Efficacy and safety of recombinant human parathyroid hormone (1–84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study

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Summary

Background Hypoparathyroidism results in impaired mineral homoeostasis, including hypocalcaemia and hyperphosphataemia. Treatment with high-dose oral calcium and active vitamin D does not provide adequate or consistent control of biochemical indices and can lead to serious long-term complications. We aimed to test the efficacy, safety, and tolerability of once-daily recombinant human parathyroid hormone 1–84 (rhPTH[1–84]) in adults with hypoparathyroidism.

Methods In this double-blind, placebo-controlled, randomised phase 3 study (REPLACE), we recruited patients with hypoparathyroidism (≥18 months duration) aged 18–85 years from 33 sites in eight countries. After an optimisation period, during which calcium and active vitamin D doses were adjusted to achieve consistent albumin-corrected serum calcium, patients were randomly assigned (2:1) via an interactive voice response system to 50 µg per day of rhPTH(1–84) or placebo for 24 weeks. Active vitamin D and calcium were progressively reduced, while rhPTH(1–84) could be titrated up from 50 µg to 75 µg and then 100 µg (weeks 0–5). The primary endpoint was the proportion of patients at week 24 who achieved a 50% or greater reduction from baseline in their daily dose of oral calcium and active vitamin D while maintaining a serum calcium concentration greater than or the same as baseline concentrations and less than or equal to the upper limit of normal, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00732615.

Findings Between June 23, 2009, and Feb 28, 2011, 134 eligible patients were recruited and randomly assigned to rhPTH(1–84) (n=90) or placebo (n=44). Six patients in the rhPTH(1–84) group and seven in the placebo group discontinued before study end. 48 (53%) patients in the rhPTH(1–84) group achieved the primary endpoint compared with one (2%) patient in the placebo group (percentage difference 51·1%, 95% CI 39·9–62·3; p<0·0001). The proportions of patients who had at least one adverse event were similar between groups (84 [93%] patients in the rhPTH[1–84] group *vs* 44 [100%] patients in the placebo group), with hypocalcaemia, muscle spasm, paraesthesias, headache, and nausea being the most common adverse events. The proportions of patients with serious adverse events were also similar between the rhPTH(1–84) group (ten [11%] patients) and the placebo group (four [9%] patients).

Interpretation 50 µg, 75 µg, or 100 µg per day of rhPTH(1–84), administered subcutaneously in the outpatient setting, is efficacious and well tolerated as a PTH replacement therapy for patients with hypoparathyroidism.

Funding NPS Pharmaceuticals.

Introduction

Hypoparathyroidism is a rare disorder characterised by absent or deficient production of parathyroid hormone (PTH). PTH deficiency is responsible for impaired mineral homoeostasis, which is disrupted in several ways: calcium absorption is impaired due to reduced renal conversion of 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D; hypercalciuria results from reduced PTH-dependent renal calcium reabsorption; and bone turnover is decreased.[1–3] Hormone deficiency states are usually treated by replacing the deficient hormone; however, this disorder is currently managed with large doses of oral calcium and active vitamin D metabolites or analogues, an approach that does not always provide adequate or consistent control of biochemical and clinical aspects of the disease. Adverse short-term and long-term complications include large swings in serum calcium concentrations and risks of calcifications in the kidney, brain, and elsewhere.[4] Without the calcium-conserving effects of PTH in the distal renal tubule, hypercalciuria, kidney stones, and reduced renal function can occur.[5,6]

Human PTH(1–34), an active fragment of full length endogenous PTH(1–84), has been studied as a PTH replacement therapy in hypoparathyroidism.[7–12] Winer and colleagues[7–12] have shown the feasibility of PTH

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replacement therapy; however, PTH(1–34) has a short half-life and has not been approved for this indication. By contrast, recombinant human (rh)PTH(1–84), which is identical in structure to the full-length endogenous hormone, is associated with a longer calcaemic effect when injected into the thigh[13] than is rhPTH(1–34) injected into the abdomen.[14] Serum calcium returns to baseline concentrations 24 h after administration of rhPTH(1–84), making this compound suitable for once-daily administration for hypoparathyroidism.[15–18]

In the REPLACE study, we aimed to test the efficacy, safety, and tolerability of a once-daily flexible dose (50 µg, 75 µg, or 100 µg) regimen of rhPTH(1–84) in adults with hypoparathyroidism, to assess whether rhPTH(1–84) is an effective replacement therapy in this population of patients.

Methods

Study design and patients

In this randomised, placebo-controlled, double-blind registration trial, we recruited patients aged 18–85 years who had well documented hypoparathyroidism for 18 months or longer from 33 outpatient sites in eight countries: USA (20), Canada (3), Denmark (3), Hungary (3), Belgium (1), France (1), Italy (1), and the UK (1). Hypoparathyroidism was defined as hypocalcaemia (calcium concentration below the lower limit of normal) and documented PTH concentrations below the lower limit of the normal range, recorded on at least two occasions within the previous 12 months. Additional eligibility criteria were: a requirement for active vitamin D and oral calcium (≥1000 mg daily) treatment, normal thyroid-stimulating hormone concentrations if not on thyroid hormone replacement therapy (or if on therapy, the dose had to have been stable for ≥3 months), and normal magnesium and serum 25-hydroxyvitamin D concentrations. Creatinine clearance needed to be either greater than 30 mL per min on two separate measurements, or greater than 60 mL per min (one measurement) with an accompanying serum creatinine concentration of less than 132·6 µmol/L. We excluded patients with a known activating mutation in the calcium-sensing receptor gene; additional exclusion criteria are listed in the appendix.

See Online for appendix

The protocol and any amendments were approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all patients. An external data and safety monitoring board was assigned to assess data throughout the study.

The study consisted of three periods: optimisation of oral calcium and active vitamin D doses, correction of vitamin D and magnesium deficiencies, and discontinuation of thiazides (2–16 weeks); treatment (24 weeks); and follow-up (4 weeks; appendix). During optimisation, oral calcium was replaced with calcium citrate or calcium carbonate (both provided by NPS Pharmaceuticals, Bedminster, NJ, USA) according to patient preference. Active vitamin D (calcitriol or alfacalcidol, provided by the sites' pharmacies or by prescription) and oral calcium doses were adjusted to achieve consistent albumin-corrected serum calcium concentrations between 1·87 mmol/L and the laboratory upper limit of normal range, but ideally within the target range of 2·0–2·25 mmol/L. Any deficiencies in serum 25-hydroxyvitamin D (<75 nmol/L) or magnesium (<0·65 mmol/L) concentrations were corrected. After calcium and active vitamin D doses were optimised and had remained stable for 2 weeks—which established baseline doses—randomisation took place. Data was originally obtained and analysed using conventional units before being converted to SI units. For equivalent conventional units, please see the appendix.

Randomisation and masking

Eligible participants were randomly assigned via an interactive voice response system in a 2:1 ratio to receive 50 µg of rhPTH(1–84) (NPS Pharmaceuticals) once daily or placebo. Randomisation was centrally administered by ClinPhone (Perceptive Informatics, East Windsor, NJ, USA), using a randomisation list generated by Quintiles (Raleigh/Durham, NC, USA). Simple block randomisation was applied without use of stratification factors. Patients and investigators, including those administering the care and those assessing the outcomes, were masked to treatment allocation throughout the 24 week dosing period. Laboratory results for bone marker and PTH concentrations were not accessible to the medical monitors, sponsor personnel, or study site personnel. To maintain blinding, each multidose injection pen cartridge contained a clear, colourless solution with 14 doses of an identical injection volume (0·07 mL) for each dose, irrespective of treatment group or assigned dose. None of the blinding was broken in this study.

Procedures

The prescribed dose of rhPTH(1–84) or placebo was self-administered subcutaneously in the thigh every morning with a multidose injection pen device. Blood tests were done at each scheduled assessment before injecting the study drug or taking oral medication.

The 24 week treatment period began with a 12 week titration phase, during which the doses of active vitamin D were reduced and, if possible, eliminated, followed by reduction in oral calcium doses, while maintaining serum calcium at or above the concentration recorded at baseline. During the titration phase, the investigator could increase the daily dose of rhPTH(1–84) at week 2 to 75 µg and again at week 4 up to the maximum dose of 100 µg to allow active vitamin D and oral calcium doses to be reduced until active vitamin D could be eliminated and oral calcium could be reduced to 500 mg per day or less. Details of the titration protocol are presented in the appendix.

Patients then entered a 12 week maintenance phase, when oral calcium and active vitamin D doses were adjusted as appropriate to maintain serum calcium and avoid hypercalciuria or raised concentrations of serum calcium–phosphate product (calcium concentration × phosphate concentration). The daily dose of rhPTH(1–84) established during titration could be reduced, but not increased, in this phase.

Assessment visits during the treatment period took place weekly from weeks 0–6 and then at weeks 8, 12, 16, 20, and 24. Two visits took place during follow-up on weeks 25 and 28. At each visit, patients were seen by the study physician and the research assistant. Laboratory values, symptoms described by the patient, adverse events, and medication changes since the last visit were recorded. When doses of oral calcium, active vitamin D, or rhPTH(1–84) were changed, a safety calcium measurement was obtained 3–5 days afterwards.

Albumin-corrected serum calcium concentrations were measured at every visit throughout the treatment period (weekly for weeks 0–6, and then at weeks 8, 12, 16, 20, and 24). Total serum calcium was corrected for albumin concentration using the following formula: serum calcium in mmol/L + (0·02 × [40 – serum albumin in g/L]) or serum calcium in mg/dL + (0·8 × [4·0 – serum albumin in g/dL]). 24 h urinary calcium was measured at baseline (week 0) and weeks 3, 5, 6, 8, 12, 16, and 24. At week 24, rhPTH(1–84) was discontinued and patients resumed their earlier, optimised doses of oral calcium and active vitamin D. Serum calcium concentrations were measured 1 week and 4 weeks after treatment was stopped (weeks 25 and 28 after initiation of treatment).

We assessed compliance by reviewing the rhPTH(1–84) self-dosing records in patients' diaries and by checking, at each visit, the amount of drug injected, wasted, and returned (if any), computed as (number of doses administered/[last dose date – first dose date + 1]) × 100%.

The primary endpoint was the proportion of patients at week 24 who achieved all three of the following criteria: 50% or greater reduction from baseline of oral calcium dose; 50% or greater reduction from baseline of active vitamin D dose; and maintenance of a stable albumin-corrected total serum calcium concentration greater than or equal to baseline concentration and less than or equal to the upper limit of normal, but ideally within the target range of 2·0–2·25 mmol/L. As components of the primary efficacy endpoint, daily doses of oral calcium and of the active vitamin D analogue used were obtained from site investigator prescription data and patient diary data.

Secondary endpoints were the proportion of patients who achieved independence from active vitamin D while taking 500 mg per day or less of oral calcium at week 24, percentage change from baseline in prescribed oral calcium dose by week 24, and changes in frequency of clinical symptoms of hypocalcaemia during maintenance (weeks 16–24). Symptoms of hypocalcaemia were identified by the investigator and included paraesthesias, muscle cramps, hypoaesthesia, tetany, back pain, myalgia, muscle twitching, throat tightness, musculoskeletal pain, anxiety, and seizures. A comprehensive list of all symptoms used to identify hypocalcaemic episodes for this efficacy endpoint is presented in the appendix.

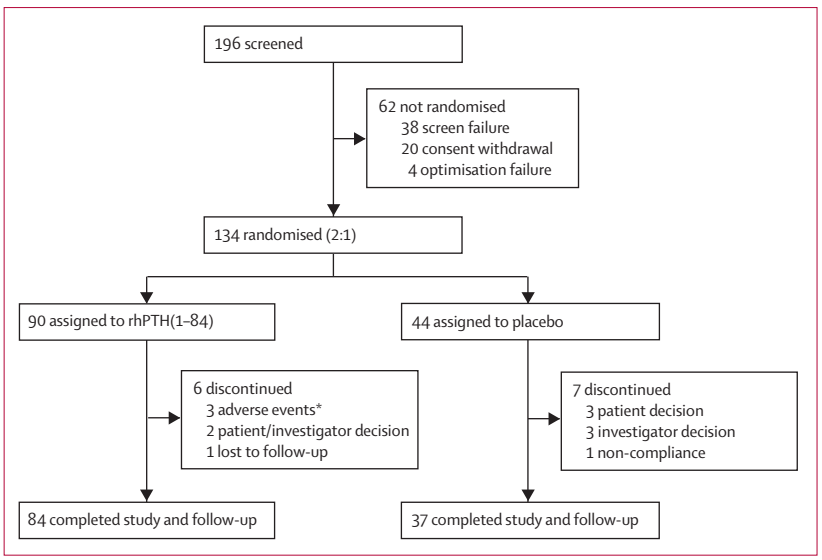

Figure 1: **Trial profile**
rhPTH(1–84)=recombinant human parathyroid hormone 1–84. *Due to hypertension (n=1), stroke (n=1), and several events (n=1, including injection site erythema, arthralgia, asthenia, blepharospasm, decreased appetite, depression, headache, nausea, pain in extremity, and hypercalcaemia).

Prespecified exploratory endpoints included changes in 24 h urine calcium excretion from baseline, and the proportion of patients who had a calcium–phosphate product in the normal range (≤4·4 mmol²/L²) at week 24.

The safety analysis focused on the reports of adverse events and laboratory data, including reports of hypocalcaemia or an increase in blood calcium. For laboratory values, the protocol defined the serum calcium target range to be 1·87 mmol/L to the upper limit of normal. The investigator decided whether values outside that range were of clinical significance and therefore reported as hypocalcaemia or hypercalcaemia.

Statistical analysis

The statistical analysis was done by two employees of NPS Pharmaceuticals. On the basis of 84 patients completing the study in a 2:1 ratio (rhPTH[1–84] *vs* placebo) with an expected proportion of 40% and 10%, respectively, of patients achieving the primary endpoint, the study had 80% power to detect a difference according to a two-tailed Fisher's exact test and an alpha error of 0·05. The intention-to-treat population, for which the primary efficacy analysis was done, included all randomly assigned patients who received at least one dose of study drug and had at least one postbaseline efficacy

	rhPTH(1–84) (n=90)	Placebo (n=44)
Age, years	47·0 (12·2)	48·5 (13·7)
Sex		
Women	69 (77%)	36 (82%)
Men	21 (23%)	8 (18%)
Race		
White	85 (94%)	43 (98%)
Other	5 (6%)	1 (2%)
Geographic region*		
North America	49 (54%)	25 (57%)
Europe	41 (46%)	19 (43%)
Duration of hypoparathyroidism, years	14·1 (11·14)	11·0 (7·98)
≤5 years	19 (21%)	12 (27%)
5–10 years	28 (31%)	14 (32%)
≥10 years	43 (48%)	18 (41%)
Cause of hypoparathyroidism		
Postsurgical	68 (76%)	31 (70%)
Idiopathic	14 (16%)	8 (18%)
Autoimmune disease	5 (6%)	4 (9%)
Known genetic disorder	2 (2%)	1 (2%)
Radiation	1 (1%)	0
Prescribed active vitamin D metabolite/analogue†		
Low dose	6 (7%)	4 (9%)
Medium dose	23 (26%)	12 (27%)
High dose	61 (68%)	28 (64%)
Prescribed calcium		
0–2000 mg per day	61 (68%)	31 (70%)
>2000 mg per day	29 (32%)	13 (30%)
Laboratory variables		
Albumin-corrected total serum Ca, mmol/L	2·12 (0·20)	2·15 (0·15)
Serum phosphate, mmol/L	0·47 (0·07)	0·48 (0·07)
Serum magnesium, mmol/L	0·82 (0·08)	0·82 (0·08)
Serum 25-hydroxyvitamin D, nmol/L	108·08 (45·93)	110·32 (45·18)
Serum 1,25-dihydroxyvitamin D, pmol/L	82·33 (50·16)	78·25 (27·60)
Urine calcium, mg per 24 h	356·6 (189·0)	345·4 (170·7)
Creatinine, μmol/L	87·52 (18·48)	83·10 (21·75)
Calcium-to-creatinine ratio, mg/mg	0·271 (0·1)	0·287 (0·1)
Calcium–phosphate product >4·4 mmol²/L²	1 (1·1%)	0

Data are mean (SD), median (IQR), or number (%), unless otherwise stated. rhPTH(1–84)=recombinant human parathyroid hormone 1–84. *North America consists of Canada and the USA; Europe consists of Belgium, Denmark, France, Hungary, Italy, and the UK. †For calcitriol (as defined in the study), low dose is ≤0·25 μg per day, medium dose is >0·25–0·5 μg per day, and high dose is >0·5 μg per day; for alfacalcidol low dose is ≤0·50 μg per day, medium dose is >0·50–1·0 μg per day, and high dose is >1·0 μg per day.

Table 1: **Patient demographics and baseline characteristics**

measurement. If a patient did not have week 24 data, the efficacy assessment was made using the last observation carried forward. The safety population included all randomly assigned patients who received at least one dose of study drug. All statistical procedures were completed using SAS version 9.1.

The site investigators' prescription records were the primary source for documenting amounts of oral calcium and active vitamin D used. To assess the proportion of patients who achieved the primary endpoint, the two-sided Fisher's exact test was used. Differences between the two groups are presented as their two-sided asymptotic 95% CI. Alfacalcidol dose was converted to calcitriol dose on the basis that 2 μg of alfacalcidol equals 1 μg of calcitriol.

This trial is registered with ClinicalTrials.gov, number NCT00732615.

Role of the funding source

The sponsor of the study participated in study design, data collection, data analysis, data interpretation, and review and approval of the report, and supplied the study drug. All authors had full access to all the data in the study and all had final responsibility for the decision to submit for publication.

Results

Between June 23, 2009, and Feb 28, 2011, 196 patients were screened, of whom 134 were eligible for random assignment to the rhPTH(1–84) (n=90) or placebo groups (n=44; figure 1). All 134 patients were included in the primary efficacy and safety analyses. Patient demographics, baseline characteristics, and laboratory values were similar between the rhPTH(1–84) and placebo groups (table 1). Most patients were women (78%), and the mean age of all patients was 47·5 years (SD 12·71). The most common cause of hypoparathyroidism was postsurgical hypoparathyroidism (74%), with a mean duration of 13 years (SD 10·29). At baseline after optimisation, mean oral calcium dose was 2101 mg per day (SD 1286, range 1000–12 000) and mean calcitriol dose was 0·89 μg per day (0·48, range 0·25–3·0). Baseline mean albumin-corrected total serum calcium concentrations were similar in the two groups (table 1). Mean urinary calcium excretion exceeded 300 mg per 24 h in both groups. At baseline, one patient in the rhPTH(1–84) group and no patients in the placebo group had a calcium–phosphate product that was greater than 4·4 mmol²/L².

Compliance with injection was excellent for both groups, with 80% or higher compliance in 88 (98%) of 90 patients in the rhPTH(1–84) group and 42 (96%) of 44 patients in the placebo group. 47 (52%) patients in the rhPTH(1–84) group completed the study on a rhPTH(1–84) dose of 100 μg per day, 24 (27%) on a dose of 75 μg per day, and 19 (21%) on a dose of 50 μg per day.

A higher proportion of patients in the rhPTH(1–84) group achieved all three criteria for the composite primary endpoint than did those in the placebo group (48 [53%] patients *vs* one [2%] patient; percentage difference 51·1%, 95% CI 39·9–62·3; p<0·0001). Of the patients for whom we had week 24 data, 36 (43%) of 84 patients who received rhPTH(1–84) were able to stop taking active vitamin D and were receiving ≤500 mg per day of oral calcium at week 24, compared with two (5%) of 37 patients who received placebo (p<0·0001).

Analysis of self-dosing data recorded in the patient diaries corresponded with the prescribed dosing data (figure 2).

Between-group differences in the mean decrease from baseline for prescribed doses of both oral calcium (p=0·0016) and active vitamin D (p=0·0035) were apparent from week 3 and continued until week 24 (figure 3); similar results were seen with patient diary data (not shown). Oral calcium and active vitamin D doses throughout the trial are summarised in the appendix. Additionally, the rhPTH(1–84) group had a mean percentage decrease from baseline in oral calcium dose of –52% compared with a 6% mean percentage increase in the placebo group (p<0·0001), and the active vitamin D dose decreased by –78% and –30% in the rhPTH(1–84) and placebo groups, respectively (p<0·0001).

During maintenance (weeks 16–24), a smaller proportion of patients in the rhPTH(1–84) group reported clinical symptoms associated with hypocalcaemia than did those in the placebo group (30 [33%; 95% CI 23·7–44·1] patients *vs* 18 [41%; 26·3–56·8] patients), although the difference was not statistically significant (p=0·39).

At week 24, mean 24 h urinary calcium excretion rates had decreased by 73·6 mg per 24 h (SD 190·2) in the rhPTH(1–84) group and by 83·8 mg per 24 h (169·1) in the placebo group (p=0·57). The mean urinary calcium excretion rate in the placebo group declined by a

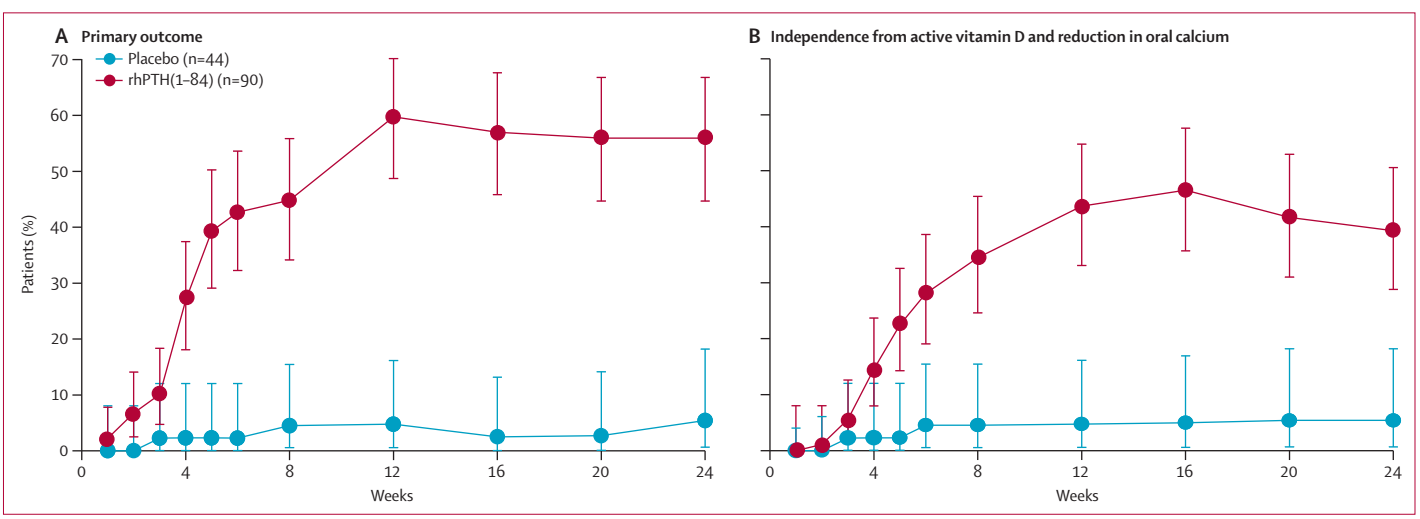

Figure 2: **Achievement of primary outcome and independence from active vitamin D and reduction in oral calcium during treatment period, according to patient diary data**
(A) Proportion of patients achieving the criteria for the primary endpoint throughout the 24 week treatment period. (B) Proportion of patients who were able to stop taking active vitamin D and to reduce their dose of oral calcium dose to ≤500 mg per day throughout the 24 week treatment period. rhPTH(1–84)=recombinant human parathyroid hormone 1–84.

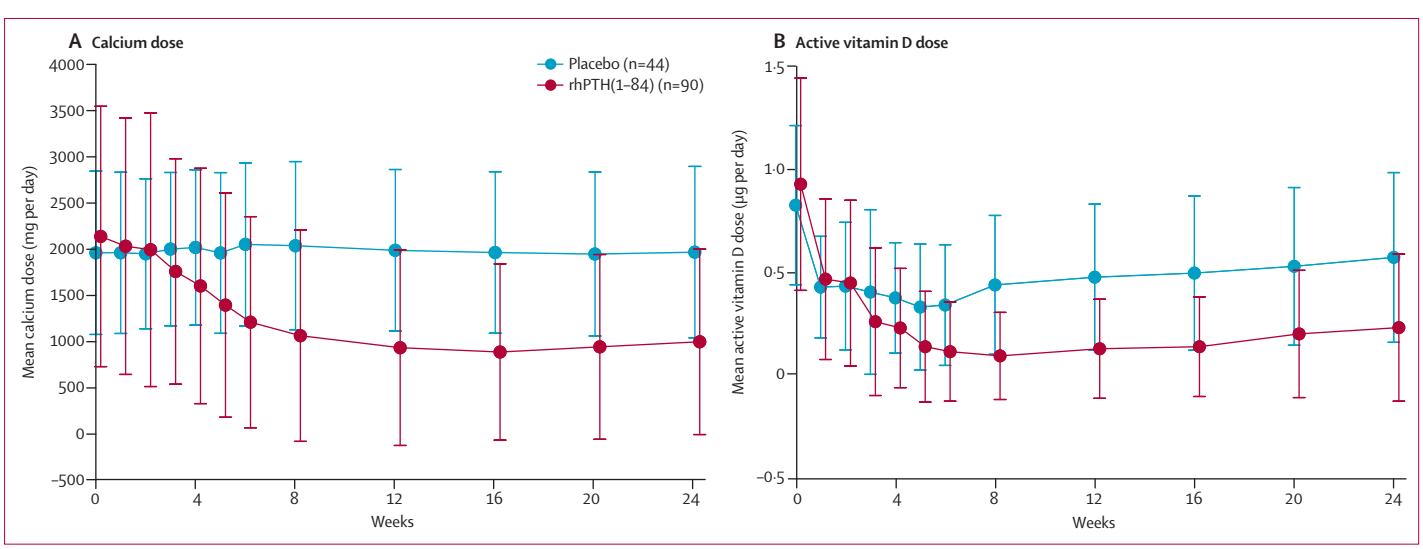

Figure 3: **Changes in calcium and active vitamin D doses throughout treatment period, by treatment group**
Mean oral calcium dose (A) and mean active vitamin D dose (B) in the placebo group and rhPTH(1–84) group throughout the 24 week treatment period. Error bars show SD. rhPTH(1–84)=recombinant human parathyroid hormone 1–84. From weeks 3–24, each mean measurement of calcium dose and active vitamin D dose differed significantly between groups (all p<0·005).

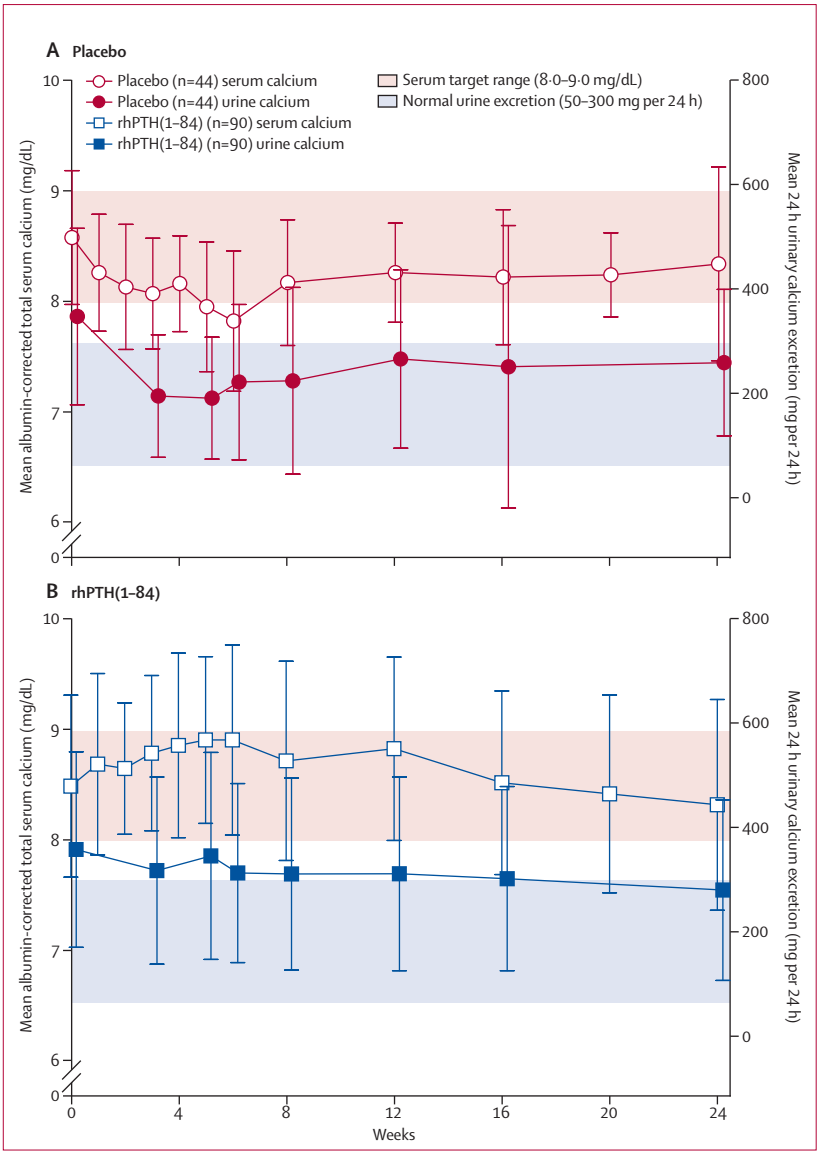

Figure 4: **Changes in albumin-corrected total serum calcium concentrations and 24 h urine calcium excretion throughout treatment period, by treatment group**

Mean albumin-corrected serum calcium concentration and mean 24 hr urinary calcium excretion in the placebo group (A) and rhPTH(1–84) group (B) throughout the 24 week treatment period. Error bars show SD. Every measurement of serum calcium from week 1 to week 16 differed significantly between treatment groups (p=0·018). Each measurement of urine calcium excretion from week 3 to week 8 differed significantly between groups (p=0·015). rhPTH(1–84)=recombinant human parathyroid hormone 1–84.

significantly greater amount from baseline to week 8 than did the urinary calcium concentration in the rhPTH(1–84) group (p=0·015; figure 4). In the placebo group, total serum calcium concentrations fell rapidly and remained close to the lower end of the target range for the duration of the study; mean urinary calcium excretion rate also decreased (figure 4A). By contrast, in the rhPTH(1–84) group, albumin-corrected serum calcium concentrations increased at the start of treatment, despite large reductions in both oral calcium and active vitamin D doses, whereas urinary calcium excretion showed a slight decrease (figure 4B). Post-hoc analysis gave similar results for uncorrected total calcium concentrations (data not shown).

Mean serum phosphate concentrations were similar (at the upper limit of normal) in both groups at baseline (table 1), but fell substantially in the rhPTH(1–84) group upon treatment and remained lower than in the placebo group throughout treatment (p=0·0025 at all timepoints). At week 24, mean serum phosphate concentrations had decreased by 0·05 mmol/L (SD 0·08) in the rhPTH(1–84) group and 0·01 mmol/L (0·07) in the placebo group (p=0·00098). From week 5 to week 23, no patient in either treatment group had greater than 4·4 mmol²/L² of calcium–phosphate product, until week 24, when one patient in the placebo group had a raised calcium–phosphate product of 4·45 mmol²/L². In the rhPTH(1–84) group, the mean calcium–phosphate product decreased from 3·2 mmol²/L² (SD 0·6) at baseline to 2·8 mmol²/L² (0·5) at week 24 (p<0·0001), and in the placebo group from 3·3 mmol²/L² (0·5) to 3·2 mmol²/L² (0·4; p=0·11). Results of a post-hoc analysis showed that the difference in the mean change from baseline to week 24 between the rhPTH(1–84) and placebo groups was significant (p=0·0005).

Mean serum concentration of 25-hydroxyvitamin D decreased in the rhPTH(1–84) group by –28·0 nmol/L (SD 47·4, range –279·6 to 114·8) from baseline to week 24; minimal change was seen in the placebo group (–3·5 nmol/L [32·7, range –102·3 to 44·9]). Mean serum 1,25-dihydroxyvitamin D concentrations were maintained in the normal range in both groups (82·3 pmol/L [SD 50·2] at baseline and 79·4 pmol/L [30·0] at week 24 in the rhPTH[1–84] group *vs* 78·3 pmol/L [27·6] at baseline and 79·0 pmol/L [44·2] at week 24 in the placebo group).

The overall incidences of adverse events were similar in both groups (table 2). By week 28, 84 (93%) patients in the rhPTH(1–84) and 44 (100%) patients in the placebo group had at least one adverse event, with hypocalcaemia, muscle spasm, paraesthesias, headache, and nausea being the most common adverse events (appendix). Ten (11%) patients in the rhPTH(1–84) group and four (9%) in the placebo group had serious adverse events; only one serious adverse event (hypercalcaemia requiring a brief hospital stay) in the rhPTH(1–84) group was regarded as treatment related. The episode of hypercalcaemia occurred 32 days after starting rhPTH(1–84), the study drug had been up-titrated from 50 µg to 75 µg 7 days before the event. The hypercalcaemia resolved and the event did not lead to study discontinuation. The patient enrolled in subsequent extension studies and has been receiving rhPTH(1–84) for more than 24 months without any further episodes of hypercalcaemia.

No significant changes in mean cardiovascular variables (blood pressure, heart rate, or QTc interval) or renal variables (serum creatinine or estimated

creatinine clearance) were reported in either group. Three (3%) patients in the rhPTH(1–84) group discontinued treatment because of adverse events, including one patient who had several adverse events (some of which were judged to be treatment related); the other two patients had adverse events (worsening hypertension, cerebrovascular accident) that were not thought to be related to treatment or the concentration of serum calcium. No adverse events led to discontinuation in the placebo group.

Hypocalcaemia, which is a characteristic of hypoparathyroidism, was frequently reported as an adverse event in both groups throughout the study. During the treatment period, hypocalcaemia was reported as an adverse event in 23 (26%) patients in the rhPTH(1–84) group (43 events) compared with nine (21%) patients in the placebo group (nine events). During follow-up, after rhPTH(1–84) treatment ended and patients returned to baseline oral calcium and active vitamin D doses, hypocalcaemia was reported as an adverse event in a higher proportion of patients in the rhPTH(1–84) group than in the placebo group (28 [31%] patients *vs* four [9%] patients). At week 12, mean peak increases of albumin-corrected total serum calcium concentration measured before and after injection of rhPTH(1–84) were about 0·25 mmol/L or less from the predose baseline 6–10 h after injection; no clear dose–response relation was noted and these transient excursions did not raise any safety concerns. Reports of hypocalcaemia, hypercalcaemia, and hypercalciuria by treatment period are summarised in the appendix.

	rhPTH(1–84)		Placebo	
	Patients (n=90)	Events	Patients (n=44)	Events
Any AE				
No	6 (7%)	NA	0	NA
Yes	84 (93%)	854	44 (100%)	354
AE of highest severity*				
Mild	25 (28%)	..	15 (34%)	..
Moderate	44 (49%)	..	24 (55%)	..
Severe	15 (17%)	..	5 (11%)	..
AEs leading to study discontinuation	3 (3%)	15	0	NA
AEs leading to death	0	NA	0	NA
Serious AEs	10 (11%)	12	4 (9%)	5
Mild	1 (1%)	1	1 (2%)	1
Moderate	3 (3%)	5	2 (5%)	2
Severe	6† (7%)	6	1‡ (2%)	2

Data are number of patients (% of patients) and number of events. If a patient had more than one AE in a category, the patient was counted only once in that category; each event is counted. AE=adverse event. rhPTH(1–84)=recombinant human parathyroid hormone 1–84. *Patients with several adverse events were classified according to their event with the highest severity. †Includes hypocalcaemia (n=2), hypercalcaemia (n=1), pancreatitis (n=1), cerebrovascular accident (n=1), and diarrhoea (n=1); all cases resolved themselves except the case of cerebrovascular accident; none was study drug related except the case of hypercalcaemia. ‡One patient reported asthma or chronic obstructive pulmonary disease that was not study drug related and resolved itself.

Table 2: **Summary of adverse events**

Discussion

This randomised controlled trial provides evidence that rhPTH(1–84) replacement therapy is effective in treating hypoparathyroidism when compared with oral calcium and active vitamin D alone (placebo group). More than half the patients in the rhPTH(1–84) group (53%) reached the primary endpoint, compared with only 2% in the placebo group.

Patients recruited for this trial were representative of the disorder in that even after optimisation of their calcium and vitamin D regimen, 89 (66%) patients were taking high doses of active vitamin D (>0·5 µg calcitriol per day) and 42 (31%) patients were taking high doses of calcium (>2 g per day; table 1). A significantly higher proportion of patients in the rhPTH(1–84) group were able to discontinue all active vitamin D therapy and to reduce their oral calcium dose to 500 mg per day or less compared with the placebo group. Even though many patients who received rhPTH(1–84) had a reduced need for oral calcium and active vitamin D on treatment, not all patients who had this clinical effect met all three criteria of the primary endpoint. This finding is due, in part, to the strict protocol algorithm that focused on eliminating all active vitamin D before reducing oral calcium during titration. This experimental design made it more challenging to achieve 50% or greater reductions in both calcium and active vitamin D while maintaining serum calcium concentrations in the target range. Nevertheless, the results clearly favour the rhPTH(1–84) regimen over placebo. Additional support for the significance of the primary efficacy outcome—which was based on investigator-prescribed doses of oral calcium and active vitamin D—was provided by analysis of data collected via patients' electronic diaries, which documented the doses that were actually taken.

Small changes in serum calcium concentrations lead to substantial changes in the filtered load of calcium.[20] Therefore, unsurprisingly, 24 h urinary calcium excretion in patients in the placebo group was lower at the end of the trial than at baseline, since their mean serum calcium concentration was also lower at the end of the study. Importantly, in the rhPTH(1–84) group, 24 h urinary calcium excretion also showed a slight decrease, whereas serum calcium concentration remained relatively stable (within the target range) despite reductions in oral calcium and active vitamin D. This finding is probably due to the potent renal calcium-conserving actions of rhPTH(1–84) and represents a potential advantage of rhPTH(1–84) replacement therapy in hypoparathyroidism. The slight decrease in mean serum calcium concentrations from week 12 to week 24 in the rhPTH(1–84) group is a result of continual adjustments of oral calcium and active vitamin D, and down-titration of the rhPTH(1–84) dose in individual patients. Serum 1,25-dihydroxyvitamin D concentrations were maintained in the normal range in both groups throughout the trial despite dramatic reductions in active vitamin D dose requirements in the rhPTH(1–84) group.

***Panel*: Research in context**

Systematic review

We searched PubMed for clinical trials published before Aug 22, 2013, with the terms "hypoparathyroidism" and "parathyroid hormone." Seven clinical trials reported the effects of the human parathyroid hormone fragment (hPTH[1–34]), in patients with hypoparathyroidism.[7–12,19] These studies progressed from a proof-of-concept study with once-daily hPTH(1–34)[7] to studies with dose-adjustable PTH(1–34) regimens.[8,10] They showed that twice-daily dosing achieves better control than once-daily dosing[8,10] and that delivery with a pump achieves normalisation of mineral metabolism.[12] Use of PTH(1–34) was also shown to be effective in children, and long-term use for up to 3 years was shown to be safe.[10] Six studies reported the effects of the full-length hormone recombinant (r)hPTH(1–84) in patients with hypoparathyroidism.[15–18,21,22] rhPTH(1–84), when given at 100 μg subcutaneously every other day, was effective and safe for up to 4 years.[15] The only double-blinded, placebo-controlled trial used rhPTH(1–84) as an add-on therapy at a fixed dose of 100 μg once daily.[17] With this regimen, initial rates of hypercalcaemia were higher than with placebo. PTH replacement therapy needs flexible dosing to correspond to different needs in different patients. No placebo-controlled trial has been reported that uses such a design that is applicable to clinical practice.

Interpretation

Our clinical trial, the largest done so far in patients with hypoparathyroidism, is the first phase 3 trial for PTH replacement therapy using the full length molecule, rhPTH(1–84), in the outpatient setting. By showing the safety and efficacy of once-daily rhPTH(1–84) by subcutaneous injection at flexible doses of 50–100 μg per day, this trial shows that rhPTH(1–84) could become a PTH replacement therapy for hypoparathyroidism by addressing the underlying defect.

Clinical symptoms associated with hypocalcaemia were assessed for both safety and efficacy. Despite substantial decreases in oral calcium and active vitamin D doses, rhPTH(1–84) was associated with fewer clinical symptoms of hypocalcaemia during maintenance than was placebo, although during follow-up (after withdrawal of study drug) hypocalcaemia was reported as an adverse event in a higher proportion of patients in the rhPTH(1–84) group than in the placebo group.

The short-term design, which precluded a detailed analysis of skeletal and renal effects of rhPTH(1–84) therapy, is a limitation of this study. Another limitation was that the dose schedule defined by the protocol did not allow up-titration of study drug after week 5 or dose increases of greater than 100 μg per day; therefore, we do not know whether some patients might have been able to achieve the endpoint with higher doses.

This is the first study to use a flexible dosing regimen of rhPTH(1–84) and a rigorous algorithm for titration of oral calcium and active vitamin D in a double-blinded and placebo-controlled trial (panel). The flexible dosing and titration algorithm can be readily implemented in an outpatient setting, which makes it immediately applicable for clinical practice.

Other strengths are the large number of patients enrolled, since hypoparathyroidism is a rare disease. The results show that replacement therapy with rhPTH(1–84) can optimise and stabilise serum calcium while substantially reducing the need for active vitamin D and calcium. Hyperphosphataemia was also improved, and hypercalciuria did not increase. Additionally, treatment with rhPTH(1–84) was well tolerated, as shown by the high compliance rate. Beneficial effects included increasing low serum calcium concentrations without a concomitant increase in calciuria, decreasing high serum phosphate, decreasing calcium–phosphate product, and activating endogenous 1,25-dihydroxyvitamin D production.

Overall, these findings show that rhPTH(1–84) is efficacious as a replacement for endogenous PTH in patients with hypoparathyroidism. This study also confirms that 50 μg per day subcutaneously is an acceptable starting dose of rhPTH(1–84), with possible up-titration by increments of 25 μg up to 100 μg, for the treatment of hypoparathyroidism in an outpatient setting.

Contributors

MM, BLC, TV, RG, LM, HL, DS, and JPB contributed to the writing and review of the report. MM, BLC, TV, MLB, LR, WDF, PL, LB, LM, DS, and JPB contributed to recruitment of patients and were study investigators. MM, BLC, TV, RG, HL, DS, and JPB contributed to the data interpretation. RG, HL, and JPB contributed to the study design.

REPLACE principal investigators

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Conflicts of interest

MM and TV have served as advisory group members for NPS Pharmaceuticals (MM through a contract with his institution). BLC, DS, and JPB have received institutional research grants from and served as advisory group members for NPS Pharmaceuticals. RG and HL are employees of NPS Pharmaceuticals.

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References

1 Bilezikian JP, Khan A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. *J Bone Miner Res* 2011; **26:** 2317–37.

2 Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med* 2008; **359:** 391–403.

3 Rejnmark L, Sikjaer T, Underbjerg L, Mosekilde L. PTH replacement therapy of hypoparathyroidism. *Osteoporos Int* 2013; **24:** 1529–36.

4 Goswami R, Sharma R, Sreenivas V, Gupta N, Ganapathy A, Das S. Prevalence and progression of basal ganglia calcification and its pathogenic mechanism in patients with idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)* 2012; **77:** 200–06.

5 Weber G, Cazzuffi MA, Frisone F, et al. Nephrocalcinosis in children and adolescents: sonographic evaluation during long-term treatment with 1,25-dihydroxycholecalciferol. *Child Nephrol Urol* 1988; **9:** 273–76.

6 Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab* 2012; **97:** 4507–14.

7 Winer KK, Yanovski JA, Cutler GB Jr. Synthetic human parathyroid hormone 1-34 *vs* calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* 1996; **276:** 631–36.

8 Winer KK, Yanovski JA, Sarani B, Cutler GB Jr. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998; **83:** 3480–86.

9 Winer KK, Ko CW, Reynolds JC, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.

10 Winer KK, Sinaii N, Peterson D, et al. Effects of once versus twice-daily parathyroid hormone 1–34 therapy in children with hypoparathyroidism. *J Clin Endocrinol Metab* 2008; **93:** 3389–95.

11 Winer KK, Sinaii N, Reynolds J, et al. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1–34 versus calcitriol and calcium. *J Clin Endocrinol Metab* 2010; **95:** 2680–88.

12 Winer KK, Zhang B, Shrader JA, et al. Synthetic human parathyroid hormone 1–34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. *J Clin Endocrinol Metab* 2012; **97:** 391–99.

13 Fox J, Wells DS, Garceau RJ. Relationships between pharmacokinetic profile of human PTH (1-84) and serum calcium response in postmenopausal women following four different methods of administration. http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=cb1c7954-4672-41f1-8b55-9a70ec107b6f (accessed June 24, 2013).

14 Satterwhite J, Heathman M, Miller PD, Marin F, Glass EV, Dobnig H. Pharmacokinetics of teriparatide (rhPTH[1-34]) and calcium pharmacodynamics in postmenopausal women with osteoporosis. *Calcif Tissue Int* 2010; **87:** 485–92.

15 Cusano NE, Rubin MR, McMahon DJ, et al. Therapy of hypoparathyroidism with PTH(1-84): a prospective four-year investigation of efficacy and safety. *J Clin Endocrinol Metab* 2013; **98:** 137–44.

16 Rubin MR, Sliney J Jr, McMahon DJ, Silverberg SJ, Bilezikian JP. Therapy of hypoparathyroidism with intact parathyroid hormone. *Osteoporos Int* 2010; **21:** 1927–34.

17 Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L, for the Hypoparathyroid Study Group. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. *J Bone Miner Res* 2011; **26:** 2358–70.

18 Sikjaer T, Amstrup AK, Rolighed R, Kjaer SG, Rejnmark L, Mosekilde L. PTH (1-84) replacement therapy in hypoparathyroidism: a randomized controlled trial on pharmacokinetic and dynamic effects following 6 months of treatment. *J Bone Miner Res* 2013; published online May 3. DOI:10.1002/jbmr.1964.

19 Gafni RI, Brahim JS, Andreopoulou P, et al. Daily parathyroid hormone 1–34 replacement therapy for hypoparathyroidism induces marked changes in bone turnover and structure. *J Bone Miner Res* 2012; **27:** 1811–20.

20 Macfadyen IJ, Nordin BE, Smith DA, Wayne DJ, Rae SL. Effect of variation in dietary calcium on plasma concentration and urinary excretion of calcium. *BMJ* 1965; **1:** 161–64.

21 Sikjaer T, Rejnmark L, Thomsen JS, et al. Changes in 3-dimensional bone structure indices in hypoparathyroid patients treated with PTH(1-84): a randomized controlled study. *J Bone Miner Res* 2012; **27:** 781–88.

22 Rubin MR, Dempster DW, Sliney J Jr, et al. PTH(1–84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. *J Bone Miner Res* 2011; **26:** 2727–36.