The *shaded* patient population was included in this analysis and comprises subjects who received PTH(1–84) for 24 months (18 months TOP plus 6 months open-label extension). *PTH/PTH* refers to subjects who received PTH(1–84) in TOP and OLES. *Placebo/PTH* refers to subjects who received placebo in TOP and PTH(1–84) in OLES

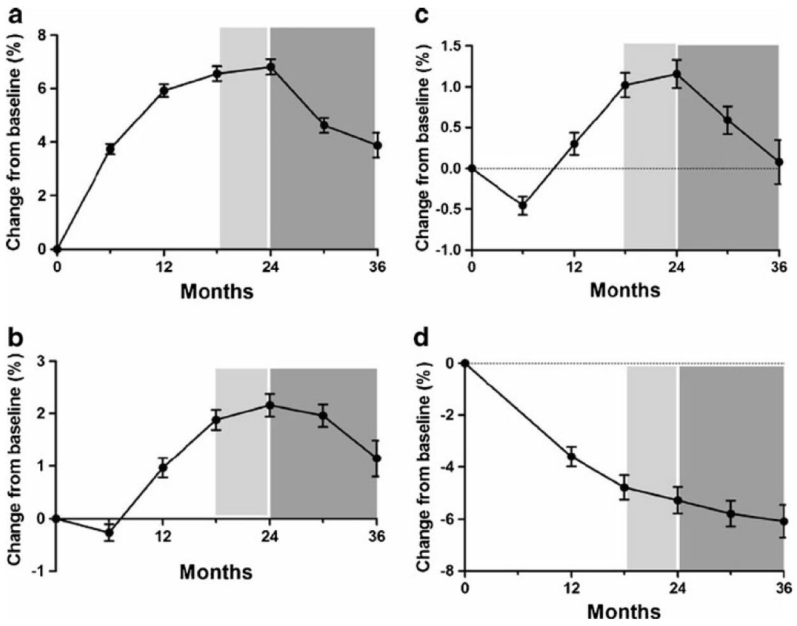

Fig. 2.

Changes in BMD for **a** the lumbar spine, **b** the femoral neck, **c** the total hip and **d** the distal one third radius after 24 months of PTH(1–84) treatment and in the 12-month follow-up period without treatment—ITT population. The open-label treatment period is shown in *light grey* shading. The follow -up period when PTH(1–84) was withdrawn is shown in *dark grey* shading

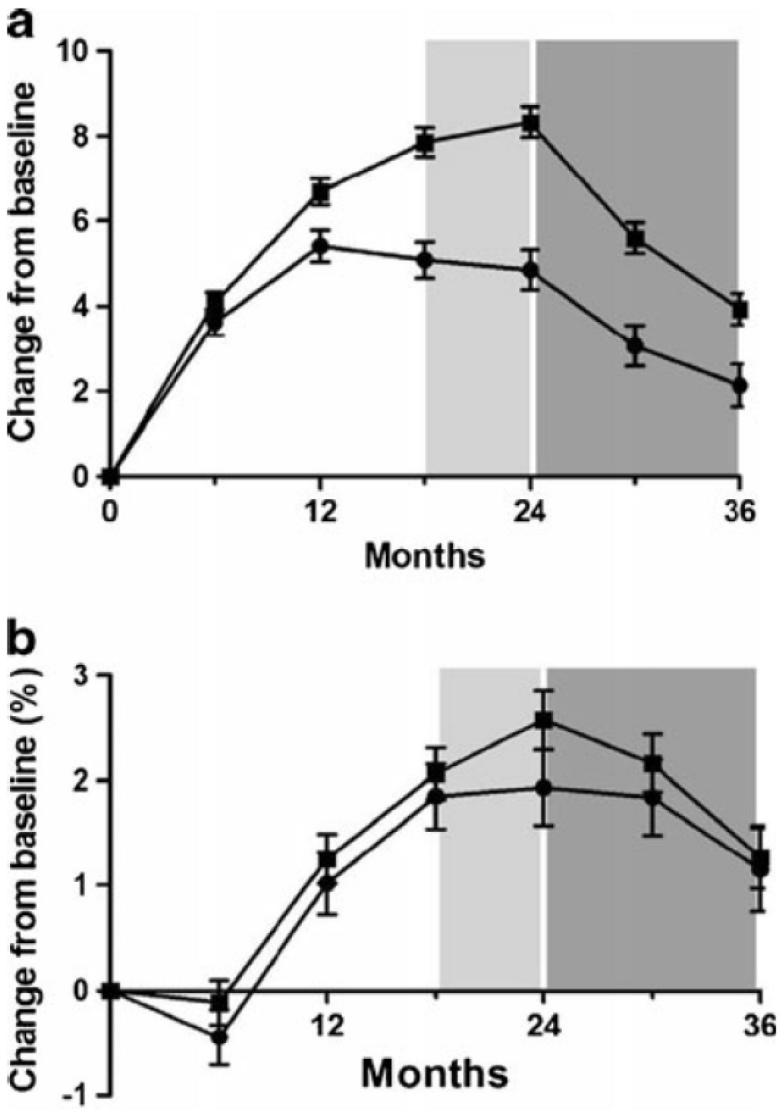

Fig. 3.

Changes in BMD in the high and low treatment adherence groups for **a** the lumbar spine and **b** the femoral neck. The *square symbols* show the changes in BMD in the group adhering to at least 80 % of daily injections of PTH(1–84) for at least 1.6 years. The *circle symbols* are for the group who used less than 80 % of their daily injections or did not remain in follow-up for at least 1.6 years. The open-label treatment period is shown in *light grey* shading along with the follow-up period when PTH(1–84) was withdrawn (*dark grey*)

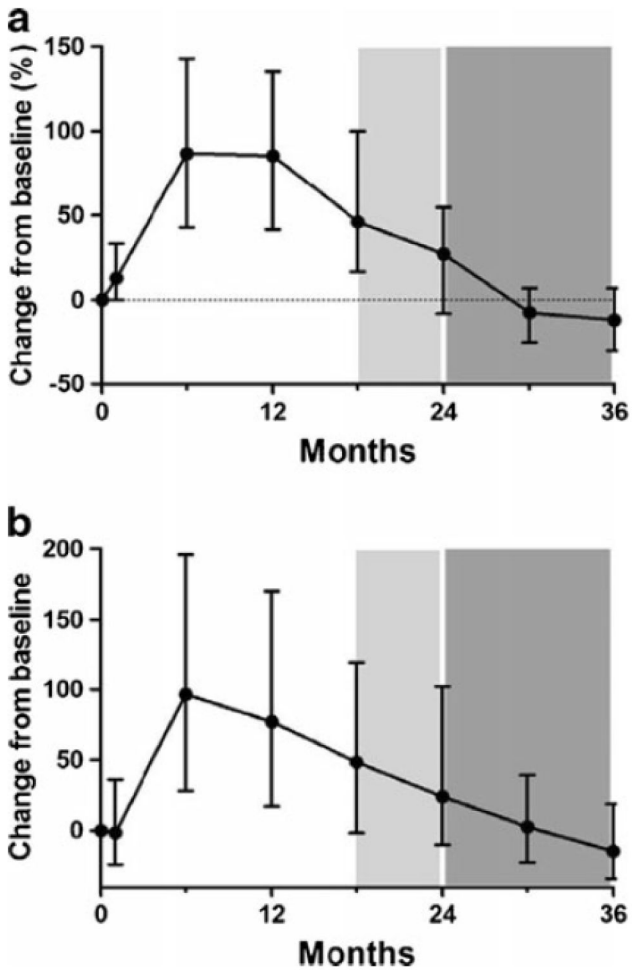

Fig. 4.

Median changes in biochemical bone markers with time: **a** serum BSAP levels from TOP baseline (percentage) and **b** urinary NTx/creatinine ratios from TOP baseline (percentage). The *bars* show the lower and upper quartile range. The OLES period up to 24 months included 6 months of PTH(1–84) treatment followed by a further follow-up period in which no treatment was received (between 24 and 36 months). The open-label treatment period is shown in *light grey* shading along with the follow-up period when PTH(1–84) was withdrawn (*dark grey*)

Table 1

Demographic characteristics for the OLES population at TOP baseline (before initiation of treatment)

	Values	≥80 % adherence	<80 % adherence	Total
Age category	*N* (%)	443	338	781
	45–54 years	31 (7.0)	26 (7.7)	57 (7.3)
	55–64 years	209 (47.2)	163 (48.2)	372 (47.6)
	65–74 years	172 (38.8)	125 (37.0)	297 (38.0)
	≥75 years	31 (7.0)	24 (7.1)	55 (7.0)
Age in years at baseline	*N*	443	338	781
	Mean ± 1 SD	63.9 ± 7.0	63.7 ± 7.0	63.8 ± 7.0
Lumbar spine T-score	*N*	404	322	726
	Mean ± 1 SD	−2.58 ± 0.82 *	−2.77 ± 0.91	−2.67 ± 0.87
Total hip T-score	N	439	334	773
	Mean ± 1 SD	−1.79 ± 0.80 *	−1.92 ± 0.85	−1.85 ± 0.82
Femoral neck T-score	N	439	334	773
	Mean ± 1 SD	−2.10 ± 0.74 *	−2.21 ± 0.73	−2.15 ± 0.74
Prevalent vertebral fractures	*N* (%)	443	338	781
	None	370 (83.5)	272 (80.5)	642 (82.2)
	1	50 (11.3)	51 (15.1)	101 (12.9)
	2	13 (2.9)	12 (3.6)	25 (3.2)
	>2	10 (2.3)	3 (0.9)	13 (1.7)

The demographic characteristics refer to the 781 subjects of the ITT population. This population is divided according to its adherence to daily doses of PTH(1–84) (high ≥80 % or poor <80 %) over ≥19 months

* $p < 0.05$ versus <80 % adherence

Table 2

Summary of incidence of new vertebral fractures in subjects treated with PTH(1–84) for 24 months, and a follow-up of 12 months with no treatment

Treatment (months)		<80 % adherence	≥80 % adherence	Total
18	*N*(%)	11 (3.25 %)	1 (0.23 %) *	12
	95 % CI	(1.36 %, 5.15 %)	(0.00 %, 0.67 %)	
24	*N*(%)	11 (3.25 %)	2 (0.45 %) *	13
	95 % CI	(1.36 %, 5.15 %)	(0.00 %, 1.08 %)	
Follow up (12 months post-treatment)	*N*(%)	12 (3.55 %)	3 (0.68 %) *	15
	95 % CI	(1.58 %, 5.52 %)	(0.00 %, 1.44 %)	

The table shows the cumulative incidence of fractures in groups <80 % adherent to daily treatment and ≥80 % adherent to daily treatment

* $p < 0.01$, differences between adherent and poorly adherent groups at all time points were significant according to Fisher's Exact *t* test