Research Article

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An open-label study examined the safety and effectiveness of oral human parathyroid hormone (1-34) in hypoparathyroidism.

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ABSTRACT

It can be difficult for patients and clinicians to manage hypophosphatemia, hyperphosphatemia, and hypercalciuria while treating primary hypoparathyroidism (hypoPT) with oral calcium supplementation and calcitriol (or an analog). Human parathyroid hormone (hPTH) (1-84) injected subcutaneously once a day was approved as an adjuvant treatment in 2015 for patients who did not respond favorably to traditional treatments. The purpose of this open-label trial was to evaluate the safety and effectiveness of an oral hPTH(1-34) formulation in adult individuals with hypoparathyroidism as a supplement to routine care. For 16 weeks straight, oral hPTH(1-34) tablets (0.75 mg human hPTH(1-34) acetate) were given four times a day. Additionally, adjustments were made to the calcium supplementation and use of alfacalcidol, albumin-adjusted serum calcium (ACa), serum phosphate, and albumin-adjusted serum calcium.Throughout the trial, quality of life and urinary calcium excretion were recorded. Fifteen of the nineteen participants that were enrolled finished the trial as directed. A median 42% decrease from baseline in the exogenous calcium dose was seen (p =.001), whereas the median blood ACa levels for hypoPT patients (>7.5 mg/dL) remained higher than the lower goal ACa values over the trial. Serum phosphate median levels dropped sharply (23%, p =.0003) two hours after the initial dose and stayed in the normal range the whole period. Between the first and last treatment days, there was a noticeable, but not statistically significant, median decrease in 24-hour urine calcium excretion (21%, p =.07). There were just four potential, mild side effects linked to the medication recorded during the the same patient participated in a 16-week study. By the end of the treatment period, a slight but statistically significant gain in quality of life (5%, p =.03) was observed from baseline. In adult patients with hypoparathyroidism, oral hPTH(1-34) medication was typically safe, well tolerated, and allowed for a reduction in exogenous calcium supplementation while maintaining normocalcemia. The American Society for Bone and Mineral Research (ASBMR) is represented by Wiley Periodicals LLC, the publisher of the Journal of Bone and Mineral Research.

Keywords : hypoparathyroidism; oral parathyroid hormone; parathyroid-related disorders; calcium/phosphate disorders; parathyroid hormone.

INTRODUCTION

With a frequency of 22 per 100,000 people, primary hypoparathyroidism (hypoPT) is an uncommon mineral metabolic condition that is biochemically defined by low serum calcium and minimal or nonexistent amounts of parathyroid hormone (PTH). Adult iatrogenic hypoPT is most commonly caused by excision or injury sustained during anterior neck surgery.(2) Less frequent causes include autoimmune diseases, birth defects, and genetic conditions that lead to improper hormone production or secretion.(3) PTH levels are the cause of the characteristic hypocalcemia in hypoPT.
inadequate for increasing renal 25-hydroxyvitamin D 1α-hydroxylase activity and consequent 1,25-dihydroxyvitamin D (1,25(OH)2D) production, mobilizing calcium from bone, or reabsorbing filtered calcium from the distal nephron. The lack of PTH's phosphaturic action leads to the development of hyperphosphatemia.(4) The conventional management of hypoPT, which involves oral calcium supplementation and calcitriol (or an analog) to prevent hypercalciuria and regulate hypocalcemia and hyperphosphatemia, continues to pose

difficulties for medical professionals and patients alike. Loss of renal PTH action results in decreased phosphate excretion and calcium reabsorption through renal tubules, leading to hyperphosphatemia and hypercalciuria, respectively.As a result, it has been discovered that individuals with chronic hypoparathyroidism are more likely to experience renal problems, including nephrocalcinosis, nephrolithiasis, renal insufficiency, and frequently ectopic calcification in other organs.The dosage of calcitriol and calcium is frequently titrated slowly, inaccurately, and may need to be adjusted frequently. Furthermore, taking supplements frequently during the day is difficult and frequently results in gastrointestinal intolerance.(6) PTH deficiency results in limited bone turnover and significantly changed microarchitectural and biomechanical characteristics of the skeleton, which cause structural and dynamic skeletal abnormalities that are not remedied by active vitamin D therapy or calcium supplementation.The goal of standard treatment is to lessen the risk of ectopic calcification and hypercalciuria by titrating blood calcium levels to the lower range of normal.(9) Patients have frequently mentioned issues with their quality of life, including mood and cognitive changes,This could be brought on by the relatively low blood calcium levels that regular therapy provides.(10–12)

Potential benefits of replacement therapy with PTH include lower urine calcium levels, better correction of hypocalcemia and hyperphosphatemia, and a reduction in the high dose of calcium supplements. The case for using PTH to treat PTH deficit is strong given these possible benefits.

In order to control hypocalcemia and hyperphosphatemia in patients with hypoPT, the US Food and Drug Administration approved the use of a daily subcutaneous injection of the full-length human PTH molecule (hPTH(1-84)), which was created through recombinant technology, as an adjunct to the treatment of calcium and calcitriol (or other calcitriol analogs). There are now two hPTH analogs that are used in clinical settings for various purposes: hPTH(1-34), the human PTH (teriparatide) 1-34 N-terminal segment for the management of hypoPT with hPTH(1-84) and osteoporosis. Both the fully active 34 amino acid peptide (17–24) and the full-length 84 amino acid hormone (13–16) have shown salutary effects in the management of hypoPT, lowering or eliminating the need for additional calcium and active vitamin D while keeping serum calcium within the reference range. Currently, the only injectable subcutaneous versions of hPTH(1-84) and hPTH(1-34) are available. While hPTH(1-84) is approved to treat hypoparathyroidism, hPTH(1-34) is only approved to treat osteoporosis. An oral formulation that eliminates the complications associated with injections is expected to improve adherence and compliance, mimicking the patients' treatment plan and overall quality of life.Entera Bio is creating an oral version of hPTH(1-34) using a unique drug delivery method that promotes protein absorption and has demonstrated therapeutically meaningful results.drug's pharmacokinetics and plasma concentrations.(25) We provide the findings of a 16-week pilot trial designed to evaluate the efficacy, safety, and tolerability (rate of discontinuation)Adults with hypoPT may benefit from an oral hPTH(1-34) formulation as an adjunct to standard care, with the goal of reducing calcium dosage.

SUPPLIES AND PROCEDURES

Examine medication

The oral hPTH(1-34) used in this investigation is based on Entera Bio Ltd.'s proprietary oral peptide delivery technology (26). The patented excipients salcaprozate sodium and soybean trypsin inhibitor (SBTI) are what make the technology work. They help the hPTH(1-34) peptide absorb through the stomach wall and shield it from proteolysis.

The amount of hPTH(1-34) acetate in each tablet was 0.75 mg, or 0.69 mg of the hPTH active moiety (formulation code EBP02). The supplier of tablets was Entera Bio Ltd. located in Jerusalem, Israel.

Research methodology

Between August 12, 2014, and June 21, 2015, a multicenter, open-label pilot research was carried out in Israel where oral hPTH(1-34) was given four times a day for sixteen days. consecutive weeks in order to treat hypocalcemia in hypoPT patients. The investigation was registered in the US clinical trials database (clinical trial number. NCT02152228) and carried out in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. Prior to the start of the study, the protocol was approved by the Institutional Review Boards at each investigational site.

Prior to their involvement in the trial, patients gave their written informed consent.

Males and females between the ages of 18 and 80, body mass index (BMI) of 18 to 30 kg/m2, hypoPT for more than 12 months, and supplemental calcium use (≥1.0 g elemental calcium/ day with a correlated calcitriol analog dose) with 25(OH)D] levels ≥20 ng/mL were the main inclusion criteria. People were found to be within reference limits for blood chemistry and hematological tests, as well as for physical, cardiac, and renal evaluations, making them eligible for the trial. It was acceptable to have abnormalities related to hypoPT, such as elevated phosphate or low serum calcium levels. The primary criteria for exclusion were nephrocalcinosis, pregnancy or planned pregnancy, elevated liver associated enzymes, alcohol or drug abuse, positive serology tests (HIV, HBsAg, HCV Ab), renal insufficiency (estimated glomerular filtration rate [eGFR] <40 mL/min/1.73m2), elevated liver associated enzymes, and positive serology tests.

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The doctors who were in charge of each patient's long-term care for their hypoPT continued to administer calcium supplements and calcitriol analogs, most often alfacalcidol.

On the first day of treatment, the participants completed a thorough assessment, which includes a full blood count, medical history, physical examination, and a serum biochemical safety and efficacy study.

Following that, patients received three in-clinic doses of 0.75 mg oral hPTH(1-34), given at roughly 8:00, 12:00, and 16:00 every four hours. Meals were provided one hour after the first and second dosage administrations, and the first dose was given following an overnight fast. On the first treatment day, the patient self-administered the fourth dose at home after 20:00. The research medicine was thereafter to be self-administered by the volunteers four times a day at home with 100 mL of water (before morning, midday, evening, and before bed) for a 16-week course of therapy. The research medication was to be taken at least 30 minutes before any food or drink was consumed, at least 30 minutes before taking calcium supplements or taking any other medication, and at least one hour after taking any medication or food. Throughout the course of the treatment, the investigator titrated the dosage up to a maximum of 12 tablets per day (total daily oral hPTH(1-34) dose of 9 mg), in accordance with each subject's supplement treatment regimen and albumin-adjusted serum calcium (ACa). The subjects' ACa was measured every week during the first four weeks, every eight weeks for the next eight weeks, and once more at the conclusion of the research.

According to the dosing parameters shown in Table 1, adjustments were made based on the clinical judgment of the investigator and each patient's pre-dose ACa levels. This included deciding whether to increase or decrease the doses of oral hPTH(1-34), supplementary calcium, or alfacalcidol. With IRB permission and prior phase 1 trials, the maximum permitted daily dosage of hPTH(1-34) acetate was set at 9.0 mg.

The degree of modification was left up to the investigator's judgment regarding how to best adjust in order to attain each patient's target ACa levels due to the diverse patient group, their sensitivity to PTH, and their fluctuating daily supplementation. Check-ups were done at the conclusion of each week 1, 2, 3, 4, 6, 8, 10, 12, 14, and at the conclusion of week 16, when oral hPTH(1-34) treatment was stopped. Serum levels of creatinine, albumin, phosphate, and calcium were measured at each visit (both before and one hour after the study was self-administered). medicine at the clinic) and dose modifications were carried out in accordance with the participants' ACa levels. A research coordinator got in touch with participants every week that didn't involve a clinical visit. Prior to starting treatment and at the conclusion of weeks 8 and 16, a urine analysis and a 24-hour urine collection for phosphate, creatinine, and calcium were carried out. A follow-up/end-of-study (FU/EOS) visit was conducted at the early trial discontinuation or 7–14 days after the treatment phase concluded.Throughout the trial, personal diaries and weekly patient status update calls were used to track treatment compliance. The percentage of patients who adhered to treatment was determined.

percent the tablets the subject took from the recommended dosages, with good being defined as more than 80%, satisfactory as between 60% and 80%, and poor as less than 60%.

The EQ-5D-5L (EuroQoL), a standardized tool used to measure health-related quality of life evaluations, was used to measure the participants' quality of life (QoL). The subjects completed this instrument at each visit during the treatment phase. This device recorded the patients' self-rated general health using a Visual Analog Scale (VAS), with 1 being the worst and 100 representing the greatest. Patients with hypoPT have had their quality of life evaluated using this tool.(10) Symptoms associated with hypocalcemia were noted at each treatment visit, starting with the initial appointment following the start of treatment.

Following the pharmacokinetic and pharmacodynamic testing the first two dosages of the medication

Following the first two medication administrations on the first research day, blood samples were taken. Samples were thus taken prior to and 10, 15, 20, 30, 45, 60, 90, 180, and 240 minutes following the administration of each of the two doses. Samples of blood were collected into EDTA tubes coated with spray, put on ice, then spun for 10 minutes at 4 C and 2500 g. Before analysis, the separated plasma was kept at -20°C. The University of East Anglia's Bioanalytical Facility in Norwich, UK, analyzed hPTH(1-34) in human plasma using an approved commercial chemiluminescence-based immunoassay (IDS-iSYS hPTH(1-34), IDS, Boldon, UK) on an Automated analyzer IDS-iSYS.

Blood samples taken during the initial study visit, as well as 60 and 180 minutes after the first, were used for pharmacodynamic analysis.

Serum calcium, albumin, and phosphate levels were measured at the time of the second dose of the medication as well as 60, 180, and 240 minutes later.

Data interpretation

All 19 enrolled patients, unless otherwise indicated, had data for pharmacokinetics, pharmacodynamics, and safety analyses. All subjects had finished the first trial day. The evaluation of treatment compliance comprised all participants (n = 17) who finished the 16-week experiment. The data gathered from all patients who finished the study according to protocol (n = 15) was used for all other analyses, which included the 16-week

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calculation of supplemental calcium and alfacalcidol dosing, serum ACa and phosphate concentrations, urine calcium excretion, quality of life evaluation, and symptoms related to hypocalcemia. In the first few weeks of the trial, calcium supplements were increased rather than having baseline ACa levels maintained for the two participants who were not treated according to protocol.

Analytical statistics

Descriptive statistics for categorical variables comprised sample size, proportions' absolute and relative frequencies, and, if applicable, the 95% confidence interval. Sample size, arithmetic mean, geometric mean, standard deviation, standard error, coefficient of variation (if applicable), median, minimum, maximum, and 95% confidence interval for means were among the descriptive statistics used for continuous variables.analysis of harmacokinetics

The maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration time curve (AUClast) (calculated by linear trapezoidal summation from the time of administration to the last measurable concentration), elimination rate constant (λz) (found by linear regression of the terminal points of the linear plasma concentration time curve), and terminal elimination half-life (t1/2) (defined as 0.693/λz) were all obtained from a noncompartmental pharmacokinetic analysis using individual hPTH(1-34) concentration data.

RESULTS

Subject-oriented behavior

The study included 19 participants who had been diagnosed with hypoPT for more than a year (Table 2). Out of the 16/19 subjects, the majority were female. The individuals' BMI was 25.5 kg/cm2, and their median age was 41.1 years (range 20.3 to 71.0 years). Two subjects withdrew on the first day of the study due to an unrelated serious adverse event (SAE) of hypercalcemia, which happened prior to the first study drug administration and was discovered only after the first dose was administered and pre-dose lab results were obtained. The remaining seventeen subjects finished the study.

reduction in the dosages of alfacalcidol (or calcitriol) and additional calcium Table 3 summarizes the average daily dosages of oral hPTH(1-34) by week. As per the study design, to maintain stable blood ACa concentrations, the daily oral hPTH(1-34) dose was gradually increased up to 9.0 mg while concurrently reducing the supplemented calcium intake. The need for calcium supplements dropped steadily over the course of the investigation (Table 4; Fig. 1A), and from week 4 to the end of the trial, it was significantly less than baseline. By week 16, the median exogenous calcium dose had dropped from 3.6 g at baseline to 2.2 g, which was a 42% (p =.0001) decrease from baseline requirements. At the conclusion of the trial, 73% of patients had reduced their calcium consumption by at least 30%, and 40% of patients had reduced it by at least 50%. Throughout the trial, there were occasional drops in the average amounts of alfacalcidol; nonetheless, the mean alfacalcidol doses decreased by 4.3%, from 1.1 to 1.0 μg daily, and this did not substantially differ from the baseline dosages. Total serum ACa levels stayed consistent and above the lower target ACa levels for hypoPT patients (>7.5 mg/dL(10)) despite significant reductions in supplemental calcium dosages (Fig. 1B). By the conclusion of week 16, 33% of patients had ACa > 8.5 mg/dL, compared to 20% at the beginning of the research were found to be 47.9 pg/mL and 41.2 pg/mL (Table 5), respectively, at a median of 20.0 and 30.0 minutes following dosage. Similarly, compared to the second dosage (Table 5) given three hours after a typical meal, the total systemic exposure (AUClast) was presumably higher following the first oral hPTH(1-34) provided following an overnight fast. Following the injection of both dosages, the mean terminal half-life of hPTH(1-34) was comparable (21.1 and 27.5 minutes for the first and second doses, respectively).

Levels of phosphate and ACa in serum

Serum ACa levels did not significantly change following the first two dose administrations on day 1 with the initial dosage of 0.75 mg oral hPTH(1-34) tablets. Having said that, an increasing trend after a brief drop at one hour after the injection, a three-hour increase in serum ACa levels was seen. As illustrated in Figure 2, oral hPTH(1-34) had an effect on blood ACa levels that persisted long after the patient was exposed to the medication, much like an indirect pharmacodynamic model.(27)

Serum phosphate levels showed a more pronounced effect, falling quickly following the first oral hPTH(1-34) dose and bringing the elevated baseline levels into the reference range (2.5 to 4.5 mg/dL) (Fig 3).

Following the second dose, the phosphate levels stayed low and within the reference range for a minimum of seven hours. Throughout the course of the investigation, the same quick impact on phosphate levels was noted; at each study visit, the median An hour after the injection, serum phosphate levels were considerably lower (1% to 12%; p ≤.04) than they were before (Fig. 4).

It should be mentioned that one research participant was not included in any of the serum phosphate assays since, at the beginning of the experiment, she was using sevelamer carbonate, a phosphate binder drug. Additionally, the day 1 serum ACa and phosphate assay did not include one individual who had hypercalcemic serum levels prior to any study drug treatment.

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Calcium levels in the urine

Prior to treatment, the mean (±SD) 24-hour urine calcium excretion was 189.8 (±131.6) mg, at midpoint (end of week 8), 192.3 (±146.0) mg, and at study's conclusion (end of week 16), it was 140.5 (±82.4) mg. Over the course of the 16-week treatment period, there was a non-significant shift from the baseline mean 24-hour urine calcium (26%, p =.07). By the time the trial ended, the urine calcium levels had decreased in 80% of the participants. Seven participants had calcium levels over the 24-hour urine calcium reference range (>200 mg for females and >250 mg for males) at the start of the trial. The participants exhibited a mean decline of 21% relative to their initial values.

Security

Of the 19 patients, eighteen experienced at least one adverse event over the 120-day study period. There were 199 AEs reported in all. Most adverse events (AEs) (195/199, 98.0%) were found to be unrelated to the medication under review. One subject experienced four adverse events (AEs) that were deemed drug-related: minor nausea, moderate back pain, moderate headache, and moderate upper abdomen discomfort. This subject withdrew consent on the first day of the trial after expressing worry connected to participation in it. Although there is no evidence to support the implausible relationship between these adverse events and dosage, they were noted as "possibly related" nonetheless. With the exception of the single patient who left the study early on day 1 due to hypercalcemia before receiving the study's first dosage,Throughout the rest of the therapy period, no patient experienced any additional instances of hypercalcemia adverse events, nor did any have blood ACa levels higher than 9.42 mg/dL.

Gastrointestinal disorders, such as diarrhea, nausea, and abdominal discomfort (reported by 37%, 32%, and 26% of the patients, respectively), as well as nasopharyngitis (32%), muscle spasms (26%), were the most frequently seen side effects. Blood chemistry and hematology measurements, physical findings, vital signs, and ECG measures did not show any clinically significant alterations.

The study began with a generally excellent quality of life (QoL) score (median 80 [range 60 to 100]; maximum score of 100), which increased over the first week of therapy, according to the quality of life components measured using the VAS score of this instrument. This improvement persisted for the duration of the research, ending at week 16 with a final QoL VAS score of 85 (60 to 100) (p =.03).

Symptoms associated with hypocalcemia

Throughout the trial, the number of symptoms due to hypocalcemia was tracked beginning at the end of the first week and continuing until the end. Over the course of the trial, each subject's average compliance was 95.6% ± 4.7% (mean ± SD). of hypocalcemia-related symptoms/signs reported dropped from 13 (emotional instability, anxiety, muscle weakness, cramps, paresthesias, and the Chvostek sign) in 5 patients at the end of week 1 to 4 (hypotension, paresthesias, and anxiety) in 4 patients at the end of the study. adherence to study medicine Following the trial, all 17 participants shown good compliance ce (>80%). Up until week five, one subject's compliance was "satisfactory–poor" (<80%), but it improved to "good."

DISCUSSION

The goal of treating hypoparathyroidism is to lessen the risk of nephrolithiasis and ectopic calcification, particularly nephrocalcinosis, by raising serum calcium levels to within 0.5 mg/dL of the reference range's lower limit but not within it.(28) The conventional treatment for hypoPT, which involves oral calcium supplements and calcitriol analogs, raises serum calcium levels but has limitations because it doesn't improve phosphate excretion or renal tubular calcium absorption. Hormonal replacement therapy utilizing both hPTH(1-34) and PTH(1-84) has demonstrated the ability to achieve this goal and the maintenance of calcium homeostasis at a stable level by PTH without hypercalciuria, while also decreasing the need for additional calcium and enhancing patient quality of life (9,29–31).

The longer elimination half-life and longer time to peak concentration for the full-length molecule in the commercial formulations of hPTH(1-34) and PTH(1-84) are the primary distinctions, leading to a prolonged pharmacologic impact following a single subcutaneous injection.(32,33) Because oral delivery and absorption of hPTH(1-34) and polypeptides in general are impeded by extensive proteolysis inside the gastrointestinal tract, limited absorption due to their molecular mass, and their hydrophilic nature, both PTH(1-84) (Natpara) and hPTH(1-34) (Forteo) require parenteral administration. (34) The most widely used, secure, and practical way to administer a medication is orally.As a result, an oral form of hPTH(1-34) that is simple to use and may be able to supply hPTH(1-34) all day long without the need for several injections will probably have a significant effect on patients' quality of life, therapeutic impact, compliance, and adherence to this long-term treatment. Based on a cutting-edge drug delivery technique that facilitates protein absorption, Entera Bio has created an oral formulation of hPTH(1-34) that has produced clinically relevant plasma concentrations of the medication. (25) Because the oral formulation has a lower absolute bioavailability than the commercially available subcutaneous PTH, the dose of oral hPTH(1-34) administered in this trial is much higher to attain equal systemic exposure.

This study showed that oral hPTH(1-34) given four times a day for 16 weeks to patients with hypoPT was safe and tolerable. Serum phosphate levels decreased with treatment, while serum ACa levels stayed constant during the course of the investigation.

There were no documented serious drug-related adverse events, and the majority of adverse events were not thought to be drug-related to the study. From week 4 to the conclusion of the 16-week treatment period, there was a statistically significant decrease in the amount of supplemental calcium required when oral hPTH(1-34) was added to conventional hypoPT therapy with supplemental calcium and alfacalcidol (42%, p =.001). 40% of the patients had a reduction in calcium intake of 50% or more compared to baseline, and 73% of patients saw a reduction of at least 30%. Since the research's design called for a gradual titration of the study drug dose, the 4-week delay in the reduction of calcium requirements was anticipated. Throughout the trial, total serum ACa levels stayed constant, but the amount of additional calcium was significantly decreased.The average doses of calcitriol analog (alfacalcidol) remained unaltered, despite a considerable decrease in calcium requirements. The brief period of the trial and its goal of reducing the intake of additional calcium are responsible for these outcomes. The trial protocol stipulated that calcitriol analog dose adjustments could only be made once the intake of calcium supplements had been sufficiently reduced.

Fast absorption and elimination were features of the pharmacokinetic profile of the oral hPTH (0.75 mg) dose (1–34) observed on the first treatment day (Table 5). The slightly increased absorption of hPTH (1-34) in the first dose when compared to the second dose—which was given three hours after a typical meal—may be explained by the overnight fast that preceded the first dose (Table 5). Following both After correcting for relative molecular weight, median plasma hPTH(1-34) concentrations (on a molar basis) attained the typical levels of endogenous hPTH (1-84) after the first and second doses. The prolonged release of injectable hPTH (1-84) from the injection site is the primary cause of the differing pharmacokinetic profiles of the oral hPTH (1–34) and injectable hPTH (1–84). This leads to a significantly longer apparent plasma half-life (21.1 to 27.5 minutes versus ~ 3 hours, respectively).(25,33)

Serum ACa levels did not significantly change following the initial 0.75 mg oral hPTH(1-34) dose on the first research day (Fig. 2), whereas serum phosphate levels dropped to below the upper limit of the reference range about an hour after dosing (Fig. 3).

Following delivery of the first two trial doses, there was a pharmacodynamic effect on phosphate levels that persisted for at least seven hours. The complete pharmacokinetic and pharmacodynamic profile of the novel oral formulation of hPTH(1-34) was not obtained, and further research into the drug's pharmacodynamics is necessary. This is due to the limited number of blood sampling time points during the first study day and the failure to repeat measurements after the doses increased from 0.75 to 2.25 mg later in the study.

Furthermore, serum phosphate levels dropped quickly to within the reference range at each of the following study visits, mirroring the pharmacodynamic profile seen on the first study day. hour following dosage. Every treatment visit saw a steady decrease in the median baseline serum phosphate levels compared to the baseline values at the start of the study.

Over the course of the 16-week research, the mean urine calcium levels dropped by 26%; this shift occurred gradually and became more noticeable in the last 8 weeks of treatment. This decline was correlated with the decreasing median supplemental calcium dose (from 3.6 g at week 1 to 2.4 g at week 8 to 2.2 g at week 16) and the progressive increase in the oral hPTH(1-34) dose (near the maximum of 9 mg in all patients by week 9). The role of oral hPTH(1-34) and supplemental calcium on urinary calcium excretion would need to be investigated further using several timed serum and urine calcium measurements in a controlled clinical setting.

Patients reported a slight but statistically significant improvement in quality of life over baseline. The relatively high QoL VAS score at the beginning of the trial and the questionnaire's lack of attention to the particular symptoms of hypoPT may both be responsible for the small rise. Furthermore, toward the end of the trial, there seemed to be fewer individuals experiencing hypocalcemia-related symptoms (e.g., paresthesias, cramping in the muscles, emotional eating, instability, anxiety, and weariness) (13 patients at week 1 versus 4 patients at week 16). The brief study period and small sample size were two of the study's major drawbacks. As a pilot project, it lacked a run-in period during which the standard treatment with additional calcium and calcitriol analogs was optimized in accordance with a protocol prior to the initiation of oral hPTH (1-34). It also did not involve blinded concurrent treatment with placebo. The first day of the trial's limited pharmacodynamic time points and the at-home urine collection method as opposed to a controlled clinical environment were two more study limitations. Furthermore, quality of life scores and reported hypocalcemia symptoms should be read cautiously because there was no placebo control group, as the placebo effect might have influenced the study's conclusion. data curation, research, project management, oversight, and first draft writing. NSK: Guidance. MG: Curating data. AS: Official evaluation. PS: Formal analysis, supervision, data curation, and conceptualization. EA: Ideation; composition of an original draft; composition of a review and editing. HG: Writing-original draft; writing-

review & editing; project administration; conceptualization; data curation; formal analysis. JCYT: Formal interpretation; research. GB: Proposal formulation, data curation, inquiry, project management, original draft writing, writing reviews, and editing. ARo: Project management; data curation. ARa: Investigation, supervision, and data curation. MB: Research. WF: Writing-original draft; writing-review & editing; formal analysis; inquiry; validation; data curation.

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