Efficacy and Safety of Palopegteriparatide in Chronic Hypoparathyroidism: A Systematic Literature Review

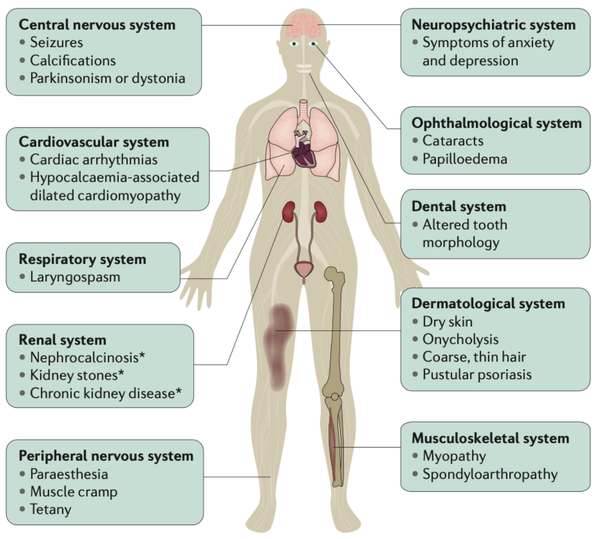
Authors: Adalton G. Ribeiro, Master[1], Fernanda Gimenes, Master[1], Celina Borges Migliavaca, PhD[2]
[1] Market Access, Adium Pharma, São Paulo, Brazil, [2] HEOR, Inova Medical, Porto Alegre, Brazil

CO217

Background

Chronic hypoparathyroidism (HypoPT) is a rare endocrine disorder characterized by insufficient parathyroid hormone (PTH) secretion, leading to disrupted calcium and phosphate homeostasis and significant clinical burden (Figure 1).[1] The disease affects approximately 23-37 individuals per 100,000, with post-surgical HypoPT accounting for up to 75% of cases.[1,2] Beyond the challenges of maintaining biochemical control, patients face an elevated risk of cardiovascular complications, including heart failure, atrial fibrillation, and coronary artery disease, as well as increased overall mortality.[3,4] Disease severity and prolonged exposure to conventional therapy are associated with worse clinical outcomes, highlighting the need for therapies that restore physiological calcium regulation and address the underlying hormone deficiency.[1,5]

Figure 1: Clinical manifestations of HypoPT.

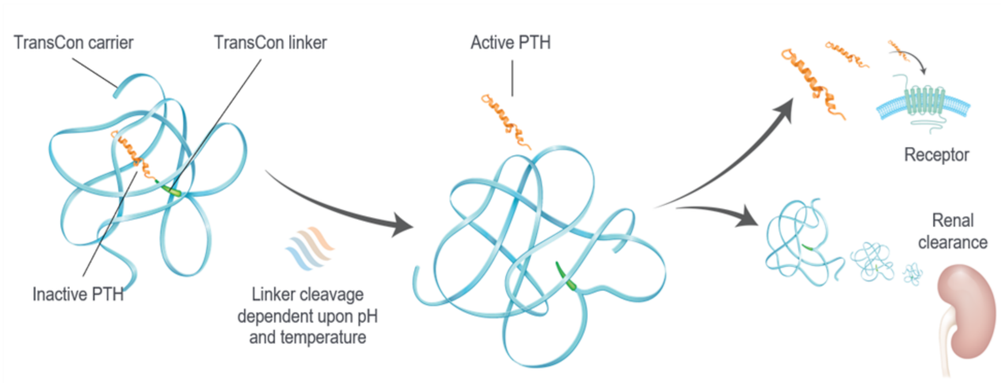


Source: Mannstadt et al., 2017.[2]

Yorvipath® (palopegteriparatide) is a prodrug of PTH (1-34), administered once daily, designed to provide active PTH within the physiological range for 24 hours/day in adults with hypoparathyroidism. It is designed to restore physiological PTH activity rather than simply manage the biochemical consequences of hormone deficiency.

Using **TransCon® technology**, palopegteriparatide provides continuous exposure of active PTH within the physiological range for 24 hours/day, supporting a more physiological regulation of calcium and phosphate homeostasis.

Figure 2: Palopegteriparatide (TransCon® PTH).



This mechanism is designed to maintain normal levels of serum calcium, normalization of serum phosphate, and reduction of calciuria, leading to an effective recovery of calcium and phosphate homeostasis in the body.

Conventional treatment controls symptoms but does not address the underlying PTH deficiency in chronic HypoPT. Palopegteriparatide is the first long-acting PTH replacement therapy designed to restore physiological hormone activity, offering a disease-targeted approach aimed at improving calcium homeostasis and reducing long-term complications.

Objectives

This systematic review aimed to evaluate the efficacy and safety of palopegteriparatide in adults with chronic hypoparathyroidism.

Methods

The research question, structured in the PICOT format (population, intervention, comparator, outcome, type of study), is presented in Table 1. A search was performed in the MEDLINE (via PubMed), Embase, and Cochrane *Controlled Register of Trials* (CENTRAL) databases, on January 5th, 2026. Risk of bias and certainty of evidence were assessed using RoB-2 and GRADE, respectively.

Table 1: Research question structured in the PICOT format.

Component	Description
P (population)	Adults (≥ 18 years) with chronic hypoparathyroidism.
I (intervention)	Palopegteriparatide in dosage (to be) recommended in the package insert.
C (comparator)	Placebo or other active treatments (such as calcium and vitamin D), no comparator.
O(outcome)	Serum calcium levels, need for calcium and vitamin D supplementation, quality of life, safety. Other clinically relevant outcomes identified in the studies have also been described.
T (type of study)	Clinical trials and systematic reviews

Results

In a literature search, 189 unique references were identified, of which 36 were selected for the evaluation of the full text. Two randomized controlled trials, reported in nine publications, were included in this review. The characteristics of the included randomized controlled trials and their main efficacy and safety outcomes are presented in Table 2 and 3, respectively.

Table 2: Characteristics of randomized controlled trials included.

Study	Phase/Design	Population	Treatment	Follow-up	Primary Endpoint (Composite Outcome)
PaTH Forward (NCT04009291)[6]	Phase II, randomized, double-blind, placebo-controlled	Adults with chronic hypoparathyroidism (n=59)	Palopegteriparatide (15-21 µg/day) vs placebo	4-week DB + 262-week OLE	Normal serum calcium; fractional excretion of urinary calcium ≤2% or ≥50% reduction from baseline; discontinuation of active vitamin D; calcium supplementation ≤1,000 mg/day
PaTHway (NCT04701203)[7,8]	Phase III, randomized, double-blind, placebo-controlled (Figure 3)	Adults with chronic hypoparathyroidism (n=82)	Palopegteriparatide 18 µg/day vs placebo	26-week DB + 156-week OLE	Normal adjusted serum calcium (8.3-10.6 mg/dL); independence from active vitamin D[a]; calcium supplementation ≤600 mg/day without dose increase during the previous 4 weeks

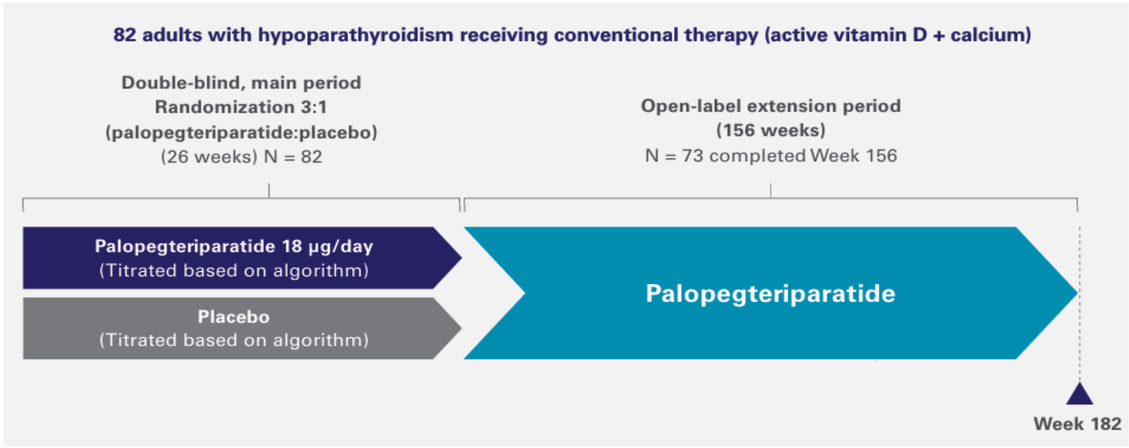
DB: double-blind; OLE: open label extension.
[a] Not taking active vitamin D and taking ≤600 mg/day of elemental calcium and use of any PRN for both vitamin D and calcium ≤7 days within 4 weeks prior to the Week 26 visit.

Table 3: Main efficacy and safety outcomes of the included randomized controlled trials.

Key Results with Palopegteriparatide	PaTH Forward[a] (n = 15 vs. 15, 4 weeks)	PaTHway (n = 61 vs. 21, 26 weeks)
🎯 Composite endpoint achieved	40% vs. 27%	79% vs. 5%
💊 Active vitamin D independence	93% vs. 40%	98% vs. 24%
🦴 Calcium supplementation independence	87% vs. 53%	93% vs. 5%
✅ Serious treatment-related adverse events	None	None

Data presented as palopegteriparatide vs. placebo.
[a] Results for palopegteriparatide based on patients who received palopegteriparatide 18 mcg/day.

Figure 3: Phase 3 PaTHway Trial Design (NCT04701203).



🟢🟢🟢🟢 **HIGH-CERTAINTY EVIDENCE (GRADE)**

Composite endpoint • Active vitamin D independence • Calcium supplementation independence

PaTHway Phase III trial (n=82)

No relevant limitations related to risk of bias, inconsistency, indirectness, imprecision or publication bias were identified

Conclusions

Palopegteriparatide maintained serum calcium within the normal range and reduced dependence on conventional therapy in adults with chronic hypoparathyroidism (HypoPT). Across the Phase II and Phase III studies, treatment demonstrated consistent efficacy, achieving high rates of independence from active vitamin D and calcium supplementation while maintaining normocalcemia and exhibiting a favorable safety profile.

References

1. Gafni RI, Collins MT. Hypoparathyroidism. N Engl J Med. 2019; 380(18):1738-47
2. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. Nat Rev Dis Primers. 2017;3:17055
3. Gosmanova EO, Chen K, Ketteler M, et al. Risk of Cardiovascular Conditions in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. Adv Ther. 2021; 38:4246-57
4. Dutta D, Mahajan K, Mittal A, et al. Cardiovascular Morbidity and Mortality in Chronic Hypoparathyroidism: A Systematic Review and Meta-Analysis. Calcif Tissue Int. 2026; 117(157)
5. Khan AA, Guyatt G, Ali DS, et al. Management of Hypoparathyroidism. J Bone Miner Res. 2022;37(12):2663-77
6. Khan AA, Rejnmark L, Rubin M, Schwarz P, Vokes T, Clarke B, et al. PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism. J Clin Endocrinol Metab. 2022; 107(1):e372-e85
7. Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. J Bone Miner Res. 2023; 38(1):14-25
8. Clarke BL, Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, et al. Efficacy and Safety of TransCon PTH in Adults With Hypoparathyroidism: 52-Week Results From the Phase 3 PaTHway Trial. J Clin Endocrinol Metab. 2025; 110(4):951-60

Contacts

Adalton Ribeiro: adalton.ribeiro@adium.com.br
Fernanda Gimenes: fernanda.gimenes@adium.com.br
Celina Migliavaca: celina@inovamedical.com.br