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Clinical Trial

Oral daily PTH(1-34) tablets (EB613) in postmenopausal women with low BMD or osteoporosis: a randomized, placebo-controlled, 6-month, phase 2 study

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Abstract

Anabolic treatment is indicated for high and very-high risk patients with osteoporosis, but acceptance is limited because current anabolic medications require subcutaneous injections. The purpose of this study was to assess the effects of a novel orally administered PTH tablet on serum markers of bone formation (PINP and osteocalcin), bone resorption (crosslinked C-telopeptide [CTX]), BMD, and safety in postmenopausal women with low BMD or osteoporosis. In this 6-mo, double-blind, placebo-controlled study, 161 patients were randomized to oral PTH tablets containing 0.5, 1.0, 1.5, or 2.5 mg or placebo daily. Biochemical markers were assessed at 1, 2, 3, and 6 mo and BMD of LS, TH, and FN was measured at 6 mo. Biochemical marker changes were dose dependent with minimal or no effect at the 2 lowest doses. At the highest dose (2.5 mg once daily), serum PINP and OC levels increased 30% within 1 mo after oral PTH initiation ($P < .0001$), remained elevated through 3 mo, and were back to baseline at 6 mo. In contrast, serum CTX levels declined 16% and 21% below baseline at 3 and 6 mo, respectively (both $P \leq .02$). At 6 mo, 2.5 mg tablets increased mean BMD vs placebo of the LS by 2.7%, TH by 1.8%, and FN by 2.8% (all $P \leq .01$). There were no drug-related serious adverse events. The most common adverse events were headache, nausea, and dizziness. In contrast to subcutaneous PTH, the oral PTH tablet appears to increase BMD rapidly by the dual mechanism of stimulating formation and inhibiting bone resorption. This might be the first effective oral anabolic alternative to subcutaneous administration for the treatment of low BMD or osteoporosis.

Keywords: osteoporosis treatment, oral teriparatide, oral PTH, oral hPTH(1-34), osteoanabolics, EBP05/EB613, Entera Bio

Lay Summary

Despite the superior benefits of bone-building (anabolic) agents and guidelines supporting their use, these medications are used in a minority of patients for whom they are appropriate, in part because they require daily or monthly injections, which limit patient acceptance. An oral anabolic tablet has potential to address this substantial treatment gap. In this double-blind, placebo controlled, dose-finding randomized study, 161 postmenopausal women with low BMD or osteoporosis were treated with varying doses of the active part of PTH(1-34) or placebo given in daily oral tablets for 6 mo. The highest oral PTH tablet dose (2.5 mg) produced an increase in markers of bone formation while simultaneously decreasing the markers of bone breakdown. Significant gains in BMD of the spine and hip were observed at the end of the 6-mo study and there were no significant safety concerns. The 2.5 mg oral PTH tablet dose was well tolerated when patients were instructed to titrate up to the full dose. We conclude that this PTH tablet might be the first effective orally administered bone building medication and should be studied further in treatment of women with osteoporosis.

Introduction

The reduction in bone strength associated with osteoporosis is characterized by both low bone mass and microarchitectural deterioration of bone tissue.[1] Bisphosphonates, the most commonly prescribed antiresorptive medications, suppress bone remodeling and increase BMD moderately, but do not stimulate bone formation or substantially repair microarchitecture. In contrast, the anabolic medications, teriparatide, abaloparatide, and romosozumab stimulate bone formation and improve cancellous and cortical microarchitecture. In head-to-head comparative studies, anabolic agents reduce fracture risk to a greater extent than bisphosphonates.[2-4] As a result, recent guidelines by the American Association of Clinical Endocrinologists (AACE), the Endocrine

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Society, the International Osteoporosis Foundation, and the North American Menopause Society recommend that women with osteoporosis at very high risk for fracture receive anabolic therapy as initial therapy.[5-8] In addition, AACE recommends considering the use of anabolic therapy for women who have a suboptimal response to other medications. Despite the superior benefits of anabolic agents and the guidelines supporting their use, anabolic agents are currently used in a minority of patients for whom these agents are appropriate. This treatment gap is related to the need for subcutaneous administration with all 3 anabolic medications, limiting patient acceptance, as well as their cost.[9-11]

Oral PTH is a novel orally administered teriparatide [hPTH(1-34)] tablet with excipients that inhibit the gastrointestinal proteases and facilitate transcellular absorption from the gastrointestinal tract into blood. Oral dosing eliminates the barrier to patient acceptance posed by daily subcutaneous injections. Oral PTH is being developed to provide a once daily oral anabolic tablet treatment for high-risk patients with osteoporosis who have not yet sustained a fracture.

This placebo-controlled phase 2 dose-ranging study of oral PTH tablets taken daily evaluated the effect of treatment on biochemical markers of bone formation and resorption and BMD of LS, TH, and FN over 6 mo in postmenopausal women with low BMD or osteoporosis. Safety was evaluated by adverse event (AE) assessment and laboratory safety tests.

Subjects and methods

Study subject population and exclusion criteria

Women aged 50 yr and older were included if they were postmenopausal for at least 3 yr and had a LS, TH, or FN T-score ≤ -2.0 but ≥ -3.5.

Women were excluded if they had a previous fracture or clinically significant cardiovascular, renal, hepatic, chronic respiratory, neurological, or psychiatric disorders, inadequately treated thyroid disease, active gastrointestinal disorders potentially affecting drug bioavailability, active substance abuse or history of cancer except for cured, resected basal cell or squamous cell skin or thyroid cancer. Subjects currently on systemic glucocorticoids $\geq$2.5 mg prednisone or equivalent or who had used $\geq$5 mg/d for more than 1 wk in the prior year were excluded. Subjects with allergy to soy, or other components of study medication were excluded. Subjects with a history of Paget's disease of bone or disorders of bone and mineral metabolism other than osteoporosis, prior external beam or implant radiation therapy involving the skeleton, active urolithiasis, or primary hyperparathyroidism were excluded. Subjects with abnormal calcium, magnesium, phosphate, alkaline phosphatase, significant renal impairment (estimated glomerular filtration rate <45 mL/min/1.73 m^2), abnormal thyroid stimulating hormone on thyroid medication, and uncorrected vitamin D deficiency were also excluded.

Osteoporosis medication exclusions were: any past treatment with Forteo® (teriparatide injection), any osteoporosis medication in the past 2 yr (including bisphosphonates, estrogen/hormone therapy, and raloxifene), any use of intravenous bisphosphonate in the last 10 yr, and any use of denosumab within the last 3 yr. Additional oral bisphosphonate exclusions were: alendronate or ibandronate for >6 mo or risedronate for >1 yr within the last 5 yr, or a total treatment with oral alendronate or ibandronate for >3 yr or risedronate >5 yr with any continued use extending into the 5 yr before enrollment. Any strontium ranelate or fluoride >1 mg/d. All subjects provided written informed consent, and the study was approved by the respective institutional review boards (IRBs) at each study site and the Israeli Ministry of Health.

During screening, after written informed consent was provided, subjects were evaluated with a DXA BMD scan, electrocardiogram, physical examination, and laboratory evaluation [complete blood count (CBC), chemistry profile and urinalysis] to confirm eligibility.

Study design

This phase 2 study was registered on clinicaltrials.gov (NCT04003467) as a double-blind, placebo controlled, randomized dose-ranging study conducted at 4 sites in Israel. Participants were randomized to receive daily oral PTH or placebo tablets. Each oral PTH tablet contained 0.5 mg hPTH(1-34), and the total dose was determined by the number of tablets taken together. Randomization was performed according to a randomization process provided by the data management vendor (Medistat Ltd.). Both the investigators and subjects were blinded to what treatment the subject was receiving. Participants knew that they were getting 1, 2, 3, 4, or 5 tablets of study medication but neither subjects nor investigators knew if these tablets were oral PTH or placebo.

Study medication

Oral PTH tablets, utilizing Entera Bio's N-Tab platform technology for oral dosing of therapeutic peptides, were manufactured by Piramal Healthcare UK Ltd., are small 6-millimeter diameter tablets which contain 0.5 mg hPTH(1-34) with added excipients to maintain stability and protect the peptide from degradation in the gastrointestinal tract and SNAC (Salcaprozate Sodium), which increases gastric epithelial membrane fluidity without affecting tight junctions, thereby allowing transcellular passage into systemic circulation of the hPTH(1-34). In earlier PK studies, oral tablets taken in the morning, with water after an overnight fast, produced plasma hPTH(1-34) levels similar to those seen after subcutaneous 20 μg injection of teriparatide, with a higher Cmax and shorter elimination half-life.[12] Entera Bio has denoted the final formulation of oral hPTH(1-34) as EBP05 and the assigned drug candidate name as EB613. The matching placebo tablet (same size, shape, and color) was composed mainly of microcrystalline cellulose and Starch 1500®.

Nutritional supplements

All participants were instructed to use marketed Vitamin D_3 and calcium supplements with the dose determined by the investigator (Vitamin D_3 mean 1000 IU, range 600 to 2000 IU, calcium between 1000 and 1200 mg/d).

Treatment arms

Eligible participants were randomized to one of the oral PTH treatment groups or to placebo. The initial allocation schedule distributed the same proportion of subjects to each treatment group: oral PTH 0.5 mg, 1.0 mg, 1.5 mg, or placebo daily tablets, for a planned total of approximately 160 subjects. The results of a prospectively planned interim analysis of biochemical marker data for the first 80 subjects who completed 3 mo of study indicated that the 2 lower doses (1.0 mg and 0.5 mg) produced a minimal or no change in serum PINP

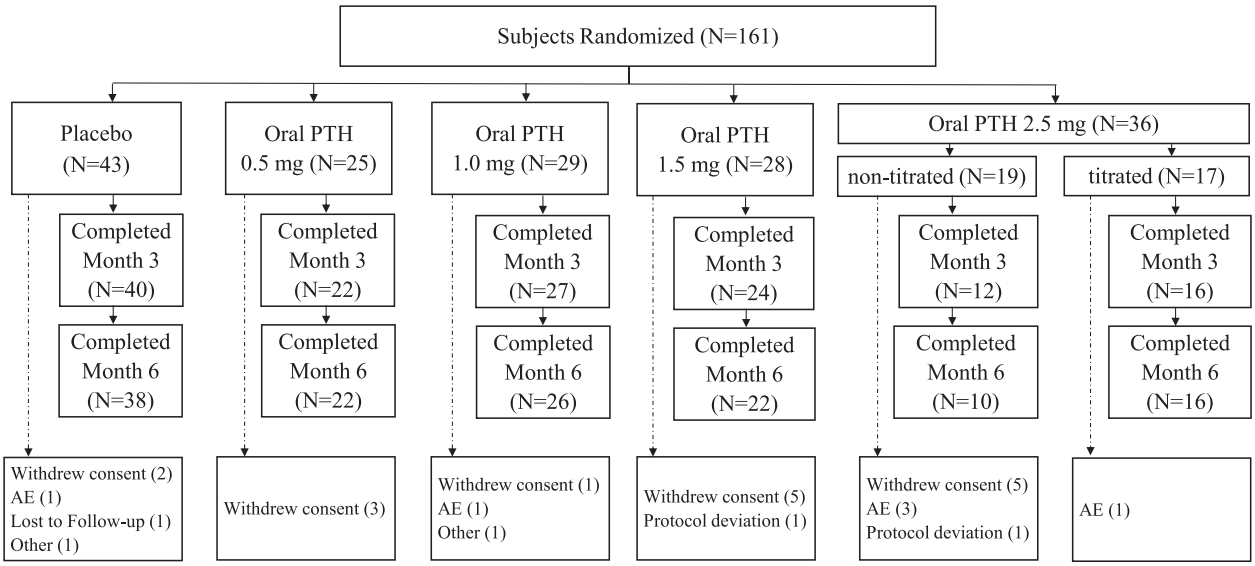

Figure 1. Subject Disposition.

vs placebo (Table 2); therefore, further recruitment into those groups was stopped. Subjects previously randomized to those doses continued in the study. Furthermore, the 1.5 mg dose produced smaller than anticipated increases in serum PINP levels. Therefore, a higher 2.5 mg treatment group was added.

The amended protocol randomly assigned 6 new participants to 1.5 mg daily tablets, 36 participants to 2.5 mg daily tablets, and 18 participants to placebo. After orthostatic symptoms typical of PTH receptor-activating agents were observed in some of the 19 subjects initiating the 2.5 mg dose, the protocol was further amended to introduce a titration regimen for the 17 participants subsequently assigned to that dose. The titration procedure began with 1.5 mg daily, increased to 2.0 mg daily at the month 1 visit and increased to 2.5 mg daily at the month 2 visit. Women who were unable to tolerate the 2.5 mg dose were instructed to continue on 1.5 mg/d (1 participant). Treatment remained blinded and women randomized to 5 placebo tablets followed the same up-titration dosing plan as those randomized to 5 tablets of oral PTH. Thus, the final study design included the original 4 treatment groups plus the 2.5 mg group (with and without dose titration). Each treatment group included between 25 and 43 participants (Figure 1).

Study medication administration

Participants were instructed to take study medication orally once daily in the morning after an overnight fast before the first intake of food, concomitant medication, or beverage of the day except for water. They were advised to swallow tablets with 100 mL water and remain in an upright position (seated, standing or walking) without other activity for at least 30 min after tablet ingestion to optimize the bioavailability of the tablets. Women were instructed to avoid additional water or food for 1 h after the dose. No restrictions were required after that time.

Visit schedule

Participants visited the clinic for screening and on study day 1, once a month at the end of months 1–3, and at 6 mo for the end-of-treatment visit. Phone contacts were made at the end of week 2, month 4, month 5, and 2 wk after the month 6 clinic visit.

At each in-person study visit, women were assessed for AEs by medical interview, a targeted physical examination was performed, and blood samples for hematology and biochemistry were obtained, while participants remained fasting for biochemical marker assessment and safety laboratory evaluation (CBC, Chemistry including serum calcium). Concomitant medications were updated, and study medication compliance was assessed by tablet counting. Additional study medication was dispensed according to the study protocol.

BMD measurement was performed during screening, at month 6, or at the early termination visit if a woman participated in the study for at least 8 wk. If a participant could not come into the clinic for a study visit within the allowed window of time, for example, due to COVID-19 restrictions, a home visit by a trained nurse was performed to draw blood samples according to the visit schedule (month 1 visit—day 29 ± 3; month 2 visit—day 57 ± 5; month 3 visit—day 85 ± 5; month 6 visit—day 168 ± 7). Biochemical marker samples were obtained in the morning after an overnight fast and prior to ingestion of food. Home visits for month 6 did not include BMD which was performed at a separate visit within 6 wk of the last dose of study medication. During telephone call visits, participants were questioned about compliance and potential AEs.

Efficacy assessments

Biochemical marker samples were obtained in the morning after an overnight fast and prior to ingestion of food. The analysis was done by an accredited central laboratory (American Medical Laboratories) using validated kits and methods, while maintaining blinding. Samples were analyzed in batches (including all samples for each participant in the same assay) throughout the study. Biochemical markers of bone formation (serum PINP and osteocalcin [OC] levels) and bone resorption (serum crosslinked C-telopeptide [CTX]) were assessed at months 1, 2, 3, and 6. Assays were performed following the standard protocol specified by the manufacturer of each assay method (Standard IDS-iSYS assays for PINP [intact],[13]

CTX-I [CrossLaps®],[14] and OC [N-MID®][15]). Inter-assay coefficients of variation for each of these assays were PINP, 4.63%; OC, 6.05%; CTX, 6.16%. Intra-assay coefficients of variation for each of these assays were PINP, 2.87%; OC, 2.53%; CTX, 3.22%.

BMD of LS (L1-4), TH, and FN was measured at baseline and at month 6 by DXA using GE Prodigy (GE Healthcare) or Hologic (Hologic, Inc.) instruments. Scans were performed at each site following a qualification process coordinated by the central BMD Quality Control (QC) and Analysis Center (Calyx Medical Imaging, formerly Parexel Informatics). BMD scans were assessed and analyzed by the QC center following standard protocols and all personnel remained blinded to treatment. Absolute calibration of DXA instruments was determined by measurements of the same phantom (European Spine Phantom) circulated to all sites, and potential changes in calibration was assessed by serial measurements of each site's phantom sent to the central BMD QC and Analysis Center.

Safety assessments

Safety assessments at each clinic visit were based on AEs reported by the participant or observed by the investigator, concomitant medication use, vital signs, and safety laboratory assessments (hematology and biochemistry). Samples for safety labs were analyzed at the time of collection throughout the study. Relation of AEs to study medication was reported by investigators using a 5-point scale. AEs coded as "not related" or "unlikely related" were considered "not drug-related" in data presentations and statistical analyses. AEs coded as "possibly related," "probably related," or "definitely related" were considered "drug-related" in data presentations and statistical analyses. Serious AEs were also reviewed and independently assessed for causality by the sponsor's Medical Monitor.

AEs of special interest

Hypercalcemia was defined as serum calcium above the upper limit of the reference range provided by the central laboratory. A designation of clinically significant hypercalcemia was determined by the investigator, reported as an AE to the sponsor and considered an event of special interest. An AE of hypercalcemia was not defined as a Serious AE unless it met at least one of the standard criteria for Serious AEs.

Statistical analyses

A statistical analysis plan was created prior to database lock and unblinding. There were 3 populations for analysis of efficacy. The intent-to-treat (ITT)/safety population included all randomized subjects who took at least 1 dose of study medication and for whom there was at least one observation after the first dose. The per-protocol 1 (PP1) population included all ITT subjects who completed 3 mo of treatment per protocol and had no major protocol deviations that altered one or more endpoints. The PP1 population was used for evaluations of biochemical marker endpoints assessed after 3 mo of treatment. The per-protocol 2 (PP2) population included all ITT subjects who completed the study in compliance with the protocol and had no major protocol deviations that could have the potential to change an endpoint. The PP2 population was used for evaluations over the full 6-mo study.

Interim analyses

Three interim analyses were prospectively designed and conducted according to protocol. The first interim analysis included analysis of the primary endpoint (PINP change) after the first 80 subjects (50% of expected total enrolled) completed the first 3 mo of the study. Partial unblinding (statisticians and data management only) was conducted and a penalty of 1% significance level was incurred. One-way ANOVA model was applied for analyzing the % change in PINP within groups and changes between the treatment arms. Analysis of covariance (ANCOVA) model was applied in order to identify covariates suspected as related to the primary endpoint, as well as to test the differences in PINP between the treatment arms adjusted to covariate parameters. The second interim analysis of the BMD and biochemical marker data was conducted after the first 50% of subjects completed 6 mo of the study using similar statistical methods. The full interim analysis included a full analysis of the primary endpoint at 3 mo once all subjects completed the 3-mo visit and a 1% statistical level penalty was applied. This analysis for 1-, 2-, and 3-mo PINP and other biochemical marker changes from baseline was considered final and based on the interim "data freeze"; it was not redone at the end of the study. Therefore, no additional penalty was incurred.

Sample size

A sample size of 36 participants per group would provide at least 80% power to detect a 67% difference in mean PINP change from baseline assuming a common standard deviation of 100 and using a 2-group *t*-test with a 0.05 2-sided significance level. The same sample size would also provide at least 80% power to detect a 2.5% mean LS BMD change from baseline assuming a common standard deviation of 3.7 and using a 2-group *t*-test with a 0.05 2-sided significance level.[16]

Each treatment group was initially designed to include approximately 40 participants, to account for withdrawals. About 103 women were randomized to treatment with oral PTH tablets at 1 of 3 dose levels (0.5 mg, 1 mg, or 1.5 mg) or matching placebo and received daily treatment for 6 mo. However, based on the outcome of the first interim analysis of the first 80 randomized participants, the modified protocol was generated for the last 60 eligible women. These participants were then randomized to treatment with oral 1.5 mg or 2.5 mg or matching placebo tablets and received daily treatment for 6 mo.

Primary efficacy endpoint

The primary efficacy endpoint was % change in PINP from baseline during treatment with daily oral PTH tablets for 3 mo compared with the change during treatment with placebo. ANOVA model was used to analyze the % PINP change within groups and between treatment arms.

Secondary efficacy endpoints

The same analysis methods used for serum PINP at 3 mo were applied to PINP changes at other time points and for serum OC and CTX levels. For the biochemical marker analyses, subjects randomized to the 2.5 mg titrated dose were grouped with the 1.5 mg group at month 1 and with the 2.5 mg group at month 2 and thereafter. All 3-mo secondary endpoints were performed on PP1. All 6-mo secondary endpoints were performed on PP2. Although the oral PTH doses in this dose-ranging study were changed during the trial, neither the primary or secondary endpoints, or the statistical analysis plan were altered. Comparisons of the 2.5 mg non-titrated and 2.5 mg titrated dosing regimens were also added to the efficacy evaluations.

The secondary efficacy endpoints included the % change in LS, TH, and FN BMD within each group and vs placebo from baseline to month 6. Within-group changes were analyzed using paired *t*-tests, while between-group comparisons were analyzed using ANOVA model. Linear regressions were applied on 6-mo BMD relative change by treatment group for testing the "p for trend". *P*-values for analyses of secondary endpoints were not adjusted for multiple comparisons.

Safety

For the safety analysis, AEs were coded according to MedDRA version 23.1 and summarized in tables by system organ class (SOC) and preferred term (PT) and by treatment group. The incidence of treatment-emergent AEs, AEs reported prior to the first dose of study medication, AE severity, and investigator assessment of relationship to study medication were summarized by treatment group, by SOC, and by PT. Baseline and change from baseline at each visit were presented for vital signs, weight, and laboratory safety assessments. For selected laboratory parameters, a predefined limit of change analysis was presented.

Data management, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed using SAS® version 9.3 or higher for Windows.

Results

Baseline characteristics and demographics

A total of 161 women were randomized. One hundred forty-one (87.6%) and 134 (83.2%) participants completed month 3 and month 6, respectively (Figure 1). Sixteen (9.9%) women withdrew their consent, 6 (3.7%) women discontinued early due to an AE, 2 (1.2%) discontinued due to major protocol deviations (exclusion criteria discovered after randomization), 1 (0.6%) was lost to follow-up, and 2 (1.2%) discontinued for reasons unrelated to an AE. No participant had drug-related serious adverse events (SAEs) or discontinued from the study due to an SAE.

As shown in Table 1, mean age for all women enrolled was 61.3 yr, mean BMI was in the overweight category at 26 kg/m^2, and mean biochemical marker levels were within normal postmenopausal ranges.[17-19] Mean BMD T-scores were −2.34, −2.15, and −1.85 for LS, FN, and TH, respectively. Baseline characteristics were similar between treatment groups with no significant differences. Baseline characteristics of participants who were enrolled after the addition of the 2.5 mg oral PTH dose were similar to those who entered treatment at the start of the study (Table 1).

Biochemical markers

As shown in Table 2, there were dose-dependent increments in serum PINP over the first 3 mo of daily oral PTH tablet administration. In the 2.5 mg group, mean serum PINP level peaked at 32.0% above baseline at 1 mo ($P < .01$) as shown in Figure 2. Serum PINP levels decreased thereafter but remained elevated at 2 and 3 mo and then returned to baseline by 6 mo. There were no significant changes in the placebo group.

The pattern was very similar with serum OC. Mean increments were largest with the 2.5 mg dose with a peak increment of 29.4% above baseline at month 1 ($P < .01$ for both titrated and non-titrated), sustained increments (of lesser degree) at months 2 and 3, and levels back to baseline by month 6.

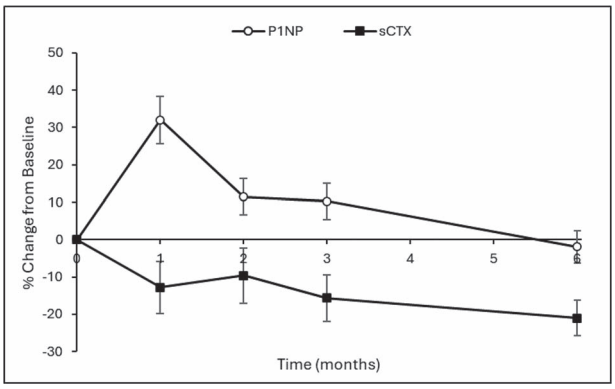

Figure 2. Serum PINP and Serum CTX During the 6-month Treatment with 2.5 mg of Oral PTH. Mean percent change from baseline ± SE. Subjects randomized to 2.5 mg titrated were grouped with the 1.5 mg group at Month 1. Subjects randomized to 2.5 mg titrated are grouped with the 2.5 mg group at Month 2 and beyond.

Changes in CTX levels were also dose dependent but the pattern was very different for CTX vs the bone formation markers. In the 2.5 mg group, mean levels declined slightly below baseline at 1 and 2 mo and at 3 mo the decline was −15.7% ($P = .02$). The CTX level remained 21% below baseline at month 6 ($P < .01$). There were no significant changes at any time point during treatment with placebo.

Using a mixed model of repeated measures analysis over 3 mo which included the placebo, 1.5 mg, and pooled 2.5 mg groups, there were group differences for all biochemical markers ($P < .05$). The time-group interaction for PINP was also statistically significant ($P < .01$), while the time group interaction for OC showed a trend ($P = .07$) and for CTX, there was no time group interaction ($P = .58$).

Bone mineral density

BMD increments were also dose dependent. As shown in Table 3 and Figure 3, in the pooled (titrated and non-titrated) 2.5 mg treatment arm, mean percent change from baseline to month 6 was 2.57% at LS, 1.34% at TH, and 1.98% at FN (all $P \leq .04$). Non-significant decreases were observed at all 3 sites in the placebo group. The change in BMD at month 6 with 2.5 mg vs the placebo group at the LS was 2.73% (95% CI, 0.64–4.82), TH 1.84% (95% CI, 0.37–3.31), and FN 2.76% (95% CI, 1.14–4.38) (all $P \leq .01$).

Additional analyses were performed to compare the effect on BMD between the participants who received the constant 2.5 mg daily tablet dose for 6 mo (non-titrated group) and those whose dose had been titrated and received 2.5 mg daily only during months 3 through 6 (a total of 4 mo), following treatment with lower 1.5 mg and 2.0 mg doses during months 1 and 2, respectively. At the LS, the increase observed in the non-titrated 2.5 mg treatment arm compared to placebo was 3.78% and in the titrated 2.5 mg arm compared to placebo, the treatment difference was 2.2%. At the FN and TH sites, the BMD gains were slightly larger in the titrated subgroup vs the non-titrated subgroup although the differences were not significant (Table 3).

Table 1. Baseline demographic and clinical characteristics.

Variable	Placebo	Oral PTH 0.5 mg	Oral PTH 1.0 mg	Oral PTH 1.5 mg	Oral PTH 2.5 mg non-titrated[a]	Oral PTH 2.5 mg titrated[a]	Total ($N = 161$)
	Demographics, mean ± SD						
N	43	25	29	28	19	17	161
Age, yr	59.9 ± 5.1	61.2 ± 6.0	62.4 ± 4.7	61.4 ± 6.5	62.4 ± 4.1	61.9 ± 5.3	61.3 ± 5.4
Height, cm	162.2 ± 4.5	159.7 ± 7.2	159.2 ± 5.6	160.6 ± 5.0	159.0 ± 6.6	158.7 ± 6.1	160.3 ± 5.8
Weight, kg	65.6 ± 13.0	68.7 ± 10.9	65.9 ± 13.7	65.2 ± 12.0	70.0 ± 10.6	65.1 ± 10.2	66.6 ± 12.0
BMI, kg/m²	25.0 ± 5.2	27 ± 4.0	25.9 ± 4.7	25.3 ± 4.9	27.7 ± 3.6	26.0 ± 4.6	26 ± 4.7
	Serum biochemical markers of bone formation and resorption, mean ± SD (PP1 Population)						
N	40	21	25	23	10	13	–
PINP, ng/mL	64.7 ± 19.0	58.7 ± 20.8	60.5 ± 22.2	66.4 ± 23.0	68.6 ± 18.1	61.8 ± 18.9	–
Osteocalcin, ng/mL	24.4 ± 8.8	21.1 ± 4.3	24.7 ± 8.7	24.9 ± 6.7	32.6 ± 18.9	22.3 ± 13.3	–
Serum CTX, ng/mL	0.44 ± 0.20	0.36 ± 0.10	0.40 ± 0.20	0.46 ± 0.21	0.51 ± 0.26	0.43 ± 0.30	–
	BMD T Score, mean ± SD (PP2 Population)						
N	43	25	29	28	19	17	161
LS	−2.37 ± 0.65	−2.45 ± 0.80	−2.35 ± 0.71	−2.32 ± 0.88	−2.38 ± 0.69	−2.02 ± 0.78	−2.34 ± 0.74
FN	−2.17 ± 0.54	−2.16 ± 0.55	−2.10 ± 0.62	−2.02 ± 0.46	−2.24 ± 0.49	−2.30 ± 0.47	−2.15 ± 0.53
TH	−1.94 ± 0.61	−1.94 ± 0.57	−1.72 ± 0.61	−1.77 ± 0.52	−1.87 ± 0.67	−1.85 ± 0.71	−1.85 ± 0.61

[a] A total of 36 patients were randomized to the 2.5 mg dose group; – = not calculated

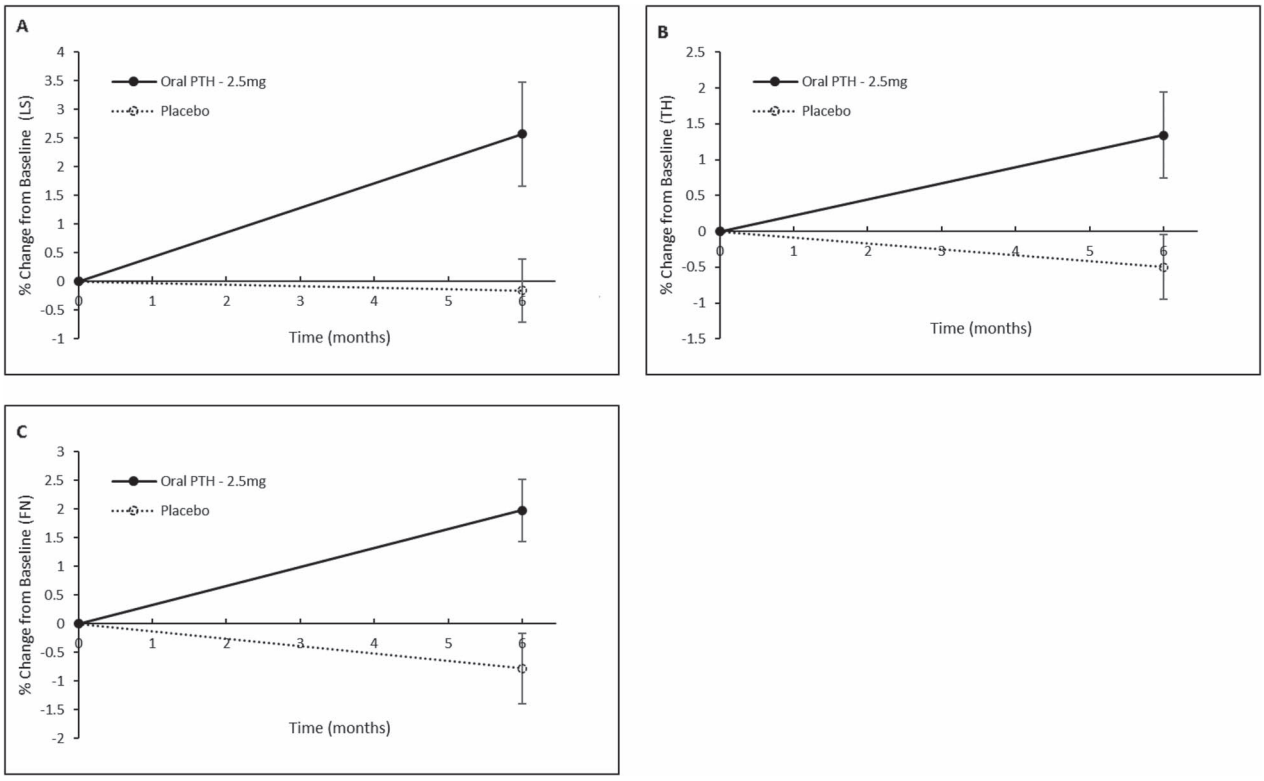

Figure 3. Percent Change from Baseline in BMD at Different Sites Following 6-month Treatment with Oral PTH 2.5 mg. Mean ± SE percent change in BMD from baseline with 2.5 mg (pooled titrated and non-titrated) oral PTH (black lines; n=21) or placebo (dashed lines; n=38) in Lumbar Spine (A), Total Hip (B), and Femoral Neck (C).

Safety and tolerability

Oral PTH daily tablets were generally safe and well tolerated. The AE rates in women treated with the lower daily oral PTH tablet doses (0.5 mg: 68%, 1.0 mg: 55.2%, and 1.5 mg: 67.9%) were similar to the incidence of AEs in those treated with placebo (67.4%), but slightly higher in the 2.5 mg groups (non-titrated: 89.5%, titrated: 82.4%). However, the slightly higher incidence of drug-related AEs (73.7%) in women treated with 2.5 mg tablets daily from day 1 (non-titrated group) was mitigated with the titrated approach (47.1%) and similar to the incidence of drug-related AEs reported in the lower dose treatment groups (32%, 31%, and 50% respectively) and close to the reported incidence in the placebo group (23.3%).

Nineteen participants discontinued the study medication due to AEs—3 in the placebo group, 2 in the 0.5 mg group, 2 in the 1 mg group, 3 in the 1.5 mg group, 7 in the 2.5 mg group, and 2 in the 2.5 mg titrated group. Not all participants who discontinued study medication withdrew from the study. In 10 women, the AEs leading to discontinuation were considered

Table 2. Percent change from baseline in PINP, osteocalcin, and CTX at months 1, 2, 3, and 6 for oral PTH and placebo groups.

Biomarker	Oral PTH dose/placebo	Month 1[a]				Month 2[b]				Month 3				Month 6			
		N[f]	Mean ± SE	*P*-value vs baseline[c]	*P*-value vs placebo[d]	*N*[f]	Mean ± SE	*P*-value vs baseline[c]	*P*-value vs placebo[d]	*N*[f]	Mean ± SE	*P*-value vs baseline[c]	*P*-value vs placebo[d]	*N*[f]	Mean ± SE	*P*-value vs baseline[c]	*P*-value vs placebo[d]
PINP	Placebo	40	0.2 ± 2.8	.95		37	-3.3 ± 3.1	.30		40	1.8 ± 3.5	.62		37	0.4 ± 3.4	.90	
	0.5 mg	21	2.7 ± 4.2	.52	.44	21	6.7 ± 3.6	.08	.01	21	3.2 ± 4.9	.53	.33	21	7.8 ± 6.2	.22	.2426
	1.0 mg	24	11.5 ± 3.1	<.01	.008	25	5.2 ± 3.3	.13	.03	25	6.1 ± 3.1	.07	.17	26	-2.0 ± 4.2	.64	.6441
	1.5 mg	36	18.9 ± 3.7	<.01	<.0001	23	9.0 ± 4.1	.04	.007	23	2.3 ± 4.4	.60	.61	21	-4.9 ± 5.2	.36	.3405
	2.5 mg non-titrated	10	32.0 ± 6.3	<.01	<.0001	10	19.1 ± 7.1	.03	.0014	10	12.0 ± 6.3	.09	.0882[e]	7	-6.1 ± 5.6	.32	.5337
	2.5 mg titrated[a]	13	18.5 ± 7.6	.03	.003	13	5.6 ± 7.6	.41	.0701	13	9.0 ± 7.3	.25	.1114[e]	14	0.2 ± 6.0	.98	.9617
Osteocalcin	Placebo	40	-2.9 ± 2.2	.19		37	-1.8 ± 2.4	.47		40	1.4 ± 2.9	.65		37	1.0 ± 3.5	.77	
	0.5 mg	21	5.5 ± 4.0	.18	.05	21	5.2 ± 4.4	.28	.14	21	11.2 ± 4.8	.03	.054	21	8.6 ± 5.5	.14	.15
	1.0 mg	24	3.7 ± 3.5	.30	.12	25	0.7 ± 3.8	.86	.55	25	2.4 ± 4.3	.44	.53	26	-4.6 ± 4.5	.32	.23
	1.5 mg	36	12.5 ± 2.3	<.01	<.0001	23	8.5 ± 3.3	.02	.02	23	12.4 ± 5.0	.02	.03	21	1.6 ± 5.3	.76	.92
	2.5 mg non-titrated	10	29.4 ± 8.2	<.01	<.0001	10	23.3 ± 8.3	.02	.0005	10	7.4 ± 5.2	.19	.3429	7	6.9 ± 6.1	.30	.5923
	2.5 mg titrated[a]	13	14.0 ± 4.3	<.01	.0021	13	17.3 ± 3.2	<.01	.0002	13	20.5 ± 5.1	<.01	.0009	14	5.2 ± 5.0	.32	.3207
Serum CTX	Placebo	40	5.7 ± 5.4	.30		37	5.8 ± 5.2	.27		40	9.9 ± 7.5	.19	—	37	14.7 ± 7.9	.07	
	0.5 mg	21	9.0 ± 8.4	.29	.66	21	5.8 ± 2.0	.26	.86	21	10.5 ± 7.7	.19	.87	21	13.7 ± 9.2	.15	.99
	1.0 mg	24	1.9 ± 5.6	.74	.70	25	-3.8 ± 4.9	.44	.26	25	-5.3 ± 5.6	.35	.73	26	-9.3 ± 6.8	.18	.90
	1.5 mg	36	-8.9 ± 3.9	.03	.64	23	0.5 ± 5.1	.93	.54	23	3.5 ± 7.0	.62	.84	21	-6.7 ± 8.9	.46	.90
	2.5 mg non-titrated	10	-12.8 ± 7.0	.10	.0006	10	-3.3 ± 11.0	.77	.0032	10	-13.1 ± 9.5	.20	.0004	7	-22.0 ± 7.9	.03	<.0001
	2.5 mg titrated[a]	13	-15.2 ± 6.9	.05	.6634	13	-14.6 ± 10.1	.17	.9122	13	-17.7 ± 8.4	.06	.5805	14	-20.5 ± 6.2	<.01	.9388

[a] Subjects randomized to 2.5 mg titrated were grouped in the 1.5 mg group for month 1 ($N = 23 + 13$), their data are also presented separately ($N = 13$) [b] Subjects randomized to 2.5 mg titrated are grouped in the 2.5 mg group [c] *P*-value: by paired *t*-test (within group) [d] ANOVA with no adjustments was applied: *P*-values are presented for each dose group compared to placebo. [e] For the pooled 2.5 mg group, PINP change was 10.3% vs placebo 1.8% ($P < .04$) [f] *N* = number of subjects PP Logarithmic transformation was applied for PINP (serum N-terminal propeptide of Type 1 collagen) values at month 1 and month 2

Table 3. Percent change from baseline in BMD at different sites following 6-mo treatment with different doses of oral PTH.

Parameter	Treatment arms						
	Placebo (*N* = 38)	0.5 mg Oral PTH (*N* = 22)	1.0 mg Oral PTH (*N* = 26)	1.5 mg Oral PTH (*N* = 21)	2.5 mg Oral PTH (pooled) (*N* = 21)	2.5 mg Oral PTH (non-titrated) (*N* = 7)	2.5 mg Oral PTH (titrated) (*N* = 14)
LS							
Mean (%)	−0.16	−0.20	0.84	1.87	2.57	3.62	2.04
SD (%)	3.38	3.11	3.08	3.13	4.19	2.66	4.78
SE (%)	0.55	0.66	0.60	0.68	0.91	1.01	1.28
P-value vs baseline[a]	.78	.76	.18	.01	.01	.01	.13
P-value vs placebo[b]		.91	.43	.01	.002	.007	.02
FN							
Mean (%)	−0.78	−0.01	−0.38	0.77	1.98	1.64	2.14
SD (%)	3.84	2.07	2.67	3.25	2.48	1.28	2.93
SE (%)	0.62	0.44	0.52	0.71	0.54	0.48	0.78
P-value vs baseline[a]	.22	.98	.48	.29	<.01	.01	.02
P-value vs placebo[b]		.35	.61	.06	.001	.06	.003
TH							
Mean (%)	−0.50	0.73	0.27	1.10	1.34	0.88	1.57
SD (%)	2.78	2.31	2.30	2.78	2.75	2.48	2.94
SE (%)	0.45	0.49	0.45	0.61	0.60	0.94	0.79
P-value vs baseline[a]	.28	.15	.56	.09	.04	.38	.07
P-value vs placebo[b]		.08	.25	.03	.01	.20	.01

Mean = Arithmetic Mean [a] *P*-value: by paired *t*-test (within group) [b] ANCOVA for difference between groups and placebo, adjusted to the following covariates: change in weight and BMI, age and years since menopause; with no adjustments for multiple comparisons was applied: *P*-values are presented for each dose group compared to placebo

drug-related by the investigator including 4 women in the non-titrated 2.5 mg dose group but none in the titrated 2.5 mg dose group.

In the 2.5 mg dose group, many of the drug-related AEs reported in the study are known to be associated with subcutaneous PTH treatment, including palpitations (non-titrated 1/19, titrated 2/17, placebo 0/43), nausea (non-titrated 7/19, titrated 5/17, placebo 1/43), dizziness (non-titrated 5/19, titrated 1/17, placebo 2/43), and headache (non-titrated 3/19, titrated 3/17, placebo 2/43). The AEs described above were mild to moderate and transient. There was no increase in the incidence of abdominal pain with oral PTH vs placebo. The 2.5 mg non-titrated group also had the highest incidence of participants who discontinued study medication due to AEs and drug-related AEs (37% and 21%). In contrast, in the 2.5 mg titrated group, only one participant discontinued the study following an AE that was not drug-related.

A total of 5 serious AEs were reported in 5 women, distributed across all treatment arms, including placebo, and none were drug-related. No participants discontinued study medication due to a serious AE.

Elevated serum calcium concentrations (exceeding the upper limit of the reference range) at any visit were observed in 4 of 43 (9.8%) women treated with placebo and observed with a lower incidence in all oral PTH treatment groups except the 1.5 mg group in which the incidence was 5 of 28 (19.3%). These were transient and no other clinically significant changes in weight, vital signs, or lab values were observed. There was no significant change in mean serum calcium in any treatment group.

Discussion

Anabolic agents produce superior effects on fracture risk reduction and BMD gain compared with antiresorptive agents and are indicated for patients with osteoporosis at high and very high risk for fractures.[5] An oral route of administration is likely to improve patients' acceptance and utilization of anabolic treatment, as many patients are reluctant to use an injectable medication.[11] In this phase 2 study, oral PTH provided statistically significant, dose-dependent effects on biochemical markers and BMD, with a rapid increase in markers of bone formation, a decrease in bone resorption, and a significant increase in spine, TH, and FN BMD over 6 mo. Oral PTH was well tolerated through the top 2.5 mg dose when the dose was titrated and there were no drug-related serious AEs. Oral PTH might substantially reduce the anabolic medication treatment gap in patients with osteoporosis who do not accept treatment with a subcutaneous anabolic medication.

The change from baseline in LS BMD seen in this study was greater in the 2.5 mg non-titrated group (3.62%) than in the 2.5 mg titrated group (2.04%). In contrast, increments in TH and FN BMD were larger in the titrated group. Although a smaller effect on BMD might be anticipated due to the lower doses given during titration in the first and second months of treatment, this was observed only at the LS BMD site. The apparent difference was not statistically significant, possibly related to the higher withdrawal rate in the non-titrated group and the resultant smaller sample size. Thus, pooled data for the 2.5 mg titrated and non-titrated treatment groups are likely to provide the best representation of the effects on BMD.

In a phase 2 study of abaloparatide[16] (which included a daily subcutaneous teriparatide injection arm) in a population of postmenopausal women with similar baseline characteristics, the spine BMD increase with teriparatide injection vs placebo (3.9%) at 6 mo was similar to the increase seen in the non-titrated 2.5 mg group (3.8%) who received the dose for the full 6-mo period. More importantly, in that study, changes in BMD of the TH (0.3% vs placebo) and FN (0.2% vs placebo) after 6 mo of daily subcutaneous teriparatide were not significant and were smaller than the BMD increments

in the TH (1.84% vs placebo) and FN (2.76% vs placebo) seen with 2.5 mg oral tablets in this study. In another study,[20] in the active control group treated with daily subcutaneous teriparatide, mean changes in LS BMD vs placebo (3.9%) were similar to the increases seen with the oral 2.5 mg dose in this study. However, again, BMD changes at the FN and TH with daily subcutaneous teriparatide injections were not significant and were numerically smaller than those observed with the oral 2.5 mg treatment.

The greater effect on TH BMD with the oral 2.5 mg is especially meaningful in light of recent meta-analyses that have shown a strong correlation between TH BMD increases and fracture risk reduction at all skeletal sites. Based on these studies,[21-23] TH BMD changes vs placebo have been proposed as a surrogate for fracture risk reduction. TH BMD changes during treatment vs placebo that exceed surrogate threshold effects (STEs) were highly predictive of fracture risk reduction. The proposed STEs for fracture risk reduction were 1.42% for vertebral fractures, 1.83% for all fractures, 2.13% for nonvertebral fractures, and 3.18% for hip fractures, based on 24-mo TH BMD increase vs placebo. In the current study, oral 2.5 mg daily produced a 1.84% increase in TH BMD vs placebo after only 6 mo of treatment.

In the current study, the effect of daily oral PTH tablets increased the biochemical markers of bone formation—PINP and OC, although the extent and duration differ from that seen with daily subcutaneous teriparatide injections.[16] In contrast to the concomitant increase in resorption markers seen with daily subcutaneous teriparatide injections,[16,18,19] with oral PTH tablets, progressive modest decreases in serum CTX were observed. Thus, 2.5 mg daily dose does not appear to increase bone remodeling. Differences in the pharmacokinetic profile with a shorter duration of exposure to hPTH(1-34) in the blood following oral vs subcutaneous PTH administration, due to prolonged absorption from the injection site, might play a role in determining the balance between bone formation (anabolic) and resorption markers and differential regional (LS vs proximal femur) skeletal responses on BMD. Although the biological plasma half-life of PTH is very short (~4 min) and similar between the oral formulation and subcutaneous injection, the length of the absorption phases is different. Subcutaneous hPTH(1-34) is gradually mobilized from the injection site into blood over several hours, with an apparent terminal elimination half-life of about 1 h. In contrast, the absorption phase of hPTH(1-34) following oral PTH administration is much shorter, resulting in a significantly shorter overall duration of exposure.

The biochemical marker pattern observed with subcutaneous teriparatide injections given once or twice weekly was similar to that seen in this study. Treatment with 56.5 μg teriparatide subcutaneously once weekly[24] produced peak OC and PINP increments of 25% and 15%, respectively, after 1 mo, similar to the 30% peak increments observed with both markers in the current study. Also, with once weekly subcutaneous teriparatide, the bone resorption marker decreased to a minimum of 12%, similar to the 20% decline observed with the oral tablet, and distinct from the increase in bone resorption indices seen with daily subcutaneous teriparatide. With subcutaneous teriparatide delivered as 28.2 μg twice weekly, a similar biochemical marker pattern was observed.[25] With once and twice weekly subcutaneous teriparatide administration, it is possible that osteoclastic activity decreases as plasma PTH levels return to baseline between doses, while osteoblast activity triggered by the single dose continues with a more persistent effect between doses. This could produce a more favorable bone balance, with a greater proportionate increase in modeling-based bone formation. At 6 mo, once weekly subcutaneous teriparatide improved BMD at the spine and hip to a similar extent as shown here with the oral 2.5 mg tablet and reduced vertebral fracture risk markedly. A dual effect with an increase in bone formation and a decrease in bone resorption is also seen with the sclerostin antibody, romosozumab,[26,27] though the maximal anabolic effects are larger than those seen here with oral PTH tablets. Agents or regimens that produce a biochemical marker pattern showing increased bone formation and decreased bone resorption, might augment bone mass with less stimulation of new bone remodeling and less concern regarding potential impact on cortical porosity, compared with the standard 20 μg daily dose of subcutaneous teriparatide. This could have potential benefit particularly for skeletal sites rich in cortical bone. Longer studies of oral PTH tablets are required to evaluate this hypothesis.

There are limitations to the current study. Like most phase 2 studies of novel treatments, the sample size was relatively small, and the duration of treatment was limited to 6 mo. Standard exclusions included participants with clinically significant cardiovascular, renal, hepatic, respiratory, neurological, psychiatric or active substance abuse. Since prior recent treatment with an osteoporosis drug might alter the effects of a subsequent treatment, untreated participants or those with only remote prior treatment were selected for this phase 2 study. The estimated PINP effect was larger than the observed effect; however, even with the smaller sample size, a significant increase in PINP was observed. The interim analysis showed that the 2 lowest doses had little to no effect and changed the protocol mid-stream to incorporate a higher dose of oral PTH. There were no clinically meaningful differences in the baseline characteristics of women who entered the study after the addition of the 2.5 mg dose vs women who entered at the start of the study, but the randomization process may not have accounted for unknown participant characteristics.

At the highest dose (2.5 mg), there were some AEs likely associated with vasodilation, as has been described in all studies evaluating PTH receptor agonist therapies including daily subcutaneous teriparatide and abaloparatide.[28] This led to a titration protocol of the dose up from 1.5 mg to the full 2.5 mg for more than half of the participants randomized to the 2.5 mg treatment regimen. Although this titration protocol was highly effective at improving dose tolerability, these women received the full 2.5 mg dose for only the latter 4 of the 6 mo. Thus, the BMD gain seen at 6 mo may be an underestimate. A longer study is required to determine the full potential of this novel orally administered teriparatide tablet.

In conclusion, this study showed dose-dependent effects of oral PTH treatment on both biochemical markers and BMD gain over 6 mo. At the 2.5 mg dose, markers of bone formation increased rapidly, and the marker of bone resorption declined. At 6 mo, the magnitude of BMD gain in the hip and spine is consistent with predicted efficacy against fractures. With a titration up to the full 2.5 mg dose, the medication was very well tolerated. These data strongly suggest that 2.5 mg oral tablets could be a safe and effective treatment for osteoporosis and the first non-injectable anabolic alternative for patients at high and very high risk of fracture.

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Conflicts of interest

1. Service on Advisory Board
2. Service on Board of Directors
3. Consulting (other than Advisory Boards or Board of Directors)
4. Position in a company, employment or executive position in pharmaceutical, medical device, or diagnostic companies; including industry scientists in the bone and mineral field
5. Honoraria or royalties for books or publications or for lectures (speaker fees) or participating in a speakers bureau
6. Research grants, direct salary support or other financial support from commercial entities
7. Stock holdings and/or stock options in pharmaceutical, medical device, or diagnostic companies

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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14. IS-3000 IDS-iSYS CTX-I (CrossLaps⌐) IFU.
15. IS-2900 IDS-iSYS N-MID⌐ Osteocalcin IFU.
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