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Clinical Unmet Needs in Hypoparathyroidism and Current Pipeline Agents

ABSTRACT

Hypoparathyroidism is a disease characterized by inadequate or absent parathyroid hormone (PTH) levels. It manifests with hypocalcemia, hyperphosphatemia, and elevated urinary fractional excretion of calcium. The conventional therapy with calcium supplementation and active vitamin D analogs is limited by the pill burden, unstable calcium concentrations, and significant renal and bone complications. Hence, the development of replacement therapies utilizing PTH or PTH-related receptor modulators has emerged as a promising therapeutic avenue. rhPTH (1-84) (NATPARA®) is a once-daily injection of full-length recombinant human parathyroid hormone that was initially approved by the U.S. Food and Drug Administration(FDA) in 2015 for hypoparathyroidism. However, it was recalled from the U.S. market in 2019, and its production will cease globally by the end of 2024. TransCon™ PTH, known as palopegteriparatide, utilizes an innovative technology to provide a sustained release of PTH (1-34) prodrug. It has received approval from the European Medicines Agency and is currently undergoing FDA review. Eneboparatide is a PTH receptor 1 agonist, designed to stimulate a specific receptor configuration.Encaleret is a negative allosteric modulator of the calcium-sensing receptor and rescues the secretion of naive PTH inAutosomal Dominant Hypocalcemia type 1. MBX 2109 is an investigational once-weekly PTH prodrug that addresses thefrequent administration challenge. EB612, the tablet form of PTH(1-34), is the first oral hormone replacement treatment for hypoparathyroidism. Recent developments in the management of chronic hypoparathyroidism hold promise as a therapeutic approach to restore physiological function, manage symptoms, and prevent associated complications.

Keywords: Hypoparathyroidism, parathyroid hormone, PTH (1-84), PTH (1-34), arathyroid hormone receptor 1, parathyroid calcium-sensing receptor

Hypoparathyroidism is an endocrine disease resulting from inadequate or absent parathyroid hormone (PTH) levels.[1] Parathyroid hormone is responsible for the maintenance of calcium and phosphorus homeostasis in the body by directly modulating bone resorption and renal uptake, and indirectly regulating gastrointestinal absorption through renal 1,25-dihydroxyvitamin D.[2] The reduction in PTH levels causes hypocalcemia, hyperphosphatemia, and increased urinary fractional excretion of calcium.[1] Hypoparathyroidism is estimated to affect 23-37 individuals per 100 000 persons.[3] Operative damage due to anterior neck surgery is the leading cause of hypoparathyroidism, accounting for 75-78% of all cases.[1,3] The second most common etiology is autoimmune disease, while the remainder of cases result from genetic disorders, non-autoimmune destructive factors such as glandular infiltration and radiation, or remain idiopathic.[2,4] A significant example of genetic hypoparathyroidism is autosomal dominant Hhypocalcemia type 1 (ADH1).[5] Blood calcium concentration is mainly regulated by a feedback mechanism that responds to input from the calcium-sensing receptor (CaSR) in the parathyroid gland and kidney. Autosomal Dominant Hypocalcemia type 1 (ADH1) occurs when de novo or inherited gain of function mutations of the CaSR gene enhance CaSR sensitivity to extracellular calcium and decrease the set-point of calcium concentration. This results in lower blood calcium concentrations being sensed as normal, consequently leading to suppression of PTH secretion and renal calcium reabsorption.[5]

The standard of care for the management of hypoparathyroidism is conventional therapy with calcium supplementation and active vitamin D analogs. The treatment goal is to maintain serum calcium levels within the lower half of the reference range or slightly below it to relieve symptomatic hypocalcemia while preventing hypercalciuria. Additionally, serum phosphate and 25-Hydroxyvitamin D concentrations should be kept within the normal reference range.[6] The most recommended daily dose of calcium supplementation is 800-2000 mg.[7] Yet, the intestine reaches its absorptive capacity for calcium with an intake of ~500 mg

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in a single dose.[7] Therefore, frequent calcium supplementation with smaller doses is advised. Different oral calcium preparations are available on the market, and the most widely used and least expensive is calcium carbonate.[7] Calcium carbonate, despite comprising only 40% elemental calcium,[1] is the preparation with the highest elemental calcium content. In addition to calcium, the mainstay of treatment involves vitamin D analogs. Activated vitamin D compounds, such as calcitriol and alfacalcidol, are favored due to the role of PTH in 25-Hydroxyvitamin D 1α-hydroxylase activation. Their shorter half-lives, unlike those of inactive vitamin D analogs, reduce the risk of prolonged hypercalcemia in the event of vitamin D intoxication.[3] On the other hand, a conventional treatment regimen has limitations of substantial pill burden, fluctuating calcium concentrations, and significant renal complications.[8] The absence of PTH-mediated calcium reabsorption in the distal nephron results in hypercalciuria.[2] This, combined with elevated serum phosphorus levels due to vitamin D supplementation and the lack of PTH, leads to three main long-term complications of standard therapy: nephrocalcinosis, nephrolithiasis, and chronic kidney disease.[1,2] A US cohort study demonstrates a 2- to 17-fold greater risk of developing stage 3-5 chronic kidney disease in patients with permanent hypoparathyroidism undergoing medical management compared to age-matched normal values.[9] Given the complications due to hypercalciuria, an adjunct therapy option is thiazide diuretics.[1] Thiazide diuretics decrease urine calcium excretion by inhibiting Na^+–Cl^- cotransporters in the distal convoluted tubule, thereby increasing sodium excretion.[10] This decrease in sodium concentrations enhances Na^+/Ca^{2+} exchanger activity in the distal convoluted tubule, which promotes calcium reabsorption.[10,11] Moreover, thiazides promote calcium reabsorption in the proximal tubule due to hypovolemia.[11] A diet rich in salt could diminish the effectiveness of thiazide diuretics; therefore, they are recommended in combination with a sodium-restricted diet.[1] However, recent data suggest that despite their common usage in preventing nephrolithiasis, hydrochlorothiazide administration does not alter the incidence of recurrence compared to placebo.[12] Thiazides may also lead to a reduction in intravascular volume and orthostatic hypotension, especially in the elderly, due to their diuretic nature, as well as induce hyperchloremic metabolic alkalosis, hyponatremia, hypokalemia, hypomagnesemia.[10]

Parathyroid hormone is a major regulator of bone remodeling with the stimulation of both bone formation and resorption.[1] This normally permits the substitution of mature bone with newly synthesized bone tissue.[13] Hypoparathyroidism is a state of markedly reduced bone turnover and distorted bone microarchitecture.[1] While both bone formation and resorption are diminished, the decrease in PTH-mediated bone resorption is more pronounced in cases of hypoparathyroidism.[1,13] This imbalanced reduction is associated with normal/increased bone mineral density.[1] In theory, higher bone mineral density would suggest a reduced risk of fractures, yet clinically individuals with hypoparathyroidism face up to a 2-fold increased vertebral fracture risk due to abnormal skeletal microstructure.[14] Furthermore, hypoparathyroidism promotes malfunctioning across various organ systems in the long term and may present with various clinical manifestations. Nervous system involvement may lead to symptoms ranging from sensorimotor disturbances to basal ganglia calcifications and seizures, while cardiovascular complications could include arrhythmias or cardiomyopathy. Population-based studies also indicate elevated cataract risk and increased susceptibility to infections.[13] Conventional treatment options fail to address the chronic effects of low/absent parathyroid hormone levels. Therefore, replacement therapy with PTH or PTH-related receptor modulators has emerged as a promising therapeutic approach, as listed in Table 1.

MAIN POINTS

- Conventional therapies for hypoparathyroidism lead to a substantial pill burden, fluctuating calcium concentrations, altered bone microarchitecture, and significant renal complications such as nephrocalcinosis, nephrolithiasis, and chronic kidney disease.
- The replacement therapy with PTH or PTH-related receptor modulators signifies a promising therapeutic strategy.
- Randomized clinical trials have evaluated the safety, efficacy, and tolerability of replacement therapies, with ongoing trials continuing to investigate these aspects. Treatment decisions should be customized to address each patient's unique needs.

Table 1. Existing PTH Replacement Treatments and Pipeline Agents for Hypoparathyroidism

Drug Name	Category	Mechanism of Action
NATPARA®	FDA approved/ recalled from the US market	Hormone Replacement Therapy
TransCon™ PTH	Approved by the European Medicines Agency/Under Approval Review by the FDA	Hormone Replacement Therapy
Eneboparatide	Phase 3 Clinical Trial	Parathyroid Hormone Receptor 1 Agonist
Encaleret	Phase 3 Clinical Trial	Calcium Sensing Receptor (CaSR) Modulator
MBX 2109	Phase 2 Clinical Trial	Hormone Replacement Therapy
EB612	Phase 1 Clinical Trial	Oral Hormone Replacement Therapy

PTH Replacement

rhPTH(1-84): rhPTH(1-84) is a once-daily injection of recombinant human parathyroid hormone, marketed under the brand name NATPARA®.[15] It is synthesized with recombinant DNA technology using *Escherichia coli*.[16] It was previously been approved in the United States in 2015 for use in patients with hypoparathyroidism as the first PTH replacement therapy in conjunction with conventional therapy, albeit with a black box warning from the U.S. Food and Drug Administration (FDA).[15,16] rhPTH(1-84) administration elevated osteosarcoma risk in animal studies, correlating with dosage and duration of treatment. Although osteosarcoma occurrence was limited to rats with parathyroid hormone levels ranging from 3 to 71 times more than the highest approved dose of rhPTH(1-84) in humans, the potential risk to humans could not be disregarded. As a result, the FDA issued a warning against the use of rhPTH(1-84) in individuals with elevated baseline osteosarcoma risk, such as those with Paget's disease or prior skeletal radiation history.[16] rhPTH(1-84) was exclusively accessible through the Risk Evaluation and Mitigation

Strategy (REMS) program. This was mandated by the FDA to establish that a drug's advantages outweigh its potential risks.[16,17] In 2019, rhPTH(1-84) was recalled in the United States because of concerns regarding rubber particulates found in the rubber septum of the cartridge. These particulates could potentially detach into the rhPTH(1-84) solution during the daily puncturing of the septum over the 14-day treatment period.[18] rhPTH(1-84) remained available in markets outside of the United States until the manufacturing company announced in 2022 that its production would cease globally by the end of 2024. This decision was made because the company could not find a solution to the issue of rubber particle formation. After 2024, available doses will be supplied until their expiration or depletion.[19] Herein, we review rhPTH(1-84)'s pharmacological properties, clinical efficacy, and tolerability.

rhPTH(1-84) is available in the form of a cartridge containing four dosage options: 25 mcg, 50 mcg, 75 mcg, and 100 mcg. The starting dosage is 50 mcg administered once daily via injection into the thigh. After subcutaneous administration, the absolute bioavailability is 53%. Serum calcium levels should be monitored every 3 to 7 days following the initiation or adjustment of the rhPTH(1-84) dose. This regular monitoring is important for the detection and management of potential risks such as severe hypercalcemia, severe hypocalcemia, hypersensitivity reactions, and digoxin toxicity resulting from hypercalcemia.[16] Parathyroid hormone is primarily eliminated by the liver with a contribution from the kidneys. Dose adjustment is not required for the elderly and for individuals with mild/moderate hepatic or renal impairment.[15]

rhPTH(1-84)'s clinical development program consists of 4 Phase 3 trials: REPLACE, RELAY, RACE, and REPEAT. The first and pivotal study that resulted in its approval and registration is the REPLACE trial (NCT00732615).[15,20] This is a double-blind placebo-controlled multinational trial that included adult patients with established hypoparathyroidism (≥18 months) receiving conventional therapy. Patients who have hypoparathyroidism due to an activating mutation in the CaSR gene or impaired responsiveness to PTH were excluded. Preceding randomization, participants underwent an optimization period during which doses of calcium and vitamin D were modified to maintain consistent albumin-corrected serum calcium concentrations. Participants were allocated in a 2 : 1 ratio to receive either rhPTH(1-84) or a placebo over 24 weeks. The starting dose was 50 µg and over the first 5 weeks, the dosage was allowed to gradually increase to 75 µg and then to 100 µg. Meanwhile, calcium and active vitamin D supplementation gradually decreased. Following this initial period, rhPTH(1-84) dosage was not allowed to be increased but could be decreased to as low as 25 µg. The primary endpoint of the trial was the participant ratio who achieved a reduction of 50% or more from the baseline in the daily doses of both oral calcium and active vitamin D, while ensuring that the serum calcium levels remained at or above baseline and within the upper limit of normal. The primary endpoint was analyzed using an intention-to-treat analysis at the end of 24 weeks. 53% of patients in the treatment arm achieved the primary endpoint as opposed to only 2% of the patients in the placebo arm. In addition, 43% of participants treated with rhPTH(1-84) completely stopped active vitamin D intake and decreased oral calcium intake to ≤500 mg/day by week 24, in contrast to only 5% in the placebo group. Other benefits included a reduction in high serum phosphate levels and calcium–phosphate product, elevation of serum calcium levels without a concurrent increase in calciuria, and stimulation of endogenous activated vitamin D production. No significant differences were observed between groups in terms of both non-serious and serious adverse events. The most reported examples included hypocalcemia, nausea, headache, paresthesia, and muscle spasms. Overall, this study demonstrated the safety, efficacy, and tolerability of once-daily subcutaneous rhPTH(1-84) injection at flexible doses of 50-100 µg/day as a PTH replacement therapy.[21] Subsequent clinical trials reaffirmed the results from the REPLACE study and further established the efficacy and safety of rhPTH(1-84) at doses as minimal as 25 µg/day for individuals with hypoparathyroidism.[22,23] Furthermore, retrospective cohort studies of rhPTH(1-84) clinical trials revealed a reduced risk of chronic kidney disease development and estimated glomerular filtration rate (eGFR) decline, as well as a decreased incidence of cardiovascular events compared with conventional therapy.[24-26]

TransCon™ PTH: TransCon™ PTH, also known as palopegteriparatide, is a novel technology that delivers a sustained-release of PTH(1-34) prodrug with a once-daily subcutaneous injection.[27] The TransCon platform stands for "transient conjugation" because it utilizes a temporary linker to bind the PTH(1-34) prodrug to an inert protective carrier. This carrier renders the prodrug inactive and shields it from elimination when bound. Upon injection, the body's physiological conditions trigger the gradual release of the active drug, which is cleaved from the linker at a set pace.[28] This unique delivery method ensures a steady pharmacokinetic profile mimicking the physiologic secretion patterns of PTH throughout the entire day.[27,28]

TransCon™ PTH is currently approved by the European Medicines Agency and is under review by the FDA until August 2024 for the management of chronic hypoparathyroidism.[27,29] The PaTH Forward, Phase 2 trial of TransCon™ PTH, has previously demonstrated promising results. The study was a randomized, double-blind clinical trial involving participants who were randomly administered either TransCon™ PTH at doses of 15, 18, or 21 µg PTH(1-34) per day or a placebo over a 4-week period. This was followed by a 22-week extension period during which the dosage of TransCon™ PTH was adjusted to range from 6 to 60 µg of PTH(1-34) daily. At the end of 26 weeks, 91% of participants became independent of oral vitamin D supplementation and decreased calcium intake to ≤500 mg per day. The participants attained normal concentrations of serum calcium, serum phosphate, serum calcium-phosphate product, and urinary calcium. Also, they reported an increased quality of life.[30] Following this, the PaTHway Trial, a Phase 3 trial of TransCon™ PTH, was initiated. It is a randomized, placebo-controlled 26-week study, with an ongoing 156-week open-label extension period to follow. Participants were randomly assigned in a 3 : 1 ratio to either receive once-daily TransCon™ PTH at an initial dosage of 18 µg/day or a placebo alongside conventional therapy. The dosage of both the investigational drug and conventional therapy was adjusted based on serum calcium levels. The primary endpoint was the percentage of patients who attained normal serum albumin-adjusted calcium concentrations and no longer required conventional therapy (defined as no need for active vitamin D and ≤600 mg of calcium per day), while also maintaining a consistent study drug dosage for at least 4 weeks prior to week 26. Significantly more patients in the treatment group reached the primary endpoint (79%) than those on placebo (5%). Most participants who did not achieve the primary endpoint on TransCon™ PTH had isolated low albumin-adjusted serum calcium levels at week 26. However, these levels mostly remained within the

acceptable clinical range, usually slightly below normal by ≤0.5 mg/dL. Moreover, 93% of patients who received TransCon™ PTH became independent of conventional drugs, leading to a significant decrease in pill burden. It is important to point out that 24-hour excretion of urine calcium was evaluated as a safety assessment. The average 24-hour urine calcium excretion levels declined from 392 mg/day at baseline to 220 mg/day in individuals administered TransCon™ PTH, contrasting with a change from 329 mg/day at baseline to 292 mg/day in those on placebo. A larger proportion of TransCon™ PTH recipients (60.7%) attained normal 24-hour urine calcium excretion (≤250 mg/day) compared to placebo (28.6%).[31] Typically, clinical laboratories set the normal upper limit for 24-hour urine calcium excretion at 300 mg.[32] In this study, opting for a cutoff of 300 mg instead of 250 mg might have further raised the proportion of participants classified as having normal 24-hour urine calcium excretion. The substantial decrease in urine calcium excretion observed in extensive Phase 2 and Phase 3 clinical trials suggests a constant PTH replacement therapy effect. It is plausible that maintaining continuous PTH exposure to the renal tubule over a 24-hour period, as facilitated by active PTH release from the TransCon™ PTH prodrug, is imperative for achieving reduced urinary calcium excretion. Additionally, the post-hoc analysis of the PaTHway trial revealed a significant improvement in eGFR associated with TransCon™ PTH treatment at week 52, which was sustained at week 104.[33] Moreover, the Week 110 extension results of the PaTH Forward Trial have been disclosed. In addition to maintaining therapeutic goals such as independence from conventional therapy and discontinuation of all supplements, there were significant improvements in bone mineral density *Z*-scores and bone turnover markers, specifically C-terminal telopeptide of type 1 collagen and procollagen type 1 N-terminal propeptide.[34] These findings indicate the long-term and sustainable effects of the treatment. However, additional long-term data would be more beneficial to fully understand the durability of these effects. Overall, TransCon™ PTH therapy was tolerable, with no instances of withdrawal related to the study drug. It had beneficial effects on both kidney function and bone health, and it also improved the health-related quality of life and hypoparathyroidism symptoms. The outcomes of the PaTHway trial validate and broaden the earlier findings on the effectiveness of TransCon™ PTH treatment in reinstating the physiological functions of PTH among individuals with chronic hypoparathyroidism.

Eneboparatide: Eneboparatide (LA-PTH or AZP-3601) is a novel agonist of the PTH receptor 1 (PTHR1), which is a G protein-coupled receptor responsible for calcium regulation and an important therapeutic target for addressing hypoparathyroidism and osteoporosis.[35,36] Eneboparatide stimulates a specific PTH1 receptor conformation to maintain stable blood calcium concentrations without conventional therapies. It also regulates urine calcium excretion, thereby preventing kidney disease and promoting balanced bone turnover, which preserves bone integrity.[35,37] It has been granted fast-track designation by the FDA.[38] In an open-label Phase 2 study, two different cohorts (C1/C2) of patients were administered daily subcutaneous eneboparatide injections for a 3-month period after optimization. The starting doses were 20 µg/day (C1) or 10 µg/day (C2), with the option to escalate to 60 µg (C1) or 80 µg (C2). Meanwhile, conventional therapy was gradually reduced. The results of this study demonstrated that ≥88% of participants became independent of conventional therapy while maintaining within-range serum calcium concentrations. It led to a prompt and sustained decrease in average 24-hour urinary calcium levels, surpassing the effectiveness of previous medications. In fact, the average daily excretion of urinary calcium decreased from approximately 329 mg to 155 mg per day in C1, and from 331 mg to 166 mg in C2 during the main treatment phase and stayed the same in the extension phase. Moreover, the daily urinary calcium concentrations were normalized in 12 out of 13 patients with baseline hypercalciuria. Bone turnover markers showed a marginal increase, while bone mineral density remained constant, aligning with the gradual return to physiologic bone turnover processes. Eneboparatide was tolerated well with no reports of serious adverse events.[36] The Phase 3 clinical trial, known as the Calypso trial (NCT05778071), is currently ongoing in over 50 centers across the United States, Canada, and Europe. Its objective is to investigate the efficacy and safety of eneboparatide in 165 individuals with chronic hypoparathyroidism. Participants are randomly allocated in a ratio of 2 : 1 to receive either eneboparatide or a placebo. The primary endpoint is the percentage of participants who achieve normal serum calcium levels adjusted for albumin and no longer require conventional treatments after 24 weeks of eneboparatide initiation. Secondary endpoints include assessing the normalization of urinary calcium levels over a 24-hour period in participants with hypercalciuria, as well as evaluating patient-reported outcomes that indicate functional symptoms and their effect on quality of life. The other exploratory endpoint is bone evaluation through DXA and CT scanning. There will be a 28-week open-label extension period during which all patients will receive eneboparatide after the initial 24-week phase of comparing the drug to a placebo.[38]

Encaleret: Encaleret is an investigational small molecule that acts as a negative allosteric modulator of the calcium-sensing receptor, offering the potential for ADH1 treatment.[39] ADH1 is characterized by a gain-of-function mutation in the CaSR gene. This gene encodes the calcium-sensing receptor, which plays a significant role in regulating blood calcium concentration by modulating PTH secretion and renal calcium reabsorption. Genetic alterations render the CaSR more sensitive in ADH1, consequently leading to the misinterpretation of low blood calcium levels as within the normal range and decreased PTH secretion.[5,40] The standard of care for ADH1 is calcium and active vitamin D supplementation. Yet, this approach exacerbates hypercalciuria, promoting renal complications. Encaleret is the first therapeutic strategy targeting the underlying pathophysiological mechanism of ADH1. In the open-label Phase 2 trial, 13 patients with nine different CaSR variants were administered encaleret. After the inpatient dose-ranging sessions, participants entered a 24-week treatment period where encaleret was administered twice daily. During this phase, drug dosage adjustments were made, and conventional therapies were withheld. Encaleret effectively improved hypocalcemia and decreased hypercalciuria both during the inpatient sessions and throughout the 24-week outpatient period. Average intact PTH, magnesium, and active vitamin D concentrations elevated, while levels of phosphorus and phosphate tubular reabsorption declined. The required dose to provide normal calcium levels was broad, ranging from 5 to 190 mg twice daily. Yet, individual doses remained stable, requiring minimal adjustments. Renal function and existing renal calcifications did not deteriorate, and there were no instances of serious adverse events, treatment discontinuations, or study withdrawals.[41] The ongoing Phase 3 clinical trial, known as CALIBRATE (NCT05680818), is actively recruiting individuals diagnosed with ADH1 worldwide.[39,42] This trial aims to assess the safety and efficacy

of encaleret in ADH1 patients compared to the conventional treatment. The trial duration, including screening and optimization, is approximately a year, with participants having the option to participate in an extension phase lasting up to four years.[39,42] Overall, CaSR antagonists represent a promising targeted approach against ADH1.

MBX 2109: MBX 2109 is an investigational long-acting PTH prodrug administered once weekly subcutaneously.[43] It was developed utilizing the innovative Precision Endocrine Peptide (PEP) platform technology to ensure continuous exposure over time. Precision endocrine peptides are peptide hormone analogs that undergo selective modifications resulting in prolonged half-life, consistent drug concentrations, and constant exposure to target tissues. This allows for less frequent dosing requirements.[43,44] In the management of chronic diseases, frequent dosing poses a challenge, while opting for less frequent drug administration proves advantageous for promoting compliance. In the randomized, placebo-controlled, double-blind Phase 1 trial, which included 76 healthy adult participants, the safety, tolerability, pharmacokinetics, and pharmacodynamics of MBX 2109 for both single ascending doses (SAD) and multiple ascending doses (MAD) were assessed. In the SAD part, volunteers were randomly allocated to receive either a placebo or a single subcutaneous dose of MBX 2109 at doses ranging from 50 µg to 600 µg. During the MAD part, participants were randomly assigned to receive either a placebo or four once-weekly subcutaneous injections of MBX 2109 at doses of 200 µg, 400 µg, 600 µg, or 900 µg. Both single and repeat administrations of MBX 2109 were mostly well tolerated with no serious adverse events. After multiple doses, average albumin-adjusted serum calcium levels escalated in correlation with the dose. Additionally, endogenous PTH(1-84) was suppressed in a dose-dependent manner, aligning with the anticipated pharmacology. The outcomes of this phase 1 trial demonstrated safety and tolerability, confirming the intended prodrug design and its pharmacokinetics as well as pharmacodynamics.[45] The once-weekly administration of MBX 2109 is a distinguishing factor. However, it is important to ensure that PTH is not constantly active, as the duration and frequency of PTH exposure determine its overall impact on bone mass and skeletal homeostasis. Continual activation may potentially prompt calcium release from the bone, resulting in both hypercalcemia and reduced bone density, thereby increasing the risk of long-term osteopenia and osteoporosis.[46,47] Hence, safety endpoints associated with these variables necessitate thorough investigation. The Phase 2 trial is enrolling patients for evaluating MBX 2109 in individuals diagnosed with hypoparathyroidism.[43]

EB612: EB612 is an oral PTH tablet developed as a hormone replacement therapy for hypoparathyroidism. Its special oral peptide delivery platform aims to provide an alternative treatment option that may offer more convenience and flexibility. In a Phase 1 open-label study, 15 healthy male subjects received 1.5 mg of EB612 in the morning after an overnight fast and a second dose of 2.5 mg four hours after lunch. The study evaluated the pharmacokinetics and pharmacodynamics of EB612 by measuring plasma PTH(1-34) and serum levels of calcium, phosphate, 1,25$(OH)_2$-Vitamin D, and endogenous PTH(1-84). Results indicated that EB612 achieved significant systemic exposure and had the desired biological effects, including an average increase in serum calcium (+3.9%), a decrease in serum phosphate (−20.8%), an increase in 1,25$(OH)_2$-Vitamin D (+73.2%), and a decrease in endogenous PTH (−43.0%). These changes were sustained over the 14-hour study period, with no treatment-emergent adverse events, including hypercalcemia, observed. The study concludes that EB612 PTH(1-34) tablets, administered twice daily (BID), demonstrate potential as a convenient, flexible, safe, and effective oral therapy for patients with hypoparathyroidism.[48] These findings build on previous Phase 2 results using a four-times-daily regimen and suggest the benefits of the new BID dosing regimen enabled by novel delivery technology.[48,49]

Each treatment option exhibits distinct advantages over the others in various aspects. rhPTH(1-84) is the first PTH replacement therapy developed in addition to conventional treatment.[15] Despite globally ceasing production by the end of 2024 due to concerns about rubber particulates, it paved the way for the development of new drugs.[19] TransCon™ PTH employs innovative technology to achieve sustained release of PTH(1-34) and ensures a consistent pharmacokinetic profile that mirrors the physiological secretion patterns of PTH.[27,28] Eneboparatide is an agonist of PTH receptor 1, an important receptor for hypoparathyroidism and osteoporosis management. It regulates urine calcium excretion and promotes balanced bone turnover to preserve bone integrity.[35,37] Encaleret is a negative allosteric modulator of the calcium-sensing receptor, a gain-of-function mutation that leads to Autosomal Dominant Hypocalcemia type 1.[39,40] It is the first medication that targets the underlying pathophysiology of ADH1. MBX 2109 is a PTH prodrug administered subcutaneously once weekly.[43,44] Its less frequent dosing offers an advantage in promoting compliance for chronic disease management. EB612 is the first oral PTH tablet developed as a hormone replacement therapy, offering convenience in administration.[48]

The half-life of parathyroid hormone in plasma is very brief, lasting only a few minutes.[1] Ensuring that hormone replacement therapy replicates the physiological secretion pattern and maintains hormone concentrations within the physiological range is vital for maximizing therapeutic efficacy and minimizing the risk of adverse effects. Previously, twice-daily PTH(1-34) injections were found to be superior to once-daily injections, while continuous subcutaneous PTH(1-34) infusion via an insulin pump proved more effective than twice-daily injections in maintaining physiological PTH levels and stabilizing electrolyte concentrations.[28] Building on these findings, TransCon™ PTH utilizes transient conjugation technology to release active PTH upon exposure to physiological conditions. This innovative approach sustains active PTH levels in the lower half of the physiological range for 24 hours, offering a continuous pharmacokinetic profile that mimics the natural baseline secretion dynamics of PTH. TransCon™ PTH has a longer half-life of approximately 60 hours compared to endogenously secreted PTH and previously developed PTH-based therapies.[28] This extended duration allows once-daily injections to sustain physiological baseline PTH concentrations and promote a steadier serum calcium level with reduced daily fluctuations. Moreover, it reduces the risk of severe acute hypocalcemia in the event of missed doses.[28,30] Significantly, the bone turnover data for TransCon™ PTH align closely with findings in published literature indicating that continuous PTH administration does not exhibit an anabolic effect on bones.[28] However, it is important to bear in mind that excessive parathyroid hormone can lead to reduced bone mineral density, deterioration of bone microarchitecture, and an overall catabolic effect.[46] Similar to TransCon™ PTH, MBX 2109 employs Precision Endocrine Peptide technology to inhibit rapid hormone degradation, resist clearance by the liver and kidneys, and extend its half-life. Its pharmacokinetic and pharmacodynamic profiles support

its potential for once-weekly administration.[44,45] At this stage, it remains uncertain whether once-weekly administration will replicate the physiological secretion pattern of PTH. The medication's effect on average daily serum PTH concentrations and its impact on bone safety are not yet fully understood. Clinical trials and longitudinal studies are indispensable for comprehensively evaluating the long-term safety and efficacy of once-weekly administration and ensuring that the treatment optimally balances therapeutic benefits with minimal adverse effects. Confirming the safety of once-weekly administration could potentially lead to significant improvements in compliance. In contrast to PTH analogs with long half-lives, eneboparatide has a short circulating half-life of less than 1 hour.[36] However, it demonstrates sustained biological effects due to its high affinity for the R^0 conformation of the PTH1 receptor, resulting in extended intracellular signaling.[36] Notably, eneboparatide is superior in reducing urinary calcium excretion compared to other replacement therapies. Compared to TransCon™ PTH, where 60.7% of individuals achieved normal 24-hour urinary calcium excretion[31], eneboparatide treatment resulted in urinary calcium excretion normalization in 12 out of 13 patients with hypercalciuria.[36] Furthermore, eneboparatide treatment resulted in a reduction in average daily urinary calcium excretion from approximately 329 mg at baseline to 155 mg (C1), and from 331 mg to 166 mg (C2).[36] In comparison, individuals administered TransCon™ PTH experienced a decline from 392 mg/day to 220 mg/day.[31] This advantage could be attributed to eneboparatide's improved renal calcium reabsorption driven by the high affinity for the PTHR1 that is abundantly found in the kidney.[36]

Despite current guidelines recommending PTH replacement therapy as a last-resort option for patients with uncontrolled hypoparathyroidism[8], we expect that accumulating data from these novel agents will strengthen the quality of evidence supporting their use. This could potentially elevate PTH replacement therapy in the recommendations for managing hypoparathyroidism, possibly suggesting it as a primary treatment option.

Recent advances in treating chronic hypoparathyroidism through PTH/PTH receptor agonists and CaSR antagonists show promise as a therapeutic approach to restore physiological function. The concept of addressing not only serum calcium levels but also acknowledging underlying causes, managing symptoms, and preventing complications associated with the disease is now emerging as a crucial aspect in the treatment of hypoparathyroidism. Randomized clinical trials have evaluated the safety, efficacy, and tolerability of replacement therapies. Moreover, the presence of numerous ongoing trials signifies a major step forward in this field. PTH replacement presents a significant option for patients who fail to achieve satisfactory control with conventional therapy, representing a potential critical alternative approach.

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