**Supplementary Table 6: Study details PTH replacement therapy**

| Study<br>-<br>Design | Population | Intervention | Outcomes of interest | Results | Adverse events of interest (*n*) | Comments |
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| **PTH(1-84)** | | | | | | |
| Ayodele (2022)[1]<br>-<br>Cohort study with historical controls<br><br>USA | Individuals with chronic hypoparathyroidism treated with rhPTH(1-84) (cohort, n = 113, 79% female) or not treated with rhPTH(1-84) (controls, n = 618, 82% female) | rhPTH(1-84) | Cardiovascular events | Over the 5-y follow-up period, 3.5% in the rhPTH(1-84) cohort had a cardiovascular event^ vs. 16.3% in controls; adjusted HR of developing a cardiovascular event in rhPTH(1-84) cohort 0.25 (95%CI 0.08-0.81, p = 0.020)<br><br>^cerebrovascular disease (n = 1), coronary artery disease (n = 2), peripheral vascular disease (n = 1) | - | Subjects derived from REPLACE, RELAY and RACE studies |
| Clarke (2017)[2]<br>-<br>REPLACE study; phase III RCT<br><br>USA, Canada, Denmark, Hungary, Belgium, France, Italy, UK | Individuals with chronic hypoparathyroidism ≥ 1 year (n = 124), 79% female<br><br>*Treatment before study entry:*<br>≥ 3 months on regular use of vitamin D supplements. All patients were on daily calcium supplement | 50 µg/day rhPTH(1-84) subcutaneously, escalated to 75 and then to 100 µg/day (downtitration allowed) (n = 84) or placebo (n = 40) for 24 weeks as add-on therapy to conventional treatment | Phosphate level, pill burden | At week 24:<br>- serum phosphate levels declined by 0.2±0.02 mmol/L in study group vs. no change in placebo (p < 0.001)<br>- 77±4% reduction in activated vitamin D dose vs. 35±7% reduction for placebo (p < 0.001)<br>- 1126±104 mg/day reduction in calcium dose compared to 113±161 mg/day reduction for placebo (p < 0.001) | - | Results of REPLACE study included in systematic review of original HypoPT guideline – this study included because of interest in different endpoints<br><br>*Supported by NPS Pharmaceuticals* |
| Khan (2024)[3]<br>- | Individuals with chronic hypoparathyroidism ≥ | 50 µg/day rhPTH(1-84) subcutaneously, if needed increased by increments of 25 µg | Serum calcium and phosphate, 24-h urinary calcium excretion, pill burden, bone markers, | At week 24:<br>- 100% (95%CI 84-100%) of patients with albumin- | Hypocalcemia n = 4<br>Hypercalcemia n = 5<br>Infection n = 8 | Subjects had previously completed the PARALLAX study |

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| Phase 4, open-label extension study<br><br>USA, Canada, Denmark, Hungary | 1 year (n = 22), 82% female | to a maximum dose of 100 µg/day (downtitration allowed) for 52 weeks as add-on therapy to conventional treatment | HRQoL (EQ-5D-5L VAS, HypoPT-SD) | corrected serum calcium levels in target range<br>- mean (SD) BALP 33.6 (14.3) U/L vs. 17.8 (5.1) U/L at baseline, p < 0.001<br>- mean (SD) osteocalcin 50.1 (23.3) µg/L vs. 15.3 (5.4) µg/L at baseline, p < 0.001<br>- mean (SD) P1NP 179.6 (86.3) µg/L vs. 37.5 (15.8) µg/L at baseline, p < 0.001<br>- mean (SD) CTX 655.5 (303.8) ng/L vs. 204.0 (86.9) ng/L at baseline, p < 0.001<br>- mean (SD) EQ-5D-5L VAS score 80.3 (19.5) vs. 75.5 (20.6) at baseline, p = 0.29<br>- mean (SD) HypoPT-SD symptom subscale 0.8 (0.8) vs. 1.2 (1.0) at baseline, p < 0.05<br>- mean (SD) HypoPT-SD impact subscale 0.4 (0.6) vs. 0.6 (0.7) at baseline, p < 0.05<br><br>At week 52:<br>- 96% (95%CI 77-100%) of patients with albumin-corrected serum calcium levels in target range<br>- mean (SD) albumin-corrected serum calcium 2.1 (0.1) mmol/L vs. 2.1 (0.2) mmol/L at baseline, p = 0.04<br>- mean (SD) serum phosphorus 1.2 (0.2) mmol/L vs. 1.3 (0.3) | Gastrointestinal symptoms n = 6<br>Muscle spasms n = 3<br>Paresthesia n = 2<br>Myalgia n = 2<br>Psychiatric disorder n = 4 | *Supported by Takeda Pharmaceuticals* |

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| | | | | mmol/L at baseline, p = 0.01<br>- mean (SD) 24-h urine calcium excretion 7.9 (3.1) mmol/24h vs. 10.7 (4.0) mmol/24h at baseline, p = 0.002<br>- 35% of patients with 24-h urine calcium excretion in normal range vs. 14% at baseline<br>- mean (SD) daily calcium supplementation 855 (759) mg vs. 2402 (2350) mg at baseline<br>- mean (SD) daily active vitamin D supplementation 0.2 (0.3) µg vs. 0.8 (0.4) µg at baseline<br>- mean (SD) BALP 34.2 (15.9) U/L vs. 17.8 (5.1) U/L at baseline, p < 0.001<br>- mean (SD) osteocalcin 60.3 (38.6) µg/L vs. 15.3 (5.4) µg/L at baseline, p < 0.001<br>- mean (SD) P1NP 201.7 (146.6) µg/L vs. 37.5 (15.8) µg/L at baseline, p < 0.001<br>- mean (SD) CTX 655.5 (303.8) ng/L vs. 204.0 (86.9) ng/L at baseline, p < 0.001<br>- mean (SD) EQ-5D-5L VAS score 82.3 (17.1) vs. 75.5 (20.6) at baseline, p = 0.02<br>- mean (SD) HypoPT-SD symptom subscale 0.8 (0.8) vs. 1.2 (1.0) at baseline, p < 0.001<br>- mean (SD) HypoPT-SD impact subscale 0.3 (0.5) vs. | | |

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| | | | | 0.6 (0.7) at baseline, p < 0.001 | | |
| Marcucci (2022)[4]<br>-<br>Open-label intervention study<br><br>Italy | Individuals with chronic hypoparathyroidism (various etiologies) for mean 25.3 (range 3-56) years (n = 14), 93% female<br><br>*Treatment before study entry:*<br>All on oral calcium supplements (mean dose 2884,6 mg/day) and calcitriol (mean dose 1.19 µg/day).<br>n = 8 previously treated with rhPTH(1-34) | Initial rhPTH(1-84) dose 50 µg/day (86%) or 25 µg/day (14%) subcutaneously, at 1 year 100 µg/day (54%), 75 µg/day (31%) or 50 µg/day (15%) (1 person discontinued at 6 months) as add-on therapy to conventional treatment | Serum calcium and phosphate, 24-h urinary calcium excretion, serum creatinine, eGFR, neuromuscular symptoms (muscle cramps, paresthesia, tingling), pill burden, cataract, fractures | At 1 month:<br>- increase in mean 24-h urinary calcium excretion (p = 0.006 – no absolute values reported) albeit remaining in the normal range and maintaining similar values over follow-up<br>- at baseline neuromuscular symptoms in 5/14 patients (36%), regressed in 4/5 patients during the first month of treatment<br><br>At 1 year:<br>- increase (normalization) in serum calcium (p < 0.001)<br>- linear decrease in phosphate level from 3 to 12 months compared to baseline; levels maintained within normal range<br>- serum creatinine and eGFR remained within the normal range with no significant differences during the study period<br>- reduction in calcium dose from 2884±1793 mg/day to 423±760 mg/day; 61.5% discontinued calcium supplementation<br>- reduction in calcitriol dose from 1.2±0.7 mcg/day to 0.21±0.56 mcg/day; 69.2% discontinued calcitriol | During first 3 months of treatment:<br>- hypocalcemia in 36%<br>- hypercalcemia in 7%<br><br>After 3 months treatment mild hypocalcemia persisted in 1 patient (7%)<br><br>No new kidney stones or nephrocalcinosis<br><br>No cardiovascular complications<br><br>No cataract<br><br>No fragility fractures | |
| Rejnmark (2023)[5]<br>- | Individuals with chronic | rhPTH(1-84) | Incident chronic kidney disease (CKD) | Over the 5-y follow-up period, 11% in the rhPTH(1- | - | Subjects derived from REPLACE, RELAY, RACE, |

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| Cohort study with historical controls<br><br>USA | hypoparathyroidism treated with rhPTH(1-84) (cohort, n = 118, 76% female) or not treated with rhPTH(1-84) (controls, n = 497, 78% female) | | Sustained eGFR decline ≥30% from baseline | 84) cohort developed incident CKD vs. 27.4% in controls; adjusted HR of developing incident CKD in rhPTH(1-84) cohort 0.47 (95%CI 0.25-0.87, p = 0.016)<br><br>For sustained eGFR decline: 4.2% in the rhPTH(1-84) cohort vs. 19.9% in controls; adjusted HR in rhPTH(1-84) cohort 0.35 (95%CI 0.13-0.89, p = 0.029) | | HEXT and its continuation study |
| Rubin (2010)[6]<br>-<br>Open-label, single-arm study<br><br>USA | Individuals with chronic hypoparathyroidism for ≥ 3 years (n = 30), 73% female | 100 µg intact PTH (1-84) subcutaneously every other day as add-on therapy to conventional treatment (calcium and active vitamin D) for 24 months | BMD | - BMD femoral neck unchanged (exact numbers n.r.)<br>- 2.9%±4% BMD increase at lumbar spine, p < 0.05<br>- 2.4%±4% BMD decrease one third radius, p < 0.05 | - | Results of this study were also included in systematic of original HypoPT guideline; here only new outcome of interest (i.e., bone) reported<br><br>*Supported by NPS Pharmaceuticals* |
| Rubin (2024)[7]<br>-<br>Phase 4, single-center, open-label, single-arm, 3-year extension of phase 3 HEXT study<br><br>USA | Individuals with chronic hypoparathyroidism for ≥ 1 year (n = 39), 80% female | Daily rhPTH(1-84) dosages varying between 25 and 100 µg as add-on therapy to conventional treatment for 35.5 mo<br><br>Mean duration of rhPTH(1-84) before present study 8.5 SD 3.5 years | Albumin-adjusted serum calcium, phosphate level, 24-h urine calcium excretion, bone markers, BMD, pill burden<br>HRQoL evaluated by:<br>- Hypoparathyroidism Symptom Diary (HypoPT-SD)<br>- Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-IF)<br>- Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)<br>- Hospital Anxiety and Depression Scale (HADS) | End of treatment (EOT):<br>- Mean albumin-adjusted serum calcium increase from 7.7 SD 0.9 mg/dL at baseline to 8.3 SD 1.1 mg/dL EOT, with most patients having levels from 7.5 mg/dL to ULN during the study<br>- mean serum phosphate level 3.9 SD 0.7 mg/dL at baseline and 4.1 SD 0.7 mg/dL at EOT; maintained in normal range during the study | 261 treatment-emergent AEs reported in 36 patients; in 4 patients considered treatment-related, a.o.:<br>- hypercalcemia (n = 1)<br>- renal disorder (n = 1)<br>- ureterolithiasis (n = 1)<br><br>24 SAE's reported in 6 patients, none considered treatment-related | Subjects derived from REPLACE, RELAY, RACE, HEXT studies or not enrolled previously in a study<br><br>48-mo treatment period planned; study terminated early because of recall of rhPTH(1-84) in US in 2019; mean length of rhPTH(1-84) exposure during present study 30.3 SD 5.8 mo |

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| | | | - RAND 36-item Short Form Health Survey (SF-36) | - 24-h urine calcium excretion 220.8 SD 129.7 mg at baseline and 264.1 SD 152.7 at EOT, maintained below or around ULN during the study<br>- no changes in BALP, osteocalcin, P1NP, s-CTX, TRAP-5b or sclerostin from baseline to EOT<br>- mean BMD Z-score fell at one-third radius at other sites no clinically meaningful changes from baseline to EOT<br>- stable requirements of conventional therapy supplementation doses during the study (NB before study, patients were already treated with rhPTH(1-84) for mean 8.5y)<br>- "patients HRQoL scores were generally maintained" | | |
| Sikjaer (2012)[8]<br>-<br>RCT<br><br>Denmark | Individuals with chronic hypoparathyroidism (various etiologies) for ≥ 1 year (n = 62), 85% female<br><br>*Treatment before study entry:*<br>≥ 3 months on regular use of vitamin D supplements. All patients were on daily calcium supplement | Daily 100 µg intact PTH (1-84) (n = 32) or placebo (n = 30) subcutaneously as add-on therapy to conventional treatment (calcium and active vitamin D) for 24 weeks | Bone markers, BMD | At 6 months:<br>- 226%±36% increase in BALP levels in study group, $p < 0.01$ compared to placebo (numbers for placebo n.r.)<br>- 807%±186% increase in osteocalcin levels in study group, $p < 0.01$ compared to placebo (numbers for placebo n.r.)<br>- 1315%±330% increase in P1NP levels in study group, $p < 0.01$ compared to placebo (numbers for placebo n.r.) | - | Results of this study were also included in systematic review of original HypoPT guideline; here only new outcome of interest (i.e., bone) reported<br><br>*Nycomed supplied study drugs for free* |

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| | | | | - 1209%±459% increase in s-CTX levels in study group, p < 0.01 compared to placebo (numbers for placebo n.r.)<br>- 830%±165% increase in NTX levels in study group, p < 0.01 compared to placebo (numbers for placebo n.r.)<br>- 1.59%±0.57% BMD decrease at hip in study group<br>- 1.76%±1.03% BMD decrease at lumbar spine in study group<br>- 1.26%±0.49% BMD decrease whole body in study group | | |
| Sikjaer (2014)[9]<br>-<br>RCT<br><br>Denmark<br><br>Extension study of Sikjaer (2011) | Individuals with chronic hypoparathyroidism (various etiologies) for ≥ 1 year (n = 62), 85% female<br><br>*Treatment before study entry:*<br>≥ 3 months on regular use of vitamin D supplements. All patients were on daily calcium supplement | Daily 100 µg intact PTH (1-84) (n = 32) or placebo (n = 30) subcutaneously as add-on therapy to conventional treatment (calcium and active vitamin D) for 24 weeks | Calcium and phosphate levels, QoL (evaluated by RAND 36-item Short Form Health Survey and WHO-5 Well-Being Index) | At 6 months:<br>- median ionized calcium level 1.20 (IQR 1.16-1.29) mmol/L in study group vs. 1.17 (IQR 1.09-1.22) in placebo, p = 0.02<br>- median phosphate level 0.97 (IQR 0.86-1.12) mmol/L in study group vs. 1.12 (IQR 0.94-1.18) in placebo, p < 0.05<br>- PTH did not improve QoL SF-36: no numerical results reported<br>WHO-5 W-B I: 11% increase in treatment group (IQR -2.8-38.3%), 13.6% increase in placebo group (IQR -2.5 – 38.3%), p = 0.80 | End of study:<br>- hypocalcemia: 21.7% in PTH treatment group and 53% in placebo group<br>- hypercalcemia: 21.7% in PTH treatment group and 10% in placebo group | Results of Sikjaer (2011) study included in SR of original hypopara guideline<br><br>*Nycomed supplied study drugs for free* |
| Tabacco (2019)[10]<br>-<br>Open-label intervention study | Individuals with postsurgical (60%) or idiopathic (40%) chronic | Daily rhPTH(1-84) dosages varying between 25 and 100 µg as add-on therapy | QoL (evaluated by RAND 36-item Short Form Health Survey) | At 8 years follow-up: significant improvement compared to baseline in domains “vitality” (45.3±5.6 | Hypercalcemia 2% | Results of Rubin (2010) study included in SR of original hypopara guideline |

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| 8-year extension study of Rubin (2010)<br><br>USA | hypoparathyroidism for ≥ 1 year who reached the 8-year time point with QoL assessment (n = 20), 80% female<br><br>*Treatment before study entry:*<br>≥ 6 months on stable regimen of calcium and/or vitamin D supplements. All patients were PTH-analogue treatment naïve | to conventional treatment | | vs 35±5), "role limitations caused by emotional health problems" (71.7±8.8 vs 63.3±9.6) and "bodily perception" (66.9±6.3 vs 55.1±5) (all $p < 0.05$), and "mental health" (71.2±4 vs 60±4.4), "social functioning" (78.1±5.2 vs 63.1±5.3), and "perception of general health" (57.5±4.7 vs 48.5±4.3) (all $p < 0.01$) | | *Funded by Shire* |
| Watts (2023)[11]<br>-<br>Open-label intervention study<br><br>6-year extension study of RACE study<br><br>USA | Individuals with chronic hypoparathyroidism after completion of the 24-w REPLACE study and/or the 8-w RELAY study (n = 49), 82% female | Daily rhPTH(1-84) dosages varying between 25 and 100 µg as add-on therapy to conventional treatment for 72 mo<br><br>25 µg/day n = 1<br>50 µg/day n = 10<br>75 µg/day n = 8<br>100 µg/day n = 30 | Albumin-adjusted serum calcium, phosphate level, % hypercalciuria (women ≥ 6.25 mmol/24h, men ≥ 7.5 mmol/24h), 24-h urine calcium excretion, eGFR, CKD, pill burden, bone markers, BMD, cramps, tetany, infection, digestion, pain | At 72 months:<br>- mean albumin-adjusted serum calcium was within target rage at baseline and through month 72. Mean change from baseline – 0.02 ± 0.0202 mmol/L<br>- mean phosphate level was above reference range at baseline and declined after rhPTH(1-84) treatment initiation; mean change from baseline – 0.3 ± 0.022 mmol/L<br>- women with hypercalciuria 69.2% at baseline to 33.3% at 72 mo, men 66.7% to 34%<br>- 24h urinary calcium excretion women 8.6 ± 4.60 mmol/24h at baseline to 5.4 ± 2.93 mmol/24h at 72 mo, men 10.3 ± 6.67 mmol/24h at baseline to | - Nephrolithiasis in 6 patients (12.2%)<br>- No nephrocalcinosis however no routine US imaging; rate of asymptomatic nephrocalcinosis not ascertained<br><br>- Hypercalcemia in 6 patients (12.2%; number of events n.r.)<br>- Hypocalcemia: 51 events in 19 patients (38.8%)<br><br>- Muscle spasms: 46 events in 19 patients (38.8%)<br>- Tetany in 4 patients (8.2%; number of events n.r.)<br>- Paresthesia: 38 events in 15 patients (30.6%) | *Funded by Takeda Pharmaceuticals* |

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| | | | | 6.9 ± 4.66 mmol/24h at 72 mo<br>- 24h urinary calcium mean change from baseline – 0.04 ± 0.063 mmol/kg/24h<br>- mean EGFR 78.1 ± 17.75 mL/min per 1.73m$^2$ at baseline and 81.5 ± 18.27 mL/min/1.73m$^2$ at 72 mo<br>- n = 2 had CKD stage 3a at baseline, n = 4 CKD 3a at 72 mo. None progressed to CKD stages 3b, 4 or 5.<br>- mean 45±114% reduction in calcium dose<br>- mean 74±39% reduction in calcitriol dose<br>- levels of BALP, P1NP and s-CTX initially increased with rhPTH(1-84) treatment, then declined by month 32 to steady-state values that remained above pretreatment levels<br>- mean BMD Z-score fell at one-third radius and was stable at other sites | - Sinusitis: 31 events in 16 patients (32.7%)<br>- Bronchitis: 16 events in 12 patients (24.5%)<br>- Nasopharyngitis: 22 events in 11 patients (22.4%)<br>- Urinary tract infection: 14 events in 10 patients (20.4%)<br>- Influenza: 11 events in 10 patients (20.4%)<br><br>- Nausea: 20 events in 15 patients (30.6%)<br>- Constipation: 11 events in 10 patients (20.4%)<br>- Diarrhea: 11 events in 10 patients (20.4%)<br><br>- Arthralgia: 19 events in 13 patients (26.5%)<br>- Back pain: 11 events in 10 patients (20.4%)<br>- Pain in extremity: 17 events in 10 patients (20.4%) | |
| **PTH(1-34)** | | | | | | |
| Gafni (2018)[12]<br>-<br>Open-label intervention study<br><br>USA | Individuals with chronic hypoparathyroidism (various etiologies) for ≥ 1 year (n = 32), 78% female<br><br>*Treatment before study entry:*<br>Calcitriol was discontinued before study entry. | Twice daily synthetic hPTH(1-34) subcutaneously (n = 29, mean starting dose 0.40±0.06 µg/kg/day) or three times daily synthetic hPTH(1-34) subcutaneously (n = 2, mean starting dose 0.47±0.04 µg/kg/day) as add-on therapy to | 24-h urine calcium excretion, eGFR, imaging (renal CT and US) for nephrocalcinosis (NC) and/or nephrolithiasis (NL) | At 6 months:<br>- significant decrease in 24-h urine calcium excretion ($p < 0.001$)<br>- significant increase in EGFR ($p < 0.01$)<br><br>At last PTH injection (mean 37.1 months, range 7.5-63.9 months):<br>- significant decrease in 24-h urine calcium excretion ($p < 0.001$) | Treatment discontinuation in 23 patients, none related to this systematic review's outcomes of interest | |

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| | Vitamin D deficient subjects were treated with ergo- or cholecalciferol. All patients had a daily calcium intake targeted at 1 or 2 grams, through diet or supplements. | conventional treatment<br><br>During the study, potassium citrate 30-60 meq/day was given to subjects with urine calcium/citrate ratios >0.7 mg/mg | | - significant increase in EGFR ($p < 0.001$)<br><br>26% had NC/NL at baseline, which did not significantly change during PTH treatment. 3% had mild NL at baseline, which resolved during PTH treatment. 32% developed new-onset NC/NL during treatment. In 19% NC/NL worsened. | | |
| Ish-Shalom (2021)[13]<br>-<br>Open-label pilot study<br><br>Israel | Individuals with chronic hypoparathyroidism (various etiologies) ≥ 1 year (n = 19), 84% female<br><br>*Treatment before study entry:*<br>All patients were on daily calcium supplements (≥ 1 g/day) and calcitriol | Four times a day 0.75 mg oral hPTH(1-34), uptitrated to 9 mg/day, as add-on therapy to conventional treatment during 16 weeks | Albumin-adjusted serum calcium, 24-h urine calcium excretion, QoL (evaluated by EuroQoL VAS score), pill burden | At 16 wk (n = 15 completed the trial):<br>- Albumin-adjusted serum calcium levels remained median around 8 mg/dL throughout the study<br>- Mean 24-h urine calcium excretion 140.5±82.4 vs 189.8±131.4 mg at baseline, $p = 0.07$<br>- EuroQoL VAS score median 80 (range 60-100) vs median 80 (range 60-100) at baseline, $p = 0.03$<br>- median 42% reduction from baseline in exogenous calcium dose | No hypercalcemia | *Patients not on-target at study baseline*<br><br>*Supported by Enteria Bio Ltd* |
| Khan (2022)[14]<br>-<br>Phase II 4-wk RCT, with 210 wk open-label extension (PaTHway); data of week 4 and 26 here reported<br><br>North America and Europe | Individuals with chronic hypoparathyroidism (various etiologies) for ≥ 26 weeks (n = 59), 81% female<br><br>*Treatment before study entry:*<br>All patients were on daily calcium supplements (≥ 800 | Once daily 15, 18 or 21 µg TransCon PTH(1-34) (n = 44) or placebo (n = 15) subcutaneously as add-on therapy to conventional treatment during 4 weeks, at follow-up visits titrated in steps of 3 µg | Proportion of patients who achieved composite endpoint, i.e. serum calcium levels in the normal range (8.3 - 10.6 mg/dL), urine fractional excretion of calcium within normal range or >50% reduced, discontinuation of all vitamin D supplements and reduction in calcium suppletion to ≤ 1000 | At 4 wk:<br>- 50% in the TransCon cohort vs. 15% in placebo achieved composite endpoint, $p < 0.03$<br>- 82% in the TransCon cohort vs. 15% in placebo could stop vitamin D and reduce calcium supplements to ≤ 500 mg/day, $p < 0.0001$ | Nausea 8.5%, arthralgia 5.1%, hypocalcemia 5.1%, muscle spasm 5.1%, urinary tract infection 5.1% | n = 12 previously treated with PTH replacement therapy<br><br>*Supported by Ascendis Pharma Bone Diseases A/S* |

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| | mg/day) and calcitriol (≥ 0.50 µg/day) or alfacalcidol (≥ 1.0 µg/day) for ≥ 3 months | Doses for extension period ranged from 6-60 µg/day | mg/day or ≤ 500 mg/day. serum calcium, phosphate levels, 24-h urine calcium excretion, absolute doses of calcium and vitamin D, P1NP, CTx. Hypoparathyroidism Patient Experience Scale (HPES), QoL (evaluated by RAND 36-item Short Form Health Survey) | - 50% in the TransCon cohort vs. 0% in placebo achieved complete independence from conventional treatment, $p < 0.0001$<br>- TransCon demonstrated improved QoL compared to baseline for all SF-36 domains compared to placebo, $p < 0.05$<br>- TransCon demonstrated significant improvement in HPES-symptom and impact scales compared to placebo, $p < 0.01$<br>At 26 wk:<br>- 71% in the TransCon cohort achieved composite endpoint<br>- 91% in the TransCon cohort vs. 15% in placebo could stop vitamin D and reduce calcium supplements to ≤ 500 mg/day<br>- 76% in the TransCon cohort vs. 0% in placebo achieved complete independence from conventional treatment<br>- mean albumin-adjusted serum calcium and phosphate levels remained in normal range in both groups<br>- mean 24h urine calcium excretion decreased from 415 mg/24h to 178 mg/24h in the TransCon cohort | | |

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| | | | | - in the TransCon cohort, mean (SD) P1NP increased to 88 (44) ng/mL, mean (SD) CTx increased to 763 (412) ng/mL<br>- TransCon demonstrated maintained QoL compared to baseline for all SF-36 domains | | |
| Khan (2023)[15]<br>-<br>Phase III 26-wk RCT, with 156 wk open-label extension (PaTHway); data of 26-wk phase here reported<br><br>North America and Europe | Individuals with chronic hypoparathyroidism (various etiologies) for ≥ 26 weeks (n = 82), 52% female<br><br>*Treatment before study entry:*<br>All patients were on daily calcium supplements (≥ 800 mg/day) and calcitriol (≥ 0.50 µg/day) or alfacalcidol (≥ 1.0 µg/day) for ≥ 3 months | Once daily 18 µg TransCon PTH(1-34) (n = 61) or placebo (n = 21) subcutaneously as add-on therapy to conventional treatment, titrated in steps of 3 µg to an allowable dose (6-60 µg/day), for 26 weeks | Proportion of patients who achieved albumin-adjusted serum calcium levels in the normal range (8.3 - 10.6 mg/dL) at 26 wk, albumin-adjusted serum calcium, phosphate levels, 24-h urine calcium excretion, eGFR, Hypoparathyroidism Patient Experience Scale (HPES), QoL (evaluated by RAND 36-item Short Form Health Survey), pill burden | At 26 wk:<br>- 80.3% in the TransCon cohort vs. 47.6% in placebo achieved albumin-adjusted serum calcium levels in the normal range<br>- mean albumin-adjusted serum calcium levels remained in normal range in both groups<br>- phosphate levels remained in normal range in both groups<br>- 60.7% in the TransCon cohort vs. 28.6% in placebo achieved 24-h urine calcium excretion in the normal range (≤ 250 mg/24h) ($p = 0.02$)<br>- mean eGFR in TransCon group rose by 7.9 SD 10.4 ml/min/1.73 $m^2$ and fell by 1.9 SD 8.6 ml/min/1.73 $m^2$ in placebo group ($p < 0.001$ for difference between groups)*<br>- TransCon demonstrated significant improvement in HPES-symptom domain scores “physical” ($p = 0.0038$), “cognitive” ($p = 0.0055$), and in HPES- | Hypercalcemia in 6/61 patients treated with TransCon, of which 1 needed hospitalization | *Supported by Ascendis Pharma Bone Diseases A/S* |

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| | | | | impact domain scores "physical functioning" (p = 0.0046) and "daily life" (p = 0.0061) compared to placebo<br>- TransCon demonstrated significant improvement in SF-36 domain score "physical functioning" (p = 0.0347)<br>- daily pill burden decreased from mean 6.7±2.2 to 0.5±1.7<br>- 93% achieved independence from conventional therapy | | |
| Marcucci (2021)[16]<br>-<br>Phase III, open-label intervention study<br><br>Italy | Individuals with postsurgical (75%) or idiopathic (25%) chronic hypoparathyroidism ≥ 1.5 year (n = 12), 58% female<br><br>*Treatment before study entry:*<br>≥ 1 g/day calcium | Once daily 20 µg rhPTH(1-34) subcutaneously (5-7 weeks), titrated up to twice daily 20 µg rhPTH(1-34) subcutaneously (7-17 weeks) as add-on therapy to conventional treatment for 3 mo | Serum calcium and phosphate levels, creatinine clearance, 24-h urine calcium excretion, QoL (evaluated by RAND 36-item Short Form Health Survey), bone markers, pill burden | At 3 months:<br>- mean serum calcium increased 3.34 mg/dL (p = 0.010)<br>- mean serum phosphate decreased 0.85 mg/dL (p = 0.421)<br>- mean creatinine clearance increase 2.77 mg/dL (p = 0.033)<br>- mean 24-h urine calcium excretion decrease 0.41 mg/24h (n.s.)<br>- improvement in all 8 domains of SF-36, with significant (p < 0.05) improvements in 'bodily pain', 'vitality' and 'social functioning'<br>- mean BALP increased 4.77 mcg/L (p = 0.003)<br>- mean urinary deoxypyridinoline increased 3.39 nmol/mmol (p = 0.015) | During once daily PTH injection:<br>- hypocalcemia without hospitalization in 50%<br><br>During twice daily PTH injection:<br>- mild hypocalcemia in 50%<br>- mild hypercalcemia in 50%<br><br>Two AE's led to treatment discontinuation (both bone-joint pain) | |

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| | | | | - mean calcium dose decreased from 1450±395 mg/day to 260±363 mg/day; discontinued in 58%<br>- mean calcitriol dose decreased from 1.00±0.26 mcg/day to 0.12±0.21 mcg/day; discontinued in 75% | | |
| Palermo (2018)[17]<br>-<br>Open-label intervention study<br><br>Italy | Individuals with postsurgical hypoparathyroidism ≥ 1 year (n = 42), 91% female<br><br>*Treatment before study entry:*<br>≥ 3 months on stable regimen of ≥2 g elemental calcium + ≥ 0.5 µg calcitriol daily without reaching normocalcemia, or intolerance to calcium carbonate. All were PTH(1-34) treatment naïve. | Twice daily 20 µg PTH(1-34) subcutaneously for 2 years as add-on therapy to conventional treatment | Serum calcium and phosphate, QoL (evaluated by RAND 36-item Short Form Health Survey), pill burden | At 3 months:<br>- serum calcium increased from 7.6±0.6 to 8.9±1.1 mg/dL ($p < 0.001$), remained stable until end of study<br>- serum phosphate decreased from 4.3±1.1 to 3.9±0.6 mg/dL ($p < 0.019$), remained stable until end of study<br><br>At 6 months:<br>- mean dose of calcium supplementation decreased from 4±1.7 g/day to 1.1±g/day, remained stable until end of study<br><br>At 2 years (end of study):<br>- serum creatinine mean 0.9 SD 0.1 mg/dL (n.s.)<br>- urinary calcium from 220 SD 146 to 270 SD 126 mg/24h ($p = 0.047$)<br>- significant ($p < 0.001$) improvement in QoL on all 8 domains of the RAND 36-item Short Form Health Survey | Three AE's led to treatment discontinuation:<br>- myalgia without elevation of muscle enzymes (after 7 & 8 months of treatment resp)<br>- gastrointestinal illness (after 10 months treatment)<br><br>Further:<br>- mild to moderate episodes of hypercalcemia (n = 11)<br>- asymptomatic episodes of hypercalciuria (n = 32)<br><br>No nephrolithiasis<br><br>No SAE's | Extension study with additional endpoints of Santonati et al. (2015)<br><br>38/42 subjects reached 2-year time endpoint and were included in analysis<br><br>*Supported by Eli Lilly* |

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| Winer (2003)[18]<br>-<br>RCT<br><br>USA | Individuals with chronic hypoparathyroidism (various etiologies) for ≥ 1 year (n = 27), 63% female | Twice daily PTH(1-34) subcutaneously, mean 37 µg (n = 14), compared with twice daily calcitriol, mean 0.91 µg (n = 13), in addition to supplementary calcium and dietary calcium (both 1000 mg/day) for 3 years | Bone markers, BMD | At 3 years:<br>- mean serum alkaline phosphatase, osteocalcin, and urinary (deoxy)pyridinoline excretion levels higher in PTH(1-34) treatment group vs. calcitriol treatment group (exact values n.r.), $p < 0.001$<br>- no significant differences in BMD in PTH(1-34) treatment group vs. calcitriol treatment group | - | Results of this study were also included in SR of original HypoPT guideline; here only new outcome of interest (i.e., bone) reported<br><br>21 patients had previously received PTH replacement therapy |
| **PTH receptor 1 agonist** | | | | | | |
| Takacs (2024)[19]<br>-<br>Phase II, open-label intervention study<br><br>Hungary, France, Spain | Individuals with chronic hypoparathyroidism (various etiologies) ≥ 1 year (n = 28), 75% female<br><br>*Treatment before study entry:*<br>All patients were on daily calcium supplements (≥ 1 g/day) and calcitriol (≥ 0.25 µg/day) or alfacalcidol (≥ 0.50 µg/day) | Eneboparatide starting dose 10 µg/day (n = 16, mean dose at end of 3 month-treatment period 28 µg/day) or 20 µg/day (n = 12, mean dose at end of 3 month-treatment period 43 µg/day) as add-on therapy to conventional treatment | Albumin-adjusted serum calcium, phosphate, 24-h urine calcium excretion, eGFR, bone markers, BMD, pill burden | End of treatment (3 months)<br>- albumin-adjusted serum calcium remained within the target range (7.8-9.0 mg/dL)<br>- decrease of serum phosphate although in normal range<br>-mean 24-h urine calcium excretion reduced by ~50% during the first month, maintained to end of treatment<br>- eGFR mean increase 6 mL/min/1.73m$^2$<br>- increase in s-CTX and P1NP, albeit in normal range<br>- BMD remained unchanged<br>- calcium supplementation discontinued in 88%<br>- activated vitamin D discontinued in 92% | Hypocalcemia: 7%<br>Hypercalcemia: 11%<br>Hypercalciuria: 4%<br>Cramp: 4%<br><br>No SAE's | Statistical significance not assessed<br><br>*Supported by Amolyt Pharma* |
| rhPTH = recombinant human parathyroid hormone<br>HR = hazard ratio | | | | | | |

RCT = randomized controlled trial
SD = standard deviation
CKD = chronic kidney disease
CT = computed tomography
SAE = serious adverse event
QoL = quality of life
HRQoL = health related quality of life
HypoPT-SD = Hypoparathyroidism Symptom Diary
US = ultrasound
BMD = bone mineral density
n.s. = not significant
n.r. = not reported
* data reported in Rejnmark et al., Adv Ther (2024) 41:2500-2518
BALP = bone specific alkaline phosphatase, P1NP = procollagen type 1 N-terminal propeptide, s-CTX = serum carboxy-terminal telopeptide of type 1 collagen, NTX = urinary cross-linked *N*-telopeptide of type 1 collagen, TRAP-5b = tartrate-resistant acid phosphatase-5b

*Mortality*

No study assessed mortality as endpoint.

*Quality of life*

Although two studies found marked improvement in several QoL domains with PTH(1-84) treatment compared to baseline [3, 6, 10], others found no difference [7, 9]. For PTH(1-34) treatment, studies consistently demonstrated a positive effect on QoL compared to baseline [13, 16, 17] and placebo [14, 15].

*Calcium and phosphate levels*

With PTH(1-84) treatment, an increase in calcium levels [4, 7, 9] and a decline in, or continuous normal serum phosphate levels were observed [2-4, 6, 7, 9, 11]. There were mixed results for 24-hour urine calcium excretion. Two studies reported a decrease in urinary calcium excretion [3, 11] with percentages of

hypercalciuria decreasing from 69.2% at baseline to 33.3% after 3 years of treatment for women, and 66.7% to 34% for men [11]; two other studies reported an increase in 24-hour urine calcium excretion, albeit remaining within the normal range [4, 7].

With PTH(1-34) treatment, calcium levels either increased [16, 17] or remained within normal range [13-15]. Phosphate levels remained within the normal range [14, 15] or decreased [16, 17]. All studies on PTH(1-34) treatment observed significant, or a trend towards, decrease in 24-hour urine calcium excretion [12-17].

After 3 months of treatment with PTHR1 agonist eneboparatide, albumin-adjusted serum calcium levels and phosphate levels remained within references ranges, while mean 24-hour urine calcium excretion was reduced by ~50% [19].

*CKD and renal calcifications*

PTH(1-84) treatment maintained renal function within the normal range [4] and lowered the risk of developing CKD; after 5 years of follow-up, Rejnmark *et al.* observed that 11% of chronic HypoPT patients treated with PTH(1-84) developed incident CKD vs. 27.4% in those not treated with PTH(1-84), adjusted HR 0.47 (95%CI 0.25-0.87) [5]. Adjusted HR for sustained eGFR decline was 0.35 (95%CI 0.13-0.89) [5].

There were no data on renal calcifications.

A small cohort study (*n* = 12) reported a mean increase in creatinine clearance of 2.77 mg/dL (p = 0.033) with PTH(1-34) treatment [16]. Gafni et al. performed renal imaging in a cohort of HypoPT patients treated for a mean of 3 years with PTH(1-34) therapy. They observed that 26% had nephrocalcinosis and/or nephrolithiasis prior to PTH(1-34) therapy which remained unchanged, while 19% progressed, and 32% developed new-onset nephrocalcinosis and/or nephrolithiasis [12].

*Cramps, tetany, seizures, and neuropsychological endpoints*

Marcucci *et al*. observed neuromuscular symptoms in 5/14 patients (36%) at baseline, which regressed in 4/5 patients during the first month of PTH (1-84) treatment [4]. Another study reported tetany in 8.2% of patients during PTH (1-84) treatment [11]. Khan *et al*. reported muscle spasms, paresthesia and psychiatric disorders in three, two and four patients under PTH (1-84) treatment, respectively [3].

Cramps occurred in 4% of patients on PTHR1 agonist treatment [19].

*CVD*

Ayodele *et al.* observed a cardiovascular event in 3.5% of chronic HypoPT patients treated with PTH(1-84) vs. 16.3% in those not treated with PTH(1-84), corresponding to an adjusted HR of 0.25 (95%CI 0.08-0.81) for developing a cardiovascular event in the PTH(1-84) treatment group [1]. No cardiovascular complications were found in a small cohort study of patients on PTH (1-84) treatment [4]. There were no data on cardiovascular outcomes for PTH(1-34) treatment or PTHR1 agonist treatment.

*Disability or sick leave*

No studies reported on disability or sick leave.

*Bone markers, fracture, BMD*

An increase in levels of bone turnover markers was seen after rhPTH(1-84) treatment initiation [3, 20], declining by month 32 to steady-state values, stabilizing above pretreatment levels [11]. Steady-state values of bone turnover markers during long-term treatment with rhPTH(1-84) were confirmed by Rubin *et al.*

[7]. Effects of rhPTH(1-84) treatment on BMD were inconsistent, [6, 7, 11, 20]. A small cohort study (*n* = 14) reported no new fractures during 1 year rhPTH(1-84) treatment [4].

An increase in bone markers was also observed after initiation of PTH(1-34) treatment [14, 16, 18] and PTHR1 agonist therapy [19], reflecting exposure to the physiologic bone-remodeling effects of PTH, however; no difference in BMD was observed [18].

*Pill burden*

Significant reductions in activated vitamin D analogues and calcium supplementation were observed under PTH(1-84) therapy [2-4, 11], with some studies reporting discontinuation of these supplements in over 60% of the study cohort [4]. With PTH(1-34) therapy, conventional therapy dosages could also be reduced [13, 15-17] or completely [16] discontinued in a majority of the study cohort [14, 15].

PTHR1 agonist therapy allowed discontinuing activated vitamin D analogues in 92% and calcium supplements in 88% of patients [19].

*Increased susceptibility to infection*

Infections (i.e., sinusitis, bronchitis, nasopharyngitis, urinary tract infection or influenza) during PTH(1-84) therapy were reported in two studies [3, 11].

*Cataract*

One study concerning PTH(1-84) assessed cataract; in the study cohort consisting of 14 patients, none had cataract [4].

*Gastrointestinal symptoms*

Gastrointestinal symptoms during PTH(1-84) therapy were reported in two studies [3, 11]. 8.5% of palopegteriparatide users reported nausea [14]; one patient had to discontinue PTH(1-34) therapy due to gastrointestinal disease [17].

*Pain (bone, muscle, and nerves)*

Arthralgia, back pain and pain in the extremities were reported in 26.5%, 20.4% and 20.4% of patients under PTH(1-84) therapy, respectively [11]. 5.1% of palopegteriparatide users reported arthralgia [14]; two patients had to discontinue PTH(1-34) therapy due to myalgia [17].

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