# Single Technology Appraisal

# Hypoparathyroidism (chronic) – palopegteriparatide [ID6380]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Ascendis Pharma:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. NHSE Commissioning Group
   b. Parathyroid UK

4. **Expert statements** from:
   a. Clinical expert statement – Gowri Malka Ratnayake
   b. Clinical expert key questions and response – Gowri Malka Ratnayake
   c. Patient expert statement – Elizabeth Glenister

5. **External Assessment Report** prepared by York Technology Assessment Group
   a. EAG Adverse event rate modelling addendum

6. **External Assessment Report – factual accuracy check**

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

## Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

## Company evidence submission

**May 2025**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6380_palopegteriparatide hypoparathyroidism_CON | 1 | Yes | 16 May 2025 |

# Contents

Contents ..... 2
List of figures ..... 5
Abbreviations ..... 8
1. Decision problem, description of the technology and clinical care pathway ..... 11
1.1 Decision problem ..... 11
1.2 Description of the technology being evaluated ..... 18
1.3 Health condition and position of the technology in the treatment pathway ..... 19
1.3.1 Disease overview ..... 19
1.3.2 Epidemiology ..... 21
1.3.3 Diagnosis and classification ..... 22
1.3.4 Clinical characteristics ..... 22
1.3.5 Burden of the disease ..... 27
1.3.6 Current treatment pathway ..... 36
1.4 Equality considerations ..... 45
2 Clinical effectiveness ..... 46
2.1 Identification and selection of relevant trials ..... 46
2.2 List of relevant clinical effectiveness evidence ..... 49
2.3 Summary of methodology of the relevant clinical effectiveness evidence ..... 50
2.3.1 The PaTHway trial ..... 50
2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence ..... 54
2.4.1 Statistical analyses ..... 54
2.4.2 Analysis sets ..... 55
2.4.3 Participant flow ..... 55
2.4.4 Participant baseline characteristics ..... 56
2.5 Critical appraisal of the relevant clinical effectiveness evidence ..... 59
2.6 Clinical effectiveness results of the relevant trials ..... 60
2.6.1 Primary efficacy outcome ..... 60
2.6.2 Secondary efficacy outcomes ..... 62
2.7 Subgroup analyses ..... 68
2.8 Meta-analysis ..... 68
2.9 Indirect and mixed treatment comparisons ..... 68
2.10 Adverse reactions ..... 69
2.10.1 Summary of treatment-emergent adverse events ..... 69
2.10.2 Clinical laboratory evaluation ..... 71
2.10.3 Safety conclusions ..... 73
2.11 Ongoing trials ..... 73
2.12 Interpretation of clinical effectiveness and safety evidence ..... 74

2.12.1 Strengths and limitations of the clinical evidence base ..... 75
3 Cost-effectiveness ..... 78
3.1.1 Published cost-effectiveness studies ..... 79
3.2 Economic analysis ..... 80
3.2.1.1 Introduction ..... 80
3.2.1.2 Patient population ..... 81
3.2.1.3 Model structure ..... 81
3.2.1.4 Model rationale ..... 83
3.2.1.5 Features of the economic analysis ..... 86
3.2.1.6 Intervention technology and comparators ..... 90
3.3 Clinical parameters and variables ..... 90
3.3.1 Efficacy ..... 91
3.3.2 Complications ..... 92
3.4 Measurement and valuation of health effects ..... 95
3.4.1 Health-related quality-of-life data from clinical trials ..... 95
3.4.2 Health-related quality-of-life studies ..... 97
3.4.3 Health-related quality-of-life data used in the cost-effectiveness analysis ..... 98
3.4.4 Adverse events ..... 101
3.5 Cost and healthcare resource use identification, measurement and valuation ..... 101
3.5.1 Intervention and comparators' costs and resource use ..... 102
3.5.1.3 Health-state unit costs and resource use ..... 105
3.5.1.4 Adverse reaction unit costs and resource use ..... 105
3.5.1.5 End of Life ..... 106
3.6 Severity ..... 106
3.7 Uncertainty ..... 107
3.8 Summary of base-case analysis inputs ..... 107
3.8.1 Assumptions ..... 117
3.9 Base-case results ..... 119
3.9.1 Base-case incremental cost-effectiveness analysis results ..... 119
3.10 Exploring uncertainty ..... 121
3.10.1 Probabilistic sensitivity analysis (with PAS) ..... 121
3.10.2 Deterministic sensitivity analysis (with PAS) ..... 124
3.10.3 Scenario analysis ..... 126
3.11 Benefits not captured in the QALY calculation ..... 132
3.12 Subgroup analysis ..... 133
3.13 Validation ..... 133
3.13.1 Validation of cost-effectiveness analysis ..... 133
3.14 Interpretation and conclusions of economic evidence ..... 134

4 Appendices ..... 137
5 References ..... 138

# List of figures

Figure 1: Mechanism of action of palopegteriparatide ..... 18
Figure 3: Calcium and phosphate homeostasis through normal PTH secretion (left) and in the case of hypoparathyroidism (right) ..... 20
Figure 3: Clinical manifestations of HypoPT ..... 23
Figure 4: Predicted yearly eGFR change from baseline in the control cohort derived from adjusted regression model ..... 26
Figure 5: HRQoL (SF-36) in participants with HypoPT versus population controls from the WHO MONICA study ..... 30
Figure 6: (A) EQ-5D-5L utility scores and (B) EQ Visual Analogue Scale scores stratified by patient self-rated symptom ..... 31
Figure 7: Overview of current treatments for HypoPT ..... 39
**Figure 8: Proposed position in the treatment pathway** ..... 43
Figure 9: PaTHway trial design ..... 51
Figure 10: PaTHway participant disposition ..... 56
Figure 11: PaTHway – Treatment effect of palopegteriparatide on HPES scores up to Week 26 (ITT population) ..... 63
Figure 12: PaTHway – Treatment effect of palopegteriparatide on HPES-Symptom Domains score up to Week 52 (ITT population) ..... 64
Figure 13: PaTHway – Treatment effect of palopegteriparatide on HPES-Impact Physical Functioning Domains score up to Week 52 (ITT population) ..... 64
Figure 14: PaTHway – Treatment effect of palopegteriparatide on SF-36 physical functioning subscale scores up to Week 52 (ITT population) ..... 65
Figure 15: PaTHway – Elemental calcium treatment dose with palopegteriparatide or placebo (ITT population) ..... 67
Figure 16: PaTHway – Active vitamin D treatment dose with palopegteriparatide or placebo (ITT population) ..... 67
Figure 17: PaTHway – 24-hour urine calcium (safety population) ..... 72
Figure 18: Palopegteriparatide model structure overviews ..... 82
Figure 19: Cost-effectiveness plane for base case analysis of palopegteriparatide versus CT ..... 123
Figure 20: Cost-effectiveness acceptability curve for base case analysis of palopegteriparatide versus CT ..... 124
Figure 21: Tornado diagram showing the top 10 parameters impacting the base-case ICER ..... 125

# List of Tables


Table 1: The decision problem ..... 13
Table 2: Technology being evaluated ..... 18
Table 3: Estimated prevalence of chronic HypoPT in the UK in 2024[4] ..... 21
Table 4: Patient-reported impacts of HypoPT on daily living from the Voices of Hypopara survey ..... 29
Table 5: AC and NAC definitions ..... 35
Table 6: Summary of key guidelines and evidence-based recommendations for the management of chronic HypoPT ..... 38
Table 7. Summary of palopegteriparatide studies identified by the SLR ..... 48
Table 8: Clinical effectiveness evidence ..... 49
Table 9: Summary of trial methodology ..... 51
Table 10: PaTHway – Analysis populations ..... 55
Table 11: PaTHway – Baseline demographics, disease characteristics and CT (ITT population) ..... 57
Table 12: Quality assessment of the PaTHway trial ..... 59
Table 13: PaTHway – Proportion of participants meeting the multi-component primary endpoint at Week 26 (ITT population) ..... 60
Table 14: PaTHway – Improvement from baseline to Week 26 in HPES-Impact and Symptom scores (ITT population) ..... 62
Table 15: EQ-5D Domain Outcomes by Week 26 ..... 65
Table 16: PaTHway – Summary of TEAEs at Week 26 (safety population) ..... 70
Table 17: PaTHway – Common (≥5% in any group) TEAEs by preferred term at Week 26 (safety population) ..... 70
Table 18: PaTHway - Summary of central clinical laboratory assessments - Low and high serum calcium incidence (%) by period - Blinded Period (Safety Analysis Population) ..... 73
Table 19: Completed and ongoing studies ..... 74
Table 20: Overview of published cost effectiveness studies – original and update ..... 79
Table 21: Features of the economic analysis ..... 88
Table 22: Complication list ..... 92
Table 23: Complication general population incidence by age category per cycle ..... 93
Table 24: Complication risk ..... 94
Table 25: Adverse event incident rate per cycle ..... 94
Table 26: Hazard ratios for mortality ..... 95
Table 27: Baseline EQ-5D-3L values for the ITT ..... 96
Table 28: EQ-5D-3L utility score at Baseline versus Week 26 (ITT) ..... 96
Table 29: Health state utilities ..... 98
Table 30: General population utility age-adjustment ..... 98
Table 31: Complication disutility ..... 99
Table 32: Adverse event disutility ..... 101
Table 33: Drug costs of palopegteriparatide, calcium and alfacalcidol ..... 103
Table 34: Drug administration costs associated with palopegteriparatide titration phase and CT ..... 104
Table 35: Summary of annual drug acquisition and administration costs for palopegteriparatide and CT (with PAS) ..... 105
Table 36: Health state maintenance costs ..... 105
Table 37: Adverse event costs ..... 106

Table 38: End of life costs ..... 106
Table 39: Summary features of QALY shortfall analysis ..... 106
Table 40: Summary of QALY shortfall analysis ..... 106
Table 41: Summary of variables applied in the economic model ..... 107
Table 42: Model assumptions ..... 117
Table 43: Base case results (list price) ..... 119
Table 44: Base case results (PAS price) ..... 120
Table 45: Net health benefit (list price) ..... 120
Table 46: Net health benefit (PAS price) ..... 120
Table 47: Probabilistic results (PAS price) ..... 121
Table 48: Probabilistic net health benefit (list price) ..... 121
Table 49: Scenario rationale ..... 126
Table 50: Scenario results (PAS price) ..... 130

# Abbreviations

| | |
|---|---|
| A&E | Accident & Emergency |
| AC | Adequately controlled |
| ACR | Albumin-creatine ratio |
| AdViSHE | A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users |
| BF | Brain fog |
| BL | Baseline |
| BMD | Bone mineral density |
| BMI | Body mass index |
| CCS | Canadian Cardiovascular Society |
| CFB | Change from baseline |
| CHMP | Committee For Medicinal Products for Human Use |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| colpc | Column percentage |
| COPD | Chronic obstructive pulmonary disease |
| CPRD | Clinical Practice Research Datalink |
| CPS | Cognitive processing speed |
| CPT | Current procedural terminology |
| CT | Conventional therapy |
| CTx | C-terminal telopeptide of type 1 collagen |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DHSC | Department of Health and Social Care |
| DF | Degree of freedom |
| dial | Dialysis |
| dL | Decilitre |
| Dsc | Discontinuation |
| DXA | Dual energy X-ray absorptiometry |
| EC | European Commission |
| ED | Emergency Department |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| EMR | Electronic medical record |
| EORTIQ QLQ | European Organisation for Research and Treatment of Cancer Quality Of Life Core Questionnaire |
| EP | Endpoint |
| EQ-5D-5L | EuroQol 5 Dimensions 5 Levels |
| EQ5D-VAS | EuroQol 5 Dimensions Visual Analogue Scale |
| ESE | European Society of Endocrinology |
| ESRD | End-stage renal disease |
| EU | European Union |
| FDA | Food and Drug Administration |
| GBP | Great British pound |
| GFR | Glomerular filtration rate |
| GP | General population |
| GPi | General population incidence |
| HCRU | Healthcare resource use |
| HE | Health economic |
| HES | Hospital Episode Statistics |
| HF | Heart failure |
| HPES | Hypoparathyroidism Patient Experience Scale |
| HPES-TS | Hypoparathyroidism Patient Experience Scale – Total Symptom |
| HPT-SD | Hypoparathyroidism Symptom Diary |

| | |
|---|---|
| HPQ | Hypoparathyroid Patient Questionnaire |
| HR | Hazard ratio |
| HRG | Healthcare Resource Group |
| HRQoL | Health-related quality of life |
| HS | Health state |
| HTA | Health Technology Appraisal |
| HUI2 | Health utilities index-2 |
| HypoPT | Hypoparathyroidism |
| ICD | International Classification of Diseases |
| ICER | Incremental cost-effectiveness ratio |
| IHD | Ischaemic heart disease |
| IPD | Individual patient data |
| IQR | Interquartile range |
| ISR | Injection site reaction |
| ITT | Intent-to-treat |
| IU | International unit |
| IV | Intravenous |
| IWRS | Interactive Web Randomisation System |
| kDa | Kilodalton |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| LCI | Lower confidence interval |
| LOS | Length of stay |
| LRTI | Lower respiratory tract infection |
| LSM | Least square mean |
| LY | Life years |
| LYG | Life years gained |
| m | Metre |
| MAIC | Matching-adjusted indirect comparison |
| Mcg | Microgram |
| MCSI | Modified Caregiver Strain Index |
| MDRD | Modification of Diet in Renal Disease |
| Mg | Milligram |
| MHRA | Medicines & Healthcare Products Regulatory Agency |
| MI | Myocardial infarction |
| min | Minute |
| Min / max | Minimum / maximum |
| mL | Millilitre |
| MMRM | Mixed-model repeated measures |
| mPEG | Methoxypolyethylene glycol |
| NA | Not applicable |
| NAC | Not adequately controlled |
| NHANES | National Health and Nutrition Examination Survey |
| NHB | Net health benefit |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMB | Net monetary benefit |
| NR | Not reported |
| OLE | Open-label extension |
| ONS | Office for National Statistics |
| OP | Outpatient |
| OR | Odds ratio |
| P1NP | Procollagen type I N-propeptide |
| PAS | Patient access scheme |
| PAR | Public assessment report |
| PARAT | Parathyroid Disorders Educational Program |
| PEG | Polyethylene glycol |

| | |
|---|---|
| PGIS | Patient Global Impression of Severity |
| PRISMA | Preferred Reporting Items for Systematic reviews and Meta-Analyses |
| PRN | Pro re nata |
| PRO | Patient-reported outcome |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| PTH | Parathyroid hormone |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| QRISK3 | Cardiovascular risk score |
| RCT | Randomised controlled trial |
| rhPTH | Recombinant human parathyroid hormone |
| rowpc | Row percentage |
| RR | Relative risk |
| RRT | Renal replacement therapy |
| RWE | Real-world evidence |
| SC | Subcutaneous |
| sCa | Serum calcium |
| SD | Standard deviation |
| SE | Standard error |
| SF-36 | 36-Item Short Form Survey |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| TRT01P | Treatment planned |
| T2DM | Type 2 diabetes mellitus |
| TA | Technology appraisal |
| TBS | Trabecular bone score |
| TEAE(s) | Treatment-emergent adverse events |
| TLR | Targeted literature review |
| TP | Transition probability |
| Trans | Transplant |
| TTO | Timed trade-off |
| UCI | Upper confidence interval |
| UK | United Kingdom |
| UKPDS | United Kingdom Prospective Diabetes Study |
| UKRR | UK Renal Registry |
| ULN | Upper limit of normal |
| URTI | Upper respiratory tract infection |
| US | United States |
| UTI | Urinary tract infection |
| VAS | Visual analogue scale |
| WHO | World Health Organization |
| WHO MONICA | World Health Organization's MONItoring of trends and determinants in CArdiovascular disease |
| WHO-5 | World Health Organization Five Well-Being Index |
| WK | Week |
| WPAI | Work Productivity and Activity Impairment |
| WTP | Willingness to pay |

# 1. Decision problem, description of the technology and clinical care pathway

## 1.1 Decision problem

### SUMMARY

- Hypoparathyroidism (HypoPT) is a rare and complex endocrine disease characterised by an absence or insufficient level of parathyroid hormone (PTH). This results in disrupted calcium and phosphate homeostasis, leading to a range of severe and potentially life-threatening short and long-term complications.[1]
- The cause of HypoPT can be divided between post-surgical (75%) and non-surgical (25%). Non-surgical causes of chronic HypoPT are frequently autoimmune, genetic or idiopathic.[2] Chronic hypoPT is considered chronic if it persists >6 months.[3]
- A targeted literature search estimated the reported prevalence of chronic hypoparathyroidism ranges from 6.4–37 per 100,000, and the incidence is reported to be 0.8–2.3 per 100,000 per year.[4]
- HypoPT affects multiple organ systems, causing debilitating physical and cognitive symptoms, that can impact daily living.[5-7] Patients with HypoPT often report pain, fatigue, cognitive symptoms (such as “brain fog” and difficulty concentrating), anxiety and depression.[8,9]
- Chronic HypoPT is associated with serious long-term complications, such as renal impairment (e.g., nephrocalcinosis, kidney stones), cardiovascular disease, neurocognitive dysfunction (e.g., memory loss), and ectopic calcifications, which can significantly impact a patient’s quality of life.
- Chronic HypoPT and its related complications are associated with significant healthcare resource use (HCRU) and associated costs.[10]
- HypoPT has a considerable negative impact on health-related quality of life (HRQoL), the ability to work and perform daily activities.[11] Furthermore, caregivers of patients with HypoPT also experience considerable burden, including reduced capacity to work and to perform daily activities.[12]
- Conventional therapy (CT) consisting of oral active vitamin D analogues and calcium, does not replace PTH or any of the physiological functions associated.[13] As a result, many patients fail to achieve adequate clinical and biochemical control.[12] In addition, this treatment can contribute to short and long-term complications, including hypocalcaemia, hypercalcaemia or increased urinary calcium excretion, resulting in nephrocalcinosis or kidney stone formation.[14]
- Patients whose disease is not adequately controlled on CT experience a greater clinical and economic burden, highlighting a significant unmet medical need within this population.[12,15]

- Consequently, there is a high unmet need for a treatment that targets the underlying cause of the symptoms and complications of chronic HypoPT, particularly in patients whose disease is not adequately controlled on CT. [12]

This submission focuses on part of the population covered by the technology's marketing authorisation, specifically adults with chronic HypoPT whose disease is not adequately controlled on conventional therapy (CT). The proposed population is narrower than the marketing authorisation because this is the population in which palopegteriparatide is clinically considered to be used in and who would benefit from a second-line treatment of PTH replacement therapy following CT.

The decision problem is shown in Table 1.

**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | Adults with chronic hypoparathyroidism | Adults with chronic hypoparathyroidism who are not adequately controlled using conventional therapy | This submission targets the subpopulation of adults with chronic hypoparathyroidism who are not adequately controlled using conventional therapy for the following reasons;<br>• This subpopulation shows the biggest clinical benefit and drives the cost-effectiveness<br>• This subpopulation has been confirmed and validated by UK clinical experts[16] |
| **Intervention** | Palopegteriparatide | Palopegteriparatide | As per final scope. |
| **Comparator(s)** | Established clinical management without palopegteriparatide, which may include:<br>• Teriparatide<br>• Recombinant parathyroid hormone<br>• Vitamin D analogues such as alfacalcidol or calcitriol<br>• Calcium supplements<br>• Magnesium supplements<br>• Thiazide diuretics | Established clinical management without palopegteriparatide, which may include:<br>• Active Vitamin D analogues such as alfacalcidol or calcitriol<br>• Calcium | This submission focuses on established clinical management with active vitamin D and calcium (known as conventional therapy) as the comparator of interest as the standard of care for the treatment of chronic HypoPT. Responses from the 2022 UK national audit on chronic hypoparathyroidism showed that first-line management primarily involves active vitamin D analogues (used by 98.8% of patients) and calcium (used by 67.5%). [17]These findings underscore the suitability of both vitamin D and calcium as suitable comparators.<br><br>The following have not been included as comparators due to the reasons provided below:<br>• Teriparatide: The PTH analogue teriparatide (rhPTH 1-34) is licenced for use in osteoporosis treatment but has been minimally used off-label for HypoPT.via individual funding requests. However, it is not |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | | | included in treatment guidelines and usage estimates are low. [18,19] Responses to a UK national chronic hypoparathyroidism audit (2022) indicated teriparatide was used in 1.3% of patients.<br><br>Clinical data are limited on the effectiveness and safety of teriparatide for the treatment of HypoPT, and its short half-life means that it does not maintain PTH levels within the physiologic range over 24 hours, as is required for optimal management of HypoPT. Usage is restricted by the Summary of Product Characteristics (SmPC) to a one-time use of no more than 24 months due to the potential risk of osteosarcoma which limits its use in a chronic condition such as HypoPT.[19]<br><br>• Recombinant parathyroid hormone: The only currently licensed recombinant human PTH therapy for HypoPT is rPTH 1-84 (Natpar®). rPTH 1-84 has not been evaluated through NICE and usage estimates are very low.[18] Responses to the UK audit mentioned above did not include any patients using rPTH 1-84.<br><br>Takeda, the manufacturer of rPTH 1-84, has publicly given notice to the Department of Health and Social Care (DHSC) and Medicines & Healthcare Products Regulatory Agency (MHRA) that the manufacturing of all strengths of rPTH 1-84 will be discontinued from the end of 2024 due to unresolved manufacturing issues.[20,21] Takeda has advised all UK healthcare professionals not to |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | | | initiate any new patients on any strength of Natpar.[20]<br><br>• Magnesium treatments: Based on the clinical guidelines and clinical expert opinion, magnesium is not considered part of CT for HypoPT rather an adjunct to CT if needed. Responses to a UK national chronic hypoparathyroidism audit (2022) indicated magnesium supplements were only used in 2.5% of patients. Therefore, magnesium supplement is not considered a direct comparator for palopegteriparatide.<br><br>• Thiazide diuretics are not considered part of CT for HypoPT rather an adjunct to CT if needed. Responses to a UK national chronic hypoparathyroidism audit (2022) indicated thiazide diuretics were only used in 6.3% of patients. Therefore, thiazide diuretics are not considered a direct comparator for palopegteriparatide. |
| **Outcomes** | The outcome measures to be considered include:<br>• change in physical symptoms such as fatigue<br>• change in cognitive symptoms<br>• hospital admissions<br>• reduction in calcium treatments and vitamin D analogues<br>• calcium levels | The below outcome measures are included in the submission:<br>• hospital admissions<br>• reduction in calcium treatments and vitamin D analogues<br>• Calcium levels<br>• Serum phosphate levels | The following outcomes have not been included in this submission, as their exclusion reflects methodological decisions made for clarity and to avoid redundancy. These decisions result in some differences from the final scope issued by NICE, as outlined below:<br>1) The outcome related to reduction in physical and cognitive symptoms was removed to avoid potential double counting of quality-of-life burden, as these aspects are already |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | • serum phosphate levels<br>• renal function (eGFR)<br>• cardiovascular outcomes<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life | • cardiovascular outcomes<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life | reflected in the health state utility values derived from the Hypoparathyroidism Patient Experience Scale (HPES) and the EQ-5D instrument used within the economic model.[22] |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.<br>The availability and cost of biosimilar and generic products should be taken into account. | As per final scope | Not applicable |
| **Subgroups to be considered** | Subgroups based on eGFR and disease severity, if evidence allows. | No subgroups considered | Given chronic HypoPT is a rare disease with limited trial size and that the PaTHway trial represents a subpopulation of the licenced population, it was not appropriate to undertake further subgroup analysis. |
| **Special considerations** | It is expected that more women than men will be treated with palopegteriparatide; this is because post-surgical HypoPT is more common in women than men (women are more likely to have thyroid disease and hence undergo thyroidectomy).[6] Furthermore, | | |

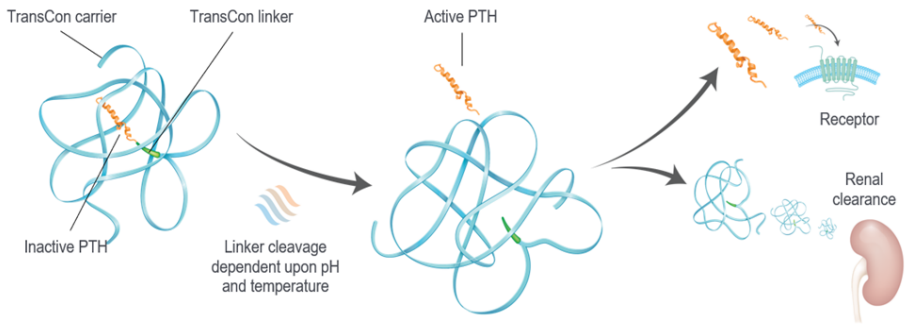
| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **including issues related to equity or equality** | the epidemiology of CKD suggests that women are at higher risk of developing CKD than men meaning that women with HypoPT may be at higher risk of impaired renal function than men with HypoPT. [23] | | |

Abbreviations: CKD, chronic kidney disease; CT, conventional therapy; DHSC, Department of Health and Social Care; eGFR, estimated glomerular filtration rate; ESE, European Society of Endocrinology; HPES, Hypoparathyroidism Patient Experience Scale; HypoPT, hypoparathyroidism; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; PTH, parathyroid hormone; rPTH, recombinant parathyroid hormone; SmPC, summary of product characteristics

## 1.2 Description of the technology being evaluated

A description of palopegteriparatide is presented in Table 2. The Summary of Product Characteristics (SmPC) and the UK Public Assessment Report (PAR), scientific discussion or drafts are provided in Appendix A.

**Table 2: Technology being evaluated**

| | |
|---|---|
| **UK approved name and brand name** | Palopegteriparatide (Yorvipath®)▼ |
| **Mechanism of action** | Palopegteriparatide is a prodrug of parathyroid hormone (PTH), composed of PTH(1–34) transiently conjugated to a branched 40 kDa methoxypolyethylene glycol (mPEG) moiety via a proprietary TransCon Linker.[24]<br>The carrier renders the prodrug inactive and protects it from clearance. Upon exposure to physiological pH and temperature, autocleavage of the linker occurs following first-order kinetics. This provides sustained release of active PTH that can bind to target receptors, including on the kidney, and bone. The linker and carrier are then excreted by the kidneys.[24] Figure 1 illustrates the mode of action of palopegteriparatide.<br>**Figure 1: Mechanism of action of palopegteriparatide**<br>  <br><br>Abbreviations: PTH, parathyroid hormone<br>Source: Karpf et al. 2020[24] |
| **Marketing authorisation/CE mark status** | On 24 April 2024, the UK MHRA granted marketing authorisation for palopegteriparatide as a PTH replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism.[25]<br>GB Orphan Designation number: PLGB 51127/0001-0003/OD1[26] |
| **Indications and any restriction(s) as described in the SmPC** | Palopegteriparatide is a PTH replacement therapy indicated for the treatment of adults with chronic HypoPT.[19] |
| **Method of administration and dosage** | Once-daily subcutaneous (SC) administration.[19]<br>The recommended starting dose is 18 mcg once daily with dose adjustments in 3 mcg increments thereafter. The dose range is 6 to 60 mcg per day. |

| | |
|---|---|
| | Palopegteriparatide may be increased in increments of 3 mcg if at least 7 days have elapsed since a prior dose change. The dose should not be increased more often than every 7 days. Palopegteriparatide may be reduced in increments of 3 mcg no more often than every 3 days in response to hypercalcaemia.<br>Serum calcium should be measured 7 days after the first dose and doses of palopegteriparatide, active vitamin D and calcium treatments should be adjusted accordingly (see Appendix A). After any subsequent dose adjustment of palopegteriparatide, active vitamin D or oral calcium, serum calcium should be measured within 7 to 14 days alongside monitoring for clinical signs and symptoms of hypocalcaemia or hypercalcaemia. Dose adjustments of palopegteriparatide, active vitamin D and calcium should be made on the same day.<br>The maintenance dose should be the dose that maintains serum calcium within the normal range, without the need for active vitamin D or therapeutic doses of calcium. Optionally, calcium doses may be continued to meet daily dietary requirements. Serum calcium and 25(OH) vitamin D should be measured as per standard of care once a maintenance dose is achieved |
| **Additional tests or investigations** | None required. |
| **List price and average cost of a course of treatment** | List price of palopegteriparatide: £7,406 (per two-pen pack, for 28 days of treatment).<br>Annual price of palopegteriparatide: £96,278 (based on 13 packs per year) |
| **Patient access scheme (if applicable)** | A simple discount patient access scheme (PAS) has been proposed for palopegteriparatide and is expected to be approved ahead of the committee meeting. The proposed price of palopegteriparatide with a PAS is [redacted] per two-pen pack). |

Abbreviations: kDa, kilodaltons; mPEG, methoxypolyethylene glycol; MHRA, Medicines & Healthcare products Regulatory Agency; PAS, patient access scheme; PTH, parathyroid hormone; SC, subcutaneous; SmPC, summary of product characteristics.

## 1.3 Health condition and position of the technology in the treatment pathway

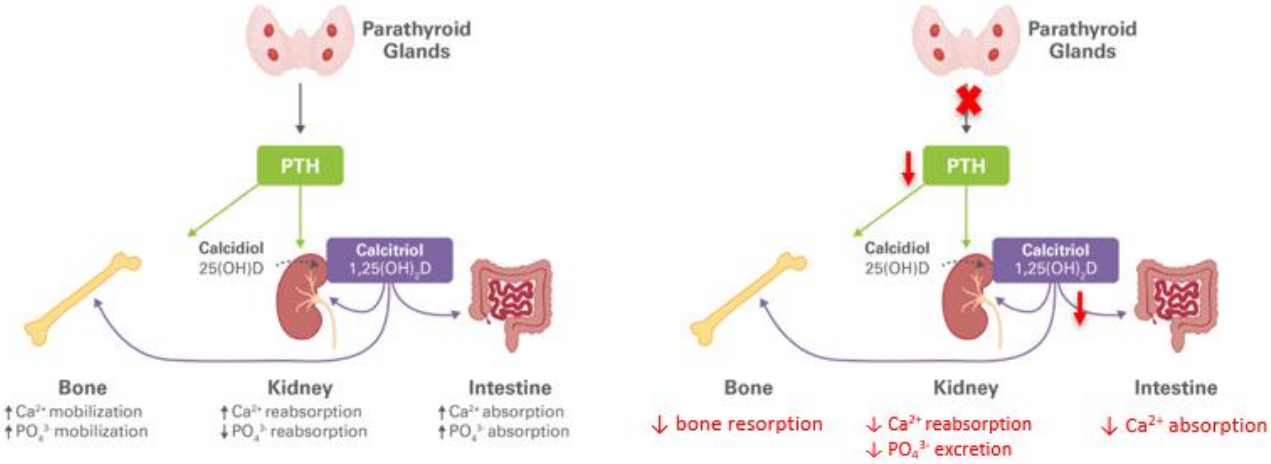
### 1.3.1 Disease overview

Chronic hypoparathyroidism (HypoPT) is a rare endocrine disease caused by insufficient parathyroid hormone (PTH), leading to disrupted calcium and phosphate homeostasis. Patients experience a range of debilitating symptoms and chronic HypoPT is associated with complications such as renal impairment, cardiovascular disease, bone fractures, cataracts and increased risk of infection.

Approximately 75% of chronic HypoPT cases are post-surgical, most often following head or neck procedures in which the parathyroid glands are inadvertently damaged or removed. The remaining 25% of cases are attributed to non-surgical etiologies, including autoimmune, genetic, or idiopathic conditions.[1,27]

PTH and vitamin D are key regulators of calcium and phosphate homeostasis, acting on bone, kidneys, and—indirectly—the gastrointestinal tract as illustrated in Figure 3. Importantly, calcium homeostasis is essential for proper functioning of the nervous system and is maintained within a very narrow therapeutic window (8.5-10.5mg/dL).

**Figure 2: Calcium and phosphate homeostasis through normal PTH secretion (left) and in the case of hypoparathyroidism (right)**




Source:adapted from Mannstadt et al. 2017[6]

PTH is secreted in response to low serum calcium levels and binds to PTH1 receptors in the bones and kidneys. It stimulates bone resorption, enhances renal calcium reabsorption, promotes phosphate excretion, and activates vitamin D (calcitriol), which increases intestinal calcium absorption.[7] Together, PTH and vitamin D maintain stable serum calcium concentrations required for physiological and neurological function.

In chronic HypoPT, the absence of PTH disrupts the body's tightly regulated calcium balance, leading to persistent hypocalcaemia. This occurs through impaired bone resorption, increased renal calcium loss, and reduced calcitriol synthesis, which limits intestinal calcium absorption. Even mild deviations below the normal calcium range can significantly impair neuromuscular and neurological function. Any signs of hypocalcaemia such as paraesthesia and muscle cramps, require urgent assessment due to the possibility of being life threatening and therefore are taken

very seriously.[28] The resulting disruption in calcium homeostasis and impact of hypocalcaemia occurring has profound effects on the nervous system, contributing to neuromuscular irritability including tetany arrhythmia, cognitive dysfunction, brain fog, seizures, and mood disorders, all of which significantly impair quality of life. [1] Simultaneously, hyperphosphatemia develops due to decreased renal phosphate excretion (Figure 3-Right). [6,7] Insufficient production of PTH also leads to a reduction in bone turnover with subsequent accumulation of non-remodelled bone reflected in an increase in bone mass and density.[7]

Current treatment, known as conventional therapy (CT), consists of oral administration of active vitamin D and calcium. It seeks to increase calcium levels in the body and avoid the symptoms of hypocalcaemia. However, CT does not replace the functions of PTH, and some patients continue to experience symptoms and a poor quality of life.

### 1.3.2 Epidemiology

HypoPT is a rare disease with limited data available on both incidence and prevalence. Reported prevalence of chronic HypoPT ranges from 6.4–37 per 100,000, and the incidence ranges from 0.8–2.3 per 100,000 per year.[4]

A targeted literature search estimated that the prevalence of chronic HypoPT in the United Kingdom (UK) is 20.7 per 100,000 in 2024.[29]

The prevalence of non-surgical HypoPT is similar for males and females, but post-surgical HypoPT is more common in females due to their increased risk of thyroid disease and the associated likelihood of undergoing thyroidectomy.[6]

**Table 3: Estimated prevalence of chronic HypoPT in the UK in 2024[4]**

| | **Best estimate** |
|---|---|
| Post-surgical chronic HypoPT (N) | 9,039 |
| Non-surgical chronic HypoPT (N) | 5,046 |
| **Total chronic HypoPT (N)** | **14,085** |
| **Chronic HypoPT prevalence per 100K** | **20.7** |

Abbreviations: HypoPT, hypoparathyroidism; UK, United Kingdom
Source: Ascendis Chronic HypoPT report 2024, data on file[29]

### 1.3.3 Diagnosis and classification

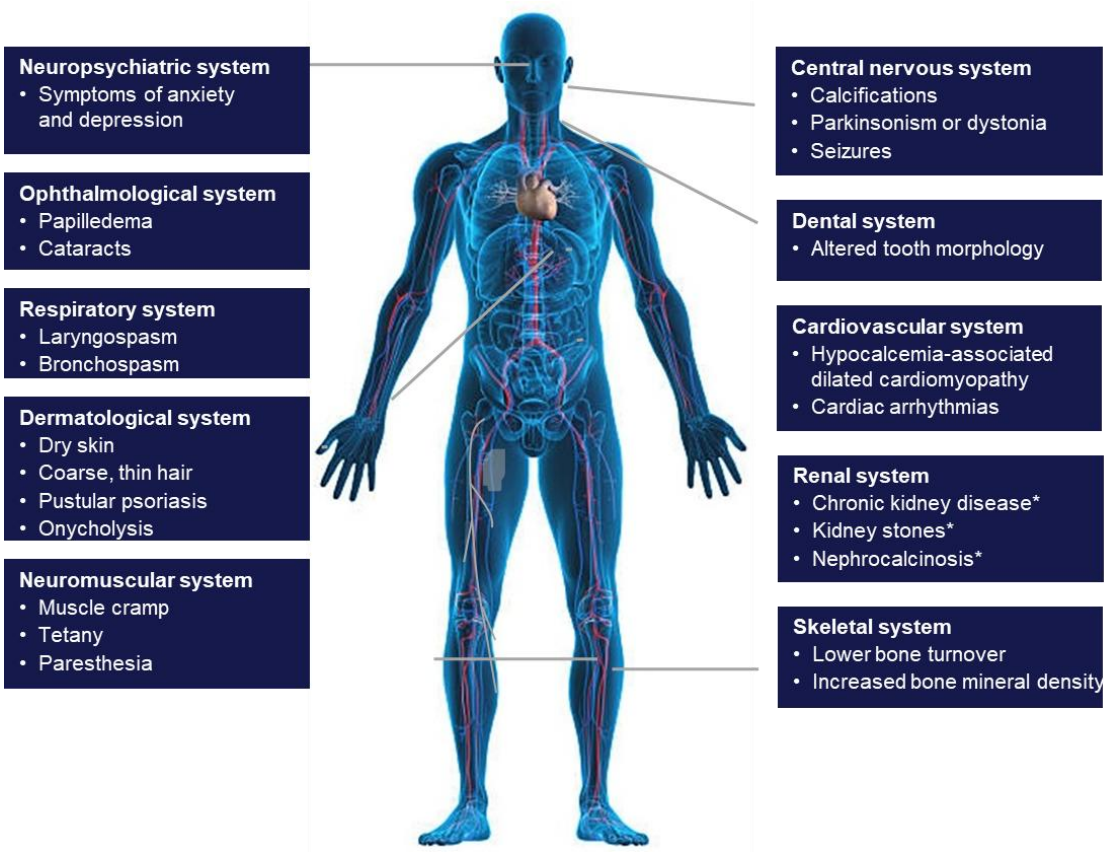
Diagnosis of HypoPT is based on biochemical evaluation.[2] The diagnosis is made when serum PTH levels are absent or insufficient in the presence of hypocalcaemia (low ionised or total serum calcium adjusted for albumin), confirmed on two separate occasions at least two weeks apart.[2,30] Additional abnormalities caused by insufficient PTH that support a HypoPT diagnosis include elevated serum phosphates, reduced 1,25-dihydroxyvitamin D and elevated 24-hour urinary calcium excretion.[6]

HypoPT is considered chronic if it persists >6 months as per the 2016 Endocrine Society Guidelines,[30] 2019 Canadian and International Consensus Statement,[31] and 2022 European Society of Endocrinology Consensus Statement.[3] The 2022 Guidelines from the Second International Workshop define hypoparathyroidism as permanent if it persists >12 months following surgery.[2]

### 1.3.4 Clinical characteristics

PTH regulates calcium and phosphate balance (see Figure 2), which is critical for many essential physiological functions and neuronal activity, chronic HypoPT can impact multiple organ systems as illustrated in Figure 3.

**Figure 3: Clinical manifestations of HypoPT**




The figure shows both common and rare manifestations of HypoPT.
*Manifestations that are mostly the result of treatment with active vitamin D and calcium rather than HypoPT itself.
Source: Figure adapted from Mannstadt et al. 2017[6]

Low or absent serum PTH levels can also contribute to long-term complications such as chronic kidney disease, kidney stones and nephrocalcinosis (see Figure 3), however this risk may also largely be exacerbated through the use of long-term CT.

Patients can experience a range of physical, cognitive, and emotional symptoms with paraesthesia, muscle cramps, fatigue, brain fog, irritability and depression commonly seen.[5] In severe cases, patients may experience arrhythmias, laryngospasm, bronchospasm, and seizures.[32-34] The symptoms of chronic HypoPT can be severe and disabling, often leading to a substantial reduction in quality of life, daily functioning and increased use of healthcare resources.[10,12]

Chronic HypoPT is associated with complications, such as renal impairment, cardiovascular disease, bone fractures, cataracts and increased risk of infection, that affect vital organs and may compromise the patient's life.[3,35-37] Acute complications

often arise from abrupt reductions in serum calcium levels, while chronic complications can affect multiple organ systems as described above. More detail on the acute and long-term complications that affect patients with chronic HypoPT is provided in section 1.3.4.1 below.

Despite treatment with CT, patients may develop complications as although a treatment goal with CT is to try and stabilise serum calcium, it does not replace the physiological function of PTH, leading to potential long-term risks. The risk of complications (frequency and severity) is increased for patients whose disease is not adequately controlled on CT (requiring a high dose of CT, experiencing severe symptoms and/or high healthcare use, renal impairment or history of renal complications– see section 1.3.6.5 for more detail on how not adequately controlled (NAC) is defined). [10,12,38] This elevated risk has been consistently demonstrated in UK real-world data.[10]

#### *1.3.4.1 Acute and serious long-term complications associated with HypoPT*

*Hypocalcaemia*

The primary acute complication of HypoPT is hypocalcemia, which can present with neuromuscular irritability, tetany, seizures, and cardiac arrhythmias. Hypocalcemia requires prompt correction, as persistent or recurrent episodes can increase the risk of complications and hospitalisations. The PaTHway trial demonstrated that patients receiving CT exhibited nearly a ten-fold increased risk of hypocalcaemia compared to those treated with palopegteriparatide.[39-41] These findings suggest that restoring and maintaining physiological levels of PTH via replacement therapy facilitates normalisation of calcium homeostasis. Importantly, this biochemical stability is achieved without reliance on calcium and active vitamin D and may be considered being adequately controlled on PTH replacement.

*Urinary tract infections*

Patients with HypoPT are at increased risk of urinary tract infections (UTIs), which may be related to altered renal handling of calcium and phosphate, or secondary to renal calcifications and impaired urinary flow.

*Renal complications*

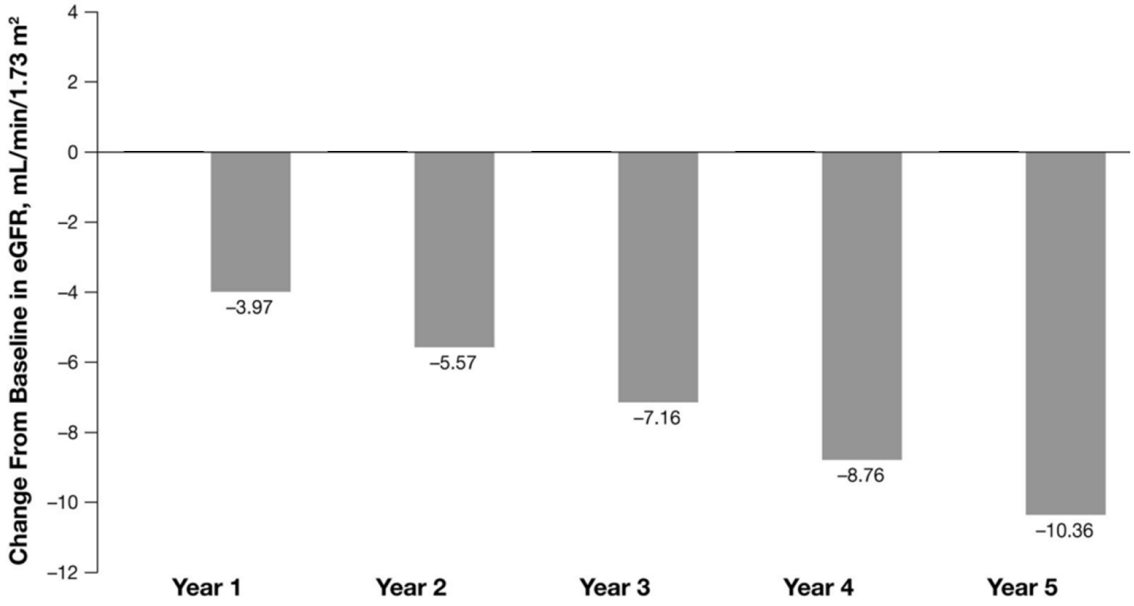
The most serious long-term complications associated with HypoPT are renal impairment and associated cardiovascular disease (CVD) complications as they have the largest effect on health outcomes for a patient with HypoPT.[42]

Patients with chronic HypoPT have an increased risk of renal complications such as kidney stones, renal failure, chronic kidney disease (CKD) and an increased likelihood of requiring dialysis. CKD (typically defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m²) is more common in patients with HypoPT than in the general population, with reported prevalence rates ranging from 2.5% to 41%.[2,8,43,44]

Renal complications are mostly secondary complications resulting from chronic hypercalciuria associated with CT. [5,7,8,31]CT increases calcium levels in the body, but without PTH, calcium reabsorption in the kidneys is reduced, leading to excessive calcium in the urine (hypercalciuria).

A retrospective cohort study that evaluated change in eGFR in adults with chronic HypoPT (n=176) treated with CT (at least one prescription for calcitriol after the first diagnosis of HypoPT) estimated a declined predicted eGFR of 10.36mL/ min/1.73 $m^2$ at five years from baseline (see Figure 4)[45].

**Figure 4: Predicted yearly eGFR change from baseline in the control cohort derived from adjusted regression model**




Abbreviations: eGFR, estimated glomerular filtration rate; m, metre; min, minute; mL, millilitre
Source: Adapted from Ayodele et al. 2022[45]

CKD is closely linked to an increased risk of CVD, particularly in advanced stages.[42] CKD causes a systemic, chronic proinflammatory state contributing to vascular and myocardial remodelling processes resulting in atherosclerotic lesions, vascular calcification, and vascular senescence as well as myocardial fibrosis and calcification of cardiac valves.[37] In this respect, CKD mimics an accelerated aging process of the cardiovascular system.[37]

*Cardiovascular complications*

Individuals with HypoPT are at increased risk of CVD, particularly when serum calcium and phosphate levels are not well controlled. A retrospective case-control study found that patients with persistently abnormal calcium, phosphate, or calcium-phosphate product levels had significantly higher odds of cardiovascular events.[46] Specifically, calcium levels outside the target range increased the risk nearly two-fold, while elevated phosphate or calcium-phosphate product levels raised the risk by over three- to four-fold.[46] Cardiovascular complications, including arrhythmias, myocardial infarction, and heart failure were more common in HypoPT patients than in matched general population controls, with particularly high rates in those with non-

surgical HypoPT.[10] Analysis of real-world evidence data (see section 1.3.5.1) also highlighted cardiac arrhythmias and cardiomyopathy as being linked to individuals with HypoPT on CT.[10]

The effect of HypoPT and CT on CKD and CVD outcomes highlights how the long-term use of CT and the chronic nature of the disease can impact multiple organ systems. Consideration of long-term complications is key, due to the impact it plays on humanistic and economic outcomes. For example, the need for dialysis is associated with reduced HRQoL as measured by SF-36, EQ-5D and other instruments.[47] Furthermore, reducing CVD and CKD risk in patients with HypoPT could lead to meaningful improvements in both patient health outcomes and healthcare resource use (HCRU).

### 1.3.5 Burden of the disease

#### 1.3.5.1 Impact on patient Quality of Life

Chronic HypoPT imposes a significant symptomatic and treatment-related burden that profoundly affects patients' health-related quality of life (HRQoL)[12,35,48,49] Despite efforts to manage symptoms through CT, many individuals experience persistent, debilitating symptoms that impact physical, cognitive, and emotional well-being.

Several studies have demonstrated this HRQoL impact:

- **Kontogeorgos et al., 2022 (Sweden)**: A cross-sectional case-control study found significantly reduced QoL in HypoPT patients vs. population controls across all SF-36 domains—independent of disease cause or calcium levels.[35]
- **Siggelkow et al., 2020 (Multinational)**: A large, multinational patient survey conducted across 13 countries (n=398), 91% of participants reported ongoing symptoms despite CT; symptom severity correlated directly with reduced QoL and work capacity.[12]
- **Astolfi et al., 2020 (US):** A national patient-reported outcomes study, found that 69% of patients reported treatment as extremely burdensome; 97% had to adjust treatment multiple times since diagnosis.[50]

- **Silkjaer et al., 2024** This cognitive assessment study documented measurable cognitive impairment and smaller hippocampal volumes in HypoPT patients compared to healthy controls—supporting the biological basis for symptoms like brain fog.[51]

These studies highlight the persistent and multidimensional burden of HypoPT on patients. Furthermore, several questionnaires have been used for the assessment of QoL in patients with chronic HypoPT, ranging from non-pathology specific, but used to assess chronic diseases such as the *36-Item Form Survey* (SF-36) or the EuroQol-5, to others that have been developed and validated specifically for the pathology such as the *Hypoparathyroidism Patient Experience Scale* (HPES).[5,52,53]

A high frequency of HypoPT symptoms correlates with worsening QoL in patients with HypoPT. [12,35]These questionnaires and disease specific tools demonstrate that symptom impairment has a direct deleterious impact on the day-to-day life of patients with chronic HypoPT. Almost half of the patients (45%) consider that their disease has a significant impact on their life and another 85% of patients stated that it does not allow them to perform household activities.[12]

A company-sponsored UK patient survey in conjunction with Parathyroid UK (n=402 respondents),[54] found that dissatisfaction and poor HRQoL were driven by the continued symptom burden i.e. the fear of long-term side effects (69.3%), lack of peer and clinician support (55.1%), and need for more effective treatments (43.5%), emphasising patient burden with CT and the need for new treatment options.

Patients who took part in the survey had the following to say about the burden of HypoPT on their lives:[54]

*"I feel like my life revolves around this illness I never have days where I feel good or normal I am always tired or fatigued, days with sore bones and cramps and aches."*

*"I was a confident self-reliant woman with a great job I am now reliant on family to support me I no longer feel confident to travel alone and have had to reduce my hours and lost my old job"*

*"I feel a lot of frustration as a parent that I get tired and can't do as much with my kids. People don't understand the impact on me both physically and mentally both at home and work, and I'm scared of the long-term impact on my health and kidneys."*

*"I had to close my business…I have severe brain fog and can't get words out, or even spell. I don't drive anymore as I get lost on journeys."*

Similarly, more than half of participants in the US Voices of Hypopara survey felt that CT did not effectively address their HypoPT symptoms, and 69% considered the treatment to be extremely burdensome.[50] Nearly all participants (97%) had to adjust their regimens since diagnosis, and 61% had adjusted more than five times.[48] Patient-reported impacts are shown in Table 4 below.

**Table 4: Patient-reported impacts of HypoPT on daily living from the Voices of Hypopara survey**

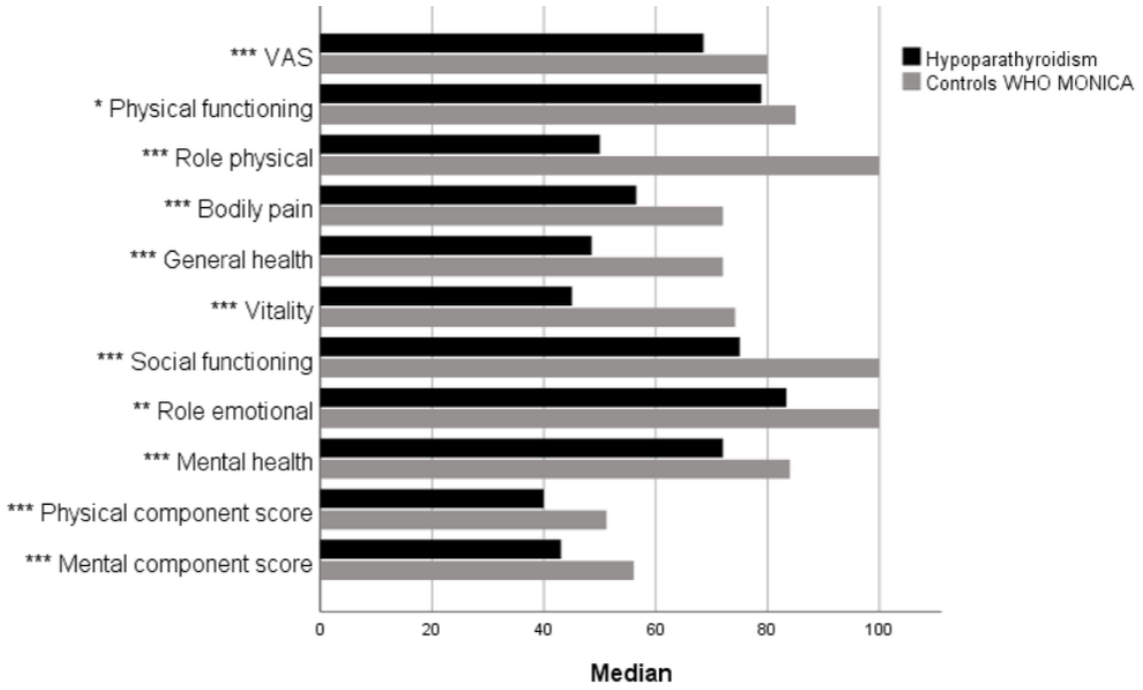
| | |
|---|---|
| **Participants were moderately to extremely concerned with the following:** | |
| Hypocalcaemia/calcium crash | 84% |
| Fatigue | 83% |
| Brain fog (e.g. memory loss, difficulty thinking, slow or confused thinking) | 82% |
| Hyperphosphataemia (e.g., muscle weakness, spasms or pain; nausea) | 73% |
| **When asked about the challenges of living with HypoPT, most patients (87%) cited minimising the impact of HypoPT on their quality of life, including:** | |
| Controlling daily symptoms | 78% |
| Handling physical activities | 75% |
| Maintaining psychological well being | 68% |
| Balancing social life and relationships with managing symptoms and complications | 63% |
| **Most patients (87%) also expressed concern about management of long-term complications; of these, patients were extremely concerned about:** | |
| Cardiovascular health | 24% |
| Kidney stones/function | 21% |
| Organ calcification beyond the kidney | 24% |

In the online US Voices of Hypopara survey conducted by the HypoPARAthyroidism Association in 2020 (with support from Ascendis Pharma), 146 patients were asked 58 questions about their experiences of living with HypoPT and their main concerns and challenges. The mean age of patients surveyed was 51 years. Most patients were female (89%), white (92%), had post-surgical HypoPT (80%), and were taking oral calcium (91%) and/or active vitamin D (77%).
Abbreviations: HypoPT, hypoparathyroidism
Source: Astolfi et al. 2020[50]

These patient testimonies highlight the profound and often invisible toll of HypoPT on daily life, identity, and independence. Together with survey data, they underscore the urgent need for more effective, targeted treatments beyond CT.

In the Kontogeorgos et al. study (n=203), HypoPT participants were treated with calcium and active vitamin D. Compared to age- and sex-matched population controls (n=414), individuals with HypoPT showed significantly lower scores in physical functioning, vitality, emotional role, and mental health domains of the SF-36 (see Figure 5) suggesting a poorer HRQoL within this group compared to the population sample.[35]

**Figure 5: HRQoL (SF-36) in participants with HypoPT versus population controls from the WHO MONICA study**



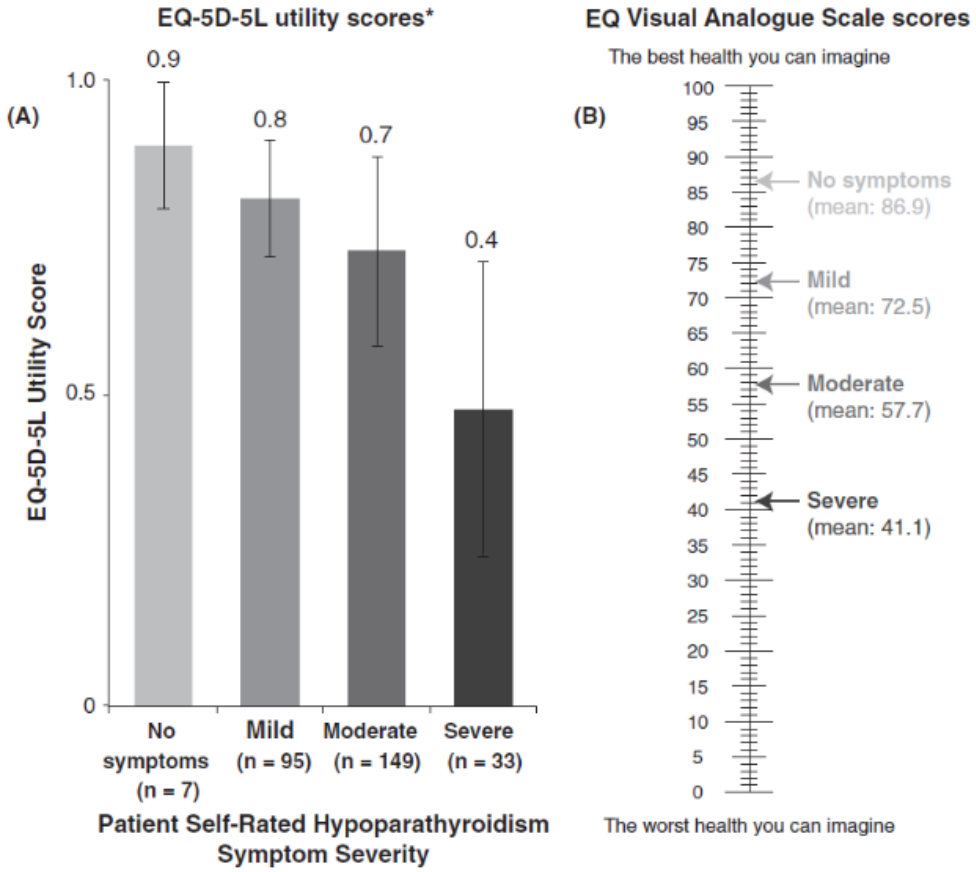

HRQoL according to the Short Form 36 and EuroQol-5 Dimensions Visual Analogue Scale 0–100 in 106 patients with HypoPT and 414 population controls from the WHO MONICA study, Gothenburg, Sweden. *p=0.009, **p=0.001, ***p<0.001.
A Swedish study by Kontogeorgos *et al.* (2022) based on patient questionnaire responses observed poorer HRQoL in individuals with HypoPT (n=203; identified from medical records between 2007–2020, disease duration not reported) versus those in a population sample from the World Health Organization's (WHO's) MONItoring of trends and determinants in CArdiovascular disease (MONICA) study (who served as a control group for endocrine disease).[35] Patients with HypoPT were mostly female (80%) with post-surgical HypoPT (80%) and the median age was 58 years. Overall, 74% of patients with HypoPT were receiving oral calcium and 82% were receiving active vitamin D.
Abbreviations: HRQoL, health-related quality of life; HypoPT, hypoparathyroidism; SF36, Short Form 36; VAS, visual analogue scale; WHO MONICA, World Health Organization's MONItoring of trends and determinants in CArdiovascular disease
Source: Kontogeorgos et al. 2022[35]

In the Siggelkow *et al.* (2020) (n=398) multi-country survey, patients with inadequately controlled chronic HypoPT (determined by participants' reports of

persistent symptoms and/or poorly controlled calcium levels as described by their physicians, despite receiving CT) reported substantial symptoms. This higher symptom burden was strongly associated with decreased patient HRQoL and poorer health status assessment scores (Figure 6).[12] At the time of the survey, 91% of patients were experiencing symptoms despite treatment and 67% of patients had poorly controlled/low serum calcium. Most patients rated their HypoPT-related symptom severity as moderate (53%) or mild (32%); 12% of patients rated their HypoPT symptoms as severe and 3% stated no symptoms.[12]

**Figure 6: (A) EQ-5D-5L utility scores and (B) EQ Visual Analogue Scale scores stratified by patient self-rated symptom**




(A) EQ-5D-5L utility scores: A US scoring algorithm was used for the United States, and an English scoring algorithm was used for Europe and Canada. Error bars for (A) represent standard deviation. Higher EQ-5D-5L utility and visual analogue scale scores indicate better health status
Abbreviations: EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; VAS, visual analogue scale
Source: Siggelkow et al. 2020[12]

Cognitive deficits are commonly associated with HypoPT, including feelings of confusion, a reduced ability to focus and think clearly, or brain fog.[51,55] The cross-

sectional study by Rubin,M.R et al (2022) [56] examined cognitive outcomes in patients with HypoPT, both post-surgical and non-surgical, compared to healthy controls. The study revealed lower quality of life and impaired cognitive functions (such as processing speed, executive functioning, visual memory, and auditory memory) in patients with HypoPT. Additionally, the hippocampal volume was reduced in these patients, with the size of the thalamus in post-surgical individuals linked to disease duration. Notably, patients experiencing severe brain fog had a smaller hippocampus than those with milder symptoms. HypoPT is linked to measurable cognitive deficits and structural brain changes that align patient-reported symptoms.[51]

HypoPT is also associated with a significant impact on mental health with 59% and 53% of adults with HypoPT experiencing anxiety and depression, respectively.[8] Patients with HypoPT have a two-fold increased risk of depression or bipolar disorder compared to healthy populations (observed in postsurgical HypoPT cases).[57]

#### *1.3.5.1.1 Effects on patients' ability to work and perform daily activities*

HypoPT has a considerable negative impact on the ability to work and perform daily activities.[11,15] Although CT may improve blood calcium levels, individuals still report reduced HRQoL and experience impaired physical functioning and well-being.[4,8,55] The multi-country survey by Siggelkow *et al.* (2020)[12] (described in Section 1.3.5.1) found that the proportion of patients in full-time work decreased from 58% (n=232/397) before HypoPT diagnosis to 34% (n=135/397) at the time of the survey.[12] Of the 161 patients who changed their employment status after HypoPT diagnosis, 59% reported this was due to their illness. Overall activity impairment was reported by 41.7% of patients, with a similar proportion of employed patients (n=190) reporting overall work impairment (40.8%). Almost 10% (9.2%) of employed patients reported absenteeism from work due to HypoPT and 36.6% reported working while sick.[12] Work and activity impairment were greater in patients with higher self-rated symptom severity. Of employed patients (n=190) reporting no (n=5), mild (n=79), moderate (n=91) and severe (n=15) symptoms, work impairment was reported by 18%, 28%, 49% and 68% of patients, respectively, with activity impairment reported by 24%, 34%, 57% and 76% of patients.[15]

Several studies have shown that 90% of patients with chronic HypoPT report symptoms interfering with work productivity;[15] 30% are not able to work;[15] and 45% need unpaid time off.[15] Therefore, the consequences of HypoPT may negatively impact employment status and work productivity.[20,35]

#### *1.3.5.1.2 Caregiver burden*

Caregivers of patients with chronic HypoPT also experience negative impacts on their ability to work and perform daily activities.[12]

The multi-country survey by Siggelkow *et al.* (2020)[12] (see Section 1.3.5.1 for details) found that the proportion of caregivers in full-time work decreased from 51% (n=106/207) before the patient's HypoPT diagnosis to 41% (n=84/207) at the time of the survey. A quarter of caregivers who changed their employment status (11/42; 26%) reported that this was due to caring for someone with HypoPT. Overall activity impairment was reported by 32.7% of caregivers; around 20% of employed caregivers (n=115) reported overall work impairment (20.8%) or working while sick (presenteeism; 19.4%) and 4.6% reported absenteeism.[12] The proportion of matched caregivers (i.e. those whose corresponding patients also participated in the survey; n=78) reporting work impairment increased with caregiver-rated severity of the patient's symptoms: no symptoms 7%, mild 20%, moderate 24% and severe 28%. A more pronounced trend was observed for matched caregivers' (n=159) activity impairment: no symptoms 11%, mild 26%, moderate 37% and severe symptoms 56%.

Studies have also shown that caregiver burden increases with increased symptom severity.[12] The survey by Siggelkow *et al. (2020)* assessed non-professional caregiver (n=207) burden using the Modified Caregiver Strain Index (MCSI). The MCSI measures strain among long-term caregivers in five domains (financial, physical, psychological, social and personal); scores range from 0 to 26, with higher scores corresponding to greater caregiver burden. As observed for the patients themselves, caregiver burden increased with patient self-rated symptom severity (MCSI scores: no symptoms, 1.7; mild, 5.4; moderate, 9.5; severe, 12.5).[12]

#### *1.3.5.1.3 Economic burden*

Management of HypoPT symptoms and associated complications leads to a significant economic burden on healthcare systems and individuals. The total direct costs (all-cause costs of primary and secondary care) of patients with HypoPT are five to seven times higher vs general population.[10] Hospitalisations, complication-related and CKD are all likely drivers of annual care costs.[58-60] Patients with HypoPT and CKD spend on average 5.6 hospital days per year more than the matched cohort (and more than 20x higher hospital costs [£1,658 and £1,505 for surgical cases and non-surgical cases respectively compared to general population £77 – £83]).[58]

An analysis of the burden of chronic HypoPT in UK was recently undertaken using linked primary care data from the CPRD Aurum database, secondary care data from Hospital Episode Statistics (HES), and death registrations from the Office for National Statistics (ONS).[15] This retrospective, observational, real-world matched cohort study used electronic medical records, hospital activity records, and death registration data to investigate the epidemiology, direct healthcare economic burden (hospitalisations and costs), and clinical burden of complications among patients with chronic HypoPT (surgical and non-surgical) (full CPRD report provided in the reference pack).

The chronic HypoPT population was further stratified by their controlled and uncontrolled status (see Table 5 for the criteria used to define the adequately controlled (AC) and not adequately controlled (NAC) status). This stratification using number of outpatients (OP) and in patients (IP) visits was based on feedback received from UK clinicians treating patients with chronic HypoPT to identify the two groups due to the limitation of not having any laboratory calcium data, full calcium dosing data or QoL data. This definition was considered to align to the clinical definition of AC and NAC disease outlined in section 1.3.6.5 and was supported by UK clinical experts.[16]

Specific objectives of the analysis were the following:

1) Describe the healthcare resource use and costs for patients with chronic post-surgical hypoparathyroidism or chronic non-surgical hypoparathyroidism and their matched general population counterparts overall and stratified by adequately controlled and not adequately controlled chronic HypoPT.

2) Estimate the risk of mortality amongst patients with chronic post-surgical and non-surgical HypoPT compared to matched patients without chronic HypoPT overall and for adequately controlled and not adequately controlled chronic HypoPT. Additionally estimate the risk of mortality amongst patients with controlled HypoPT compared to not adequately controlled chronic HypoPT.

3) Estimate the risk of common complications associated with chronic HypoPT amongst patients with chronic hypoparathyroidism compared to matched patients without hypoparathyroidism overall and for controlled and not adequately controlled chronic hypoparathyroidism.

4) Estimate the risk of common complications associated with chronic HypoPT amongst patients with controlled chronic HypoPT compared to not adequately controlled chronic hypoparathyroidism.

**Table 5: AC and NAC definitions**

| Cohort | Definition |
|---|---|
| AC (Controlled) | ≤5 OP appointments **and** <1 IP appointment PPPY |
| NAC (Uncontrolled) | >5 OP appointments **and** ≥1 IP appointment PPPY |

Abbreviations: AC, adequately controlled; NAC, not adequately controlled; OP, outpatients; IP, inpatients; PPPY, per patient per year

The study results found that patients with chronic HypoPT whose disease could be considered NAC (see section 1.3.6.4) were associated with a significantly higher resource use. Patients with NAC disease had more hospital admissions, more outpatient visits, greater emergency care and incurred higher costs than the general chronic HypoPT population. They also experienced higher risk of renal complications which were deemed as more serious and therefore associated with higher healthcare costs and resource use.[10]

Furthermore, a study on clinical burden and healthcare resource utilisation among patients with chronic HypoPT overall and by AC vs NAC showed that CKD was experienced by 3.5% of NAC patients versus 1.1% of AC patients (p=0.08), this is more than a three-fold increase.[61] CVD and metabolic disorders were experienced by 26.2% of the NAC population vs 17.9% of the AC population (p<0.05), a significant difference.[61] The difference in the AC and NAC groups for complications has a significant and noticeable impact on both HRQoL and economic resources.

### 1.3.6 Current treatment pathway

#### 1.3.6.1 Treatment guidelines

Whilst there are no UK specific guidelines for the management of HypoPT, the most current European published guidelines are the 2022 Guidelines from the Second International Workshop, and the 2022 consensus of the European Society of Endocrinology of which UK clinical experts comply with and was confirmed through three UK clinical experts.[2,3]

The updated ESE guidelines, orally presented at the Joint Congress ESPE and ESE Copenhagen, May 2025 conference and scheduled for publication in October 2025, recommend considering treatment with palopegteriparatide in patients with chronic HypoPT who are on optimised CT and meet at least one of the following criteria:

- Frequent fluctuations in serum calcium or symptomatic hypocalcaemia
- Impaired quality of life (QoL) attributable to chronic HypoPT
- Reduced kidney function (eGFR < 60 mL/min/1.73 m²)
- Hypercalciuria
- Hyperphosphatemia

These recommendations reflect emerging evidence that PTH replacement therapy, such as palopegteriparatide, may offer improved efficacy and clinical outcomes in comparison to CT across these key parameters.

Until PTH replacement therapy is routinely available however, the standard of care remains CT. The current goal of chronic HypoPT treatment with CT is to control the

symptoms of hypocalcaemia, to try to prevent short- and long-term complications and improve the patient's QoL.[6] European guidelines advocate that the management of chronic HypoPT with CT focuses on: [2,3,6]

- Maintaining serum calcium levels in the lower part of the reference range or just below and limiting the occurrence of clinical signs of hypocalcaemia.
- Alleviating symptomatic hypocalcaemia while avoiding hypercalciuria.
- Achieving a 24-hour urinary calcium level of <6.25 mmol/24 hours or 250 mg/24 hours for adult women and <7.5 mmol/24 hours or 300 mg/24 hours for adult men.
- Preventing the development of nephrolithiasis and nephrocalcinosis and renal involvement

Both the Second International Workshop,[2] and the 2022 consensus of the European Society of Endocrinology,[3] recommend as first-line treatment of chronic HypoPT, conventional therapy, consisting of oral administration of active vitamin D and calcium. Calcium administration should be carried out with calcium salts, mainly in the form of calcium carbonate. The recommended doses would be between 1-2g elemental calcium per day in divided doses to be taken with meals. In the case of active vitamin D, calcitriol (1,25-dihydroxyvitamin D) is used at a dose of 0.25 to 2.0mcg/day divided into 1 or 2 doses and alfacalcidol at a dose of 0.5 to3.0mcg/day.[6,30]

In emergency situations, it is necessary to administer intravenous (IV) calcium treatment, which is delivered as sparingly as possible due to the increased risk of local and renal toxicity.

CT does not always make it possible to attain acceptable clinical and biochemical control of HypoPT, since it does not replace the functions of PTH. In addition, the use of CT can lead to short and long-term complications, including hypo/hypercalcaemia or increased urinary calcium excretion, resulting in urinary tract infections, nephrocalcinosis or kidney stone formation.[6]

According to the recommendations of 2022 Guidelines from the second International Workshop and the 2022 consensus of the European Society of Endocrinology,[2,3] PTH replacement therapy should be considered for patients who cannot achieve calcium control/homeostasis, have poor HRQoL, exhibit renal complications, or poor gastrointestinal absorption. [2,35,62,63]

A summary of the published guidelines and evidence-based recommendations for the treatment of chronic HypoPT is provided in Table 6.

**Table 6: Summary of key guidelines and evidence-based recommendations for the management of chronic HypoPT**

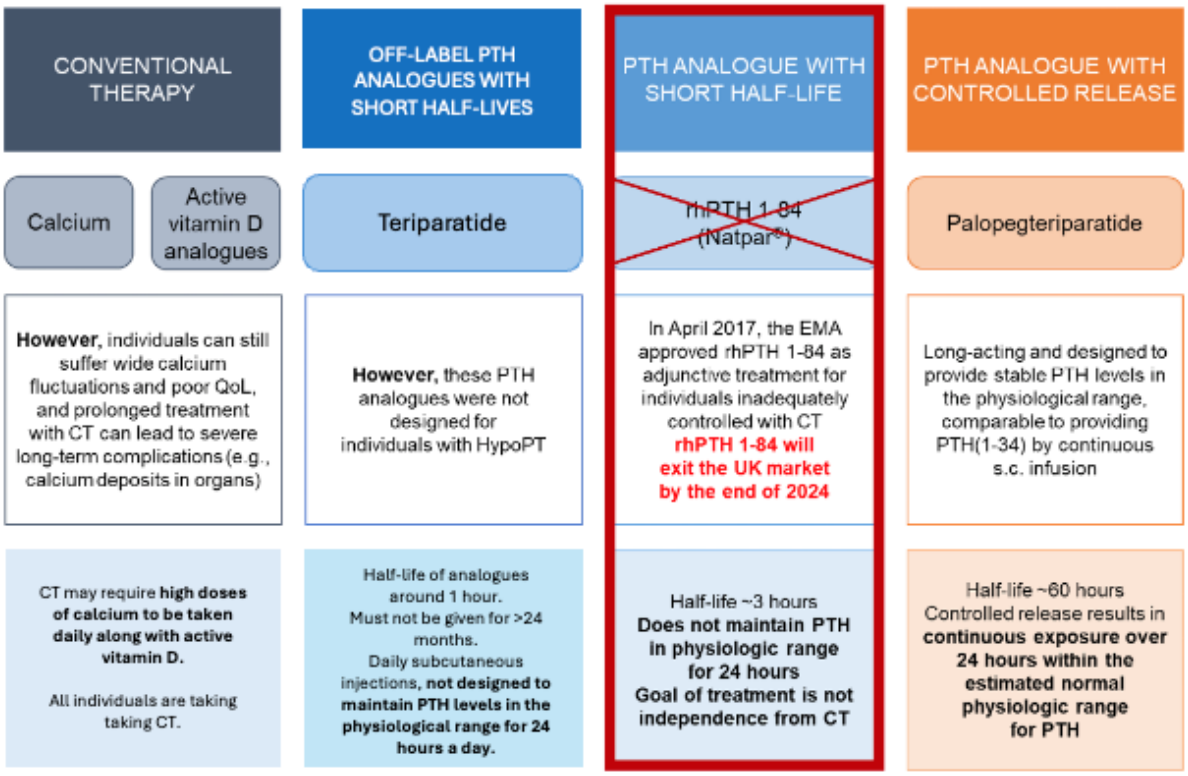
| **Guidelines from the Second International Workshop on the evaluation and management of HypoPT – 2022[2]** |
|---|
| • CT (active vitamin D and calcium) as first-line therapy is suggested for patients with chronic HypoPT<br>• PTH replacement therapy should be considered for patient who are not adequately controlled on CT:<br>– Inadequate calcaemic control with hypercalciuria<br>– Renal complications<br>– Nephrocalcinosis<br>– Gastrointestinal malabsorption<br>• Individuals with poor compliance or malabsorption or who are intolerant of large doses of active vitamin D and calcium may also benefit from PTH therapy |
| **European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2022)[3]** |
| • CT with active vitamin D and oral calcium is recommended as first line treatment<br>• Severe hypercalcaemia may be managed conservatively using IV and oral rehydration and cinacalcet<br>• Thiazide diuretics with a low phosphate diet may be used to reduce urinary calcium losses<br>• PTH replacement therapy should be considered for the following patients:<br>– with inadequate control of serum calcium levels<br>– or in whom the dose of elemental calcium exceeds 2.5 g per day or in whom large amounts of active vitamin D analogues are needed to control calcium levels or symptoms;<br>– or with hypercalciuria, kidney stones, nephrocalcinosis or impaired renal function;<br>– or with hyperphosphatemia and/or increased phosphocalcic product;<br>– or with disorders of the gastrointestinal tract associated with malabsorption;<br>– or with significantly reduced quality of life (QoL) |

Abbreviations: CT, conventional therapy; ESE, European Society of Endocrinology; HRQoL, health-related quality of life; HypoPT, hypoparathyroidism; IV, intravenous; PARAT, Parathyroid Disorders Educational Program; PTH, parathyroid hormone

Although the guidelines identify patients who would benefit from PTH replacement therapy, there are none routinely used in the UK. Of the two PTH analogues currently available as potential treatments: one (teriparatide) is not licenced in HypoPT so any use is off-label and used under individual funding request (IFR) (see 1.3.6.2 below); the other (Natpar®) is not routinely commissioned and is currently being globally discontinued by the manufacturer (Takeda) (see 1.3.6.2 below). It should be noted that both teriparatide and Natpar® have a short half-life (approximately 1 hour for teriparatide and 2.83 to 3.02 hours for Natpar®).[46,37] As such, there is an unmet need for an effective treatment for HypoPT that offers sustained and consistent PTH levels.

An overview of the current treatments for chronic HypoPT can be found in Figure 7 below. Palopegteriparatide (referred to as Transcon PTH) is mentioned in the recommendations of the second International Workshop 2022 as one of the new therapeutic options that will soon be available for patients with HypoPT.[2]

**Figure 7: Overview of current treatments for HypoPT**




Abbreviations: CT, conventional therapy; EMA, European Medicines Agency; HypoPT, hypoparathyroidism; PTH, parathyroid hormone; QoL, quality of life; rhPTH, recombinant human parathyroid hormone; UK, United Kindgom

### 1.3.6.2 Limitations of current treatments

***Conventional therapy***

Although the treatment goal of CT is to attempt to alleviate the symptoms of hypocalcaemia, it leads to adverse effects that increase the burden of the disease, furthermore, patients with HypoPT receiving CT may still report reduced HRQoL and experience impaired physical functioning and well-being.[4,8,64] This is because active vitamin D and calcium do not address the lack of PTH-mediated renal calcium reabsorption, phosphate excretion and other PTH-mediated effects.[13]

- As a result of increasing the serum calcium-phosphate levels, this predisposes patients to ectopic calcifications in addition to those in the renal parenchyma, including of the eye, central nervous system (particularly the basal ganglia) and vasculature.[65] As a result, along with the careful titration of medication and biochemical monitoring for the control of hypocalcaemia, clinicians must periodically assess renal, ocular, neurological, neuromuscular,

behavioural and skeletal parameters to avoid further long-term complications and preserve quality of life for patients.

- Individuals with chronic HypoPT who receive long-term treatment with CT have an increased risk of complications compared to the general population.[43] This is because CT can result in increased urinary excretion of calcium, and the resulting hypercalciuria can lead to nephrocalcinosis, kidney stones, and impaired renal function in the long term.[6] Renal complications (CKD) are closely linked to an increased risk of CVD, particularly in advanced stages.[42]

It is important to note that not every patient can achieve an adequately controlled biochemical homeostasis and/or experience a reduction of symptoms within the acceptable daily intake of calcium and active vitamin D treatments (CT).

***Off-label osteoporosis PTH analogue with short half-life***

Teriparatide is a PTH analogue with a short half-life that has been approved for use in osteoporosis treatment but has been used off-label for HypoPT in a small number of cases.[18] Responses to a UK national chronic HypoPT audit (2022) indicated teriparatide was used in 1.3% of patients.[17] With UK clinical experts confirming this is rarely used in practice.[16] Teriparatide is administered intermittently (providing a desirable osteoanabolic effect for the treatment of osteoporosis) and does not maintain PTH levels in the physiologic range for 24 hours, making it less well-suited to the management of chronic HypoPT. Effective management of HypoPT requires a PTH analogue that displays a prolonged state of binding to the PTH/PTHrP receptor with a more extended bioavailable pharmacokinetic profile.[66] Furthermore, teriparatide can only be used for 24 months in a patient's lifetime due to the increased risk of osteosarcoma deeming it unsuitable for chronic HypoPT, which requires longer treatment duration.

Additionally, the current marketing authorisation of teriparatide has been granted for the 20 mcg per day dosage for the treatment of osteoporosis whereas for HypoPT higher doses are generally needed (e.g. between 40 and 80 mcg per day).[67] There is a lack of evidence with respect to the safety profile of teriparatide at these

significantly higher doses, conveying an important cautionary message regarding the use of dosages above those for which safety data have been collected.[67]

***Natpar®***

Takeda, the manufacturer of Natpar®, gave notice to the DHSC, MHRA, patients and physicians on 4th October 2022 that they intended to withdraw Natpar® by end of 2024 due to unresolved manufacturing issues with the product. They also advised that no new patients should be initiated on any strength of Natpar. Since then, it has been confirmed Natpar® is no longer being supplied to patients as a treatment option and manufacturing has come to a stop.[20] As a result, the only licensed treatments for chronic HypoPT in the UK will be either CT or palopegteriparatide.[20,21]

#### 1.3.6.3 Unmet need

HypoPT treatment currently includes no PTH replacement therapy and there are limited treatment options available. As mentioned in 1.3.3 CT does not adequately control the disease for all patients, and some continue to experience the symptoms of HypoPT, poor quality of life, and may go on to develop further complications associated with the disease.

Current treatment options do not replace the function of PTH or provide consistent PTH over a sustained period mimicking the natural physiology. Conversely CT can lead to or worsen hypercalciuria resulting in an increased calcium load to the kidneys and increasing the risk of renal complications.[10,30,38,44,68,69] CKD is also an important risk factor for CVD, highlighting the adverse effect of chronic HypoPT and CT on multiple organ systems.[70]

In conclusion, there is a high unmet need for a treatment that targets the underlying cause of the symptoms and complications of patients with chronic HypoPT that are not adequately controlled with CT. The associated renal and cardiovascular impact of long-term CT highlights the need for new treatment options that enable patients with HypoPT to have independence from CT. Palopegteriparatide maintains PTH levels in the physiological range over 24 hours, which enables patients to become independent from CT, and has little or no detrimental effect on renal function.

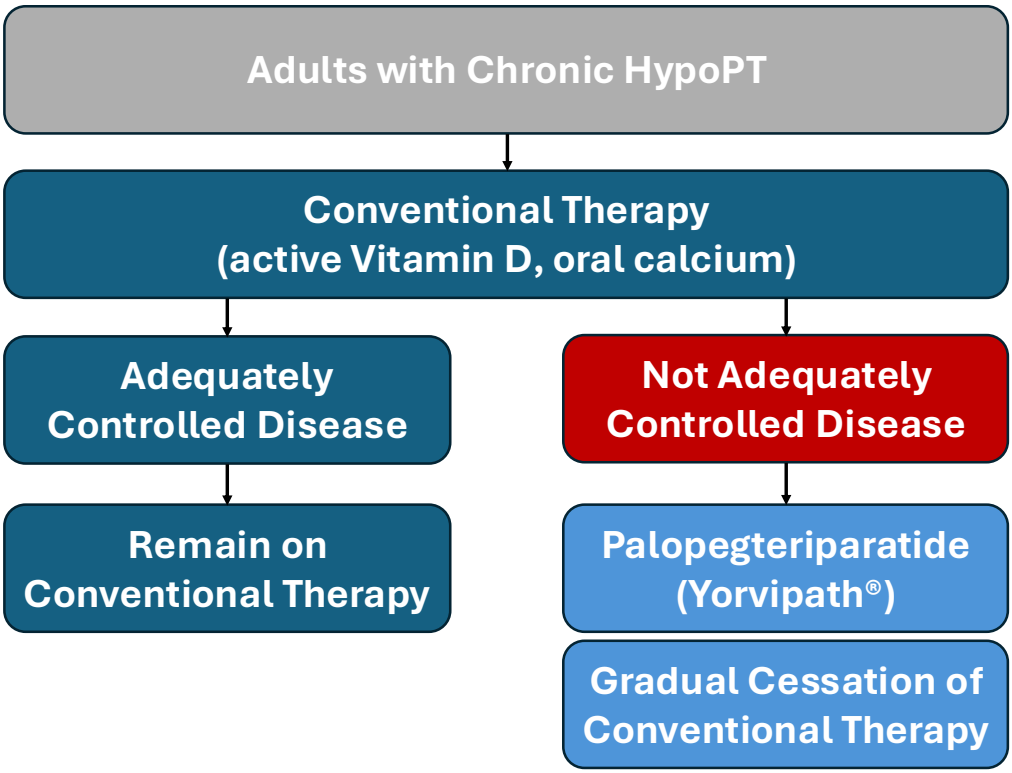
#### 1.3.6.4 Proposed place of palopegteriparatide in the current treatment pathway

Whilst palopegteriparatide is licenced for the treatment of all adults with chronic HypoPT, in the context of this submission, palopegteriparatide is positioned as a second-line treatment for adults with chronic HypoPT whose disease is not adequately controlled (NAC) with CT (see Figure 8).

As mentioned in section 1.3.6.1, European guidelines outline that there are patients for whom CT is not adequate and that these patients who are NAC would benefit from second line treatment after CT in the form of replacement PTH (see Table 8).[2,3] Furthermore, the upcoming ESE guidelines recommend considering treatment with palopegteriparatide for patients with chronic HypoPT who meet the criteria outlined in section 1.3.6.1.[2,3] Although both Natpar® and teriparatide could theoretically be considered as second-line therapy, in practice they are not routinely used due to the various reasons mentioned above (see section 1.3.6.2) and have therefore not been considered as suitable comparators.

In order to inform this submission and economic analysis, recommendations from guidelines were translated into meaningful criteria to define the relevant targeted NAC population (see section 1.3.6.5). The proposed positioning of second-line treatment with palopegteriparatide has been considered suitable with additional validation from UK clinical experts.

**Figure 8: Proposed position in the treatment pathway**




* Doses of active forms of vitamin D and calcium treatments will need to be adjusted prior to initiating and during treatment with palopegteriparatide based on serum calcium value. The optimal dose after titration is the minimum dose required to prevent hypocalcaemia. This is the dose that maintains serum calcium within the normal range without the need for active forms of vitamin D or calcium treatments beyond recommended nutritional supplementation for the general population (generally less than 600 mg per day). At Week 104 of the Phase 3 PaTHway trial, 97% (74/76) of participants achieved independence from CT (defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg). Patients receiving the maximum palopegteriparatide dose of 60 mcg per day who experience ongoing hypocalcaemia may require co-administration of therapeutic calcium and/or active forms of vitamin D.
Abbreviation: HypoPT, hypoparathyroidism
Source: Adapted from SmPC[19]

#### 1.3.6.5 Definition of AC and NAC population

Building on the definitions provided by the published guidelines, it was necessary to translate those into specific quantifiable criteria that could be used to clinically identify and operationalise the definition of chronic HypoPT patients whose disease is not NAC on CT. Based on UK clinical expert input and a publication by Chen et al (2019) which sought to assess the real-world clinical burden and HCRU by adequately controlled and not adequately controlled disease, the below criteria were defined.[61]

Patients with chronic HypoPT may be classified as having NAC disease if they meet ANY of the following criteria:

- High-dose conventional therapy
    - Active vitamin D – Calcitriol (active vitamin D) ≥ 1.0 mcg/day
      Alfacalcidol ≥ 2.0 mcg/day
    - Calcium – ≥ 2000 mg/day
- Severe symptoms and/or healthcare use
    - Emergency room or urgent care visits related to HypoPT (within 6 months)
    - Hospitalisations related to HypoPT (within 6 months)
    - Poor quality of life (SF-36 Physical Functioning score < 40)
- Renal impairment and/or history of renal complications
    - Documented renal insufficiency
    - History of kidney stones (nephrolithiasis)
    - eGFR < 60 mL/min/1.73m²

The definition was reviewed and validated by three UK-based clinical experts.[16] It also aligns to the recently presented criteria for palopegteriparatide use to be included in the updated ESE guidelines when published later this year. Patients who did not meet the above criteria were considered to have adequately controlled disease.

## 1.4 Equality considerations

It is expected that more women than men will be treated with palopegteriparatide; this is because post-surgical HypoPT is more common in women than men as the former are more likely to have thyroid disease and hence undergo thyroidectomy.[6]

# 2 Clinical effectiveness


## SUMMARY

- The pivotal evidence supporting palopegteriparatide for the treatment of HypoPT is provided by the Phase 3 PaTHway trial and its open-label extension (OLE) which were identified in a systematic literature review (SLR) conducted in April 2025. [32,40]
- The PaTHway trial is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group trial, investigating the safety, tolerability and efficacy of palopegteriparatide in adults with chronic hypoparathyroidism (HypoPT).[41]
- The primary objective of the PaTHway trial was to assess the treatment effect of daily palopegteriparatide on serum calcium levels, and therapeutic doses of active vitamin D and calcium at 26 weeks of treatment.[41]
- The multi-component efficacy primary endpoint results showed that at Week 26, 79% (48/61) of participants in the palopegteriparatide group versus 5% (1/21) ($p<0.0001$) in the placebo group achieved normal serum calcium and independence from conventional therapy (CT), without an increase in prescribed trial drug over the final 4 weeks of the blinded period.[41]
- At Week 52, 81% (63/78) of participants treated with palopegteriparatide met the OLE multi-component efficacy endpoint (serum calcium in the normal range and independence from CT). 95% (74/78) of participants treated with palopegteriparatide achieved independence from CT (requiring no active vitamin D and ≤600 mg/day of oral calcium) at Week 52.[40]
- Palopegteriparatide was well tolerated in the PaTHway trial, with most treatment-emergent adverse events (TEAEs) being mild to moderate in severity.[41]
- The efficacy, safety, and tolerability results of the PaTHway trial support palopegteriparatide as a potential option for parathyroid hormone (PTH) replacement therapy for adults with chronic HypoPT whose disease is not adequately controlled on CT.


## 2.1 Identification and selection of relevant trials

A systematic literature review (SLR) was conducted to identify clinical evidence regarding the efficacy and safety profiles associated with any systemic therapies for adult patients with HypoPT.

The SLR was conducted based on the reporting standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[71] and general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions[72] as well as general methodological

requirements outlined by key Health Technology Appraisal (HTA) bodies, such as the National Institute for Health and Care Excellence (NICE),[73]Canada's Drug Agency,[74,75] and European Network for Health Technology Assessment.[76,77]

The searches were conducted on July 8, 2024; with an updated search conducted on the March 27, 2025, the searches returned 4,508 records.

After removing duplicates, 3,064 records were screened at the title and abstract level. Of these, 2,881 were excluded, and one Japanese report published in 1979 could not be retrieved. In total, 182 reports were screened at the full-text level, 109 of which were excluded. An additional 15 reports were identified through other sources. Ultimately, 38 unique studies from 88 reports were included in the SLR.

Full details of the SLR methodology, PRISMA diagram and included and excluded studies of the SLR are provided in Appendix B. Table 7 summarises the palopegteriparatide studies identified by the SLR.

**Table 7. Summary of palopegteriparatide studies identified by the SLR**

| Author/trial, year | Population | Interventions | Trial design | Sample size | Timepoints reported | Number of publications with extractable data† |
|---|---|---|---|---|---|---|
| PaTHway[41] | Adults with chronic HypoPT of postsurgical, autoimmune, genetic, or idiopathic aetiologies | Palopegteriparatide, placebo | International, Phase 3, RCT, double blind | 84 | 26 weeks | 7 |
| PaTHway OLE[40] | Adults with chronic HypoPT of postsurgical, autoimmune, genetic, or idiopathic aetiologies | Palopegteriparatide | International, Phase 3, OLE | 79 | 52 weeks | 3 |
| PaTH Forward*[32] | Adults with postsurgical, autoimmune, genetic, or idiopathic HypoPT | Palopegteriparatide, placebo | International, Phase 2, RCT, double blind | 59 | 4 weeks | 2 |
| PaTH Forward OLE*[32] | Adults with postsurgical, autoimmune, genetic, or idiopathic HypoPT | Palopegteriparatide individualised dosing | International, Phase 2, OLE | 59 | 26 weeks<br>58 weeks<br>110 weeks | 4 |

*PaTH Forward and PaTH Forward OLE were reported in the same publication.[73]
†Not including publications (i.e., conference abstracts) with duplicate data.
Abbreviations: HypoPT, hypoparathyroidism; OLE, open-label extension; RCT, randomised control trial; SLR, systematic literature review

## 2.2 List of relevant clinical effectiveness evidence

The pivotal evidence supporting palopegteriparatide for the treatment of HypoPT is provided by the Phase III PaTHway trial and its open-label extension (OLE), which are the focus of this submission.

A summary of the PaTHway trial is presented in Table 8.

**Table 8: Clinical effectiveness evidence**

| | |
|---|---|
| **Trial name/number** | PaTHway (NCT04701203) |
| **Trial design** | Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group 26-week trial with a 156-week OLE.[41] |
| **Population** | Adults with chronic HypoPT on conventional therapy (CT) |
| **Intervention(s)** | Palopegteriparatide. All participants started with 18 mcg/day of trial drug. The trial drug dose was individually and progressively titrated in dose increments of 3 mcg/day with the goal to achieve normocalcaemia based on a titration algorithm.[41] |
| **Comparator(s)** | Placebo titrated to an optimal dose based on a titration algorithm.[41] |
| **Indicate if trial supports application for marketing authorisation** | Yes |
| **Indicate if trial used in the economic model** | Yes |
| **Rationale if study not used in the model** | NA |
| **Reported outcomes specified in the decision problem** | • **Independence from CT; (defined as normocalcaemia with independence from active Vitamin D and with calcium ≤600 mg/day)**<br>• **Calcium and active vitamin D doses**<br>• Daily "pill burden" of active Vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches)<br>• **Reduction in physical and cognitive symptoms†**<br>• **HRQoL**†<br>• **Adverse effects of treatment‡** |
| **All other reported outcomes** | • No increase in prescribed trial drug within 4 weeks prior to Week 26 visit<br>• BMD and TBS by DXA<br>• Bone turnover markers (serum P1NP and CTx)<br>• Serum magnesium<br>• Serum phosphate levels<br>• Albumin-adjusted serum calcium levels<br>• CGI-S |

| | |
|---|---|
| **Key publications** | 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 Off J Am Soc Bone Miner Res. 2023 Jan;38(1):14–25.<br><br>Clarke B, Aziz Khan A, Ruth Rubin M, Schwarz PE, Vokes TJ, Shoback DM, et al. OR23-05 Long-term Efficacy And Safety Of Transcon PTH In Adults With Hypoparathyroidism: 52-Week Results From The Open-label Extension Of The Phase 3 Pathway Trial. J Endocr Soc. 2023 Oct 5;7(Supplement_1):bvad114.563.<br><br>Rejnmark L, Gosmanova EO, Khan AA, Makita N, Imanishi Y, Takeuchi Y, et al. Palopegteriparatide Treatment Improves Renal Function in Adults With Chronic Hypoparathyroidism: 1--Year Results From the Phase 3 PaTHway Trial. Adv Ther. Published online April 30, 2024. doi:10.1007/s12325-024-02843-8. |

Outcomes listed in bold are included in the economic model. † As measured by the Hypoparathyroidism Patient Experience Score (HPES), SF-36 Physical Functioning subscale score and EQ-5D. ‡ Safety and tolerability endpoint.
Abbreviations: BMD, bone mineral density; CGI-S, Clinical Global Impression of Severity; CT, conventional therapy; CTx, C-terminal telopeptide of type 1 collagen; DXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQoL 5 Dimensions 5 Levels; HRQoL, health-related quality of life, HypoPT, hypoparathyroidism; mcg, microgram; NA, not applicable; OLE, open label extension; P1NP, procollagen type 1 N-propeptide, TBS, trabecular bone score

## 2.3 Summary of methodology of the relevant clinical effectiveness evidence

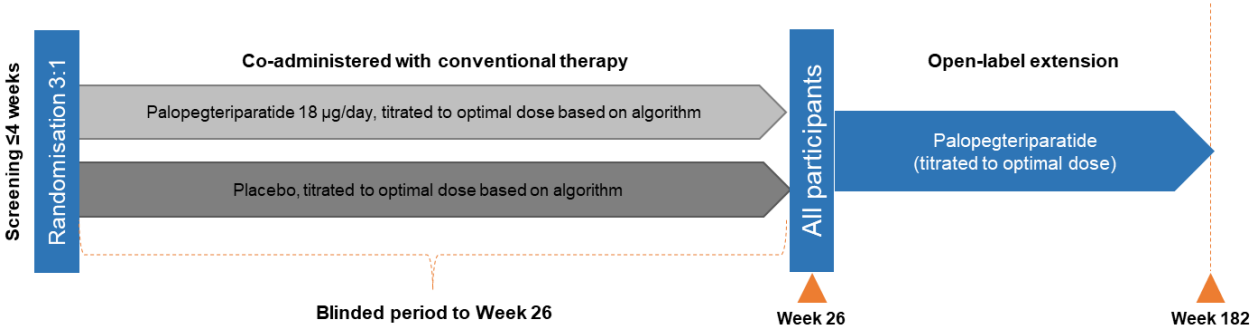
### 2.3.1 The PaTHway trial

PaTHway is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group trial followed by a 156-week open-label extension (OLE), designed to investigate the safety and efficacy of palopegteriparatide in adults with chronic HypoPT.[41] The primary objective of the PaTHway trial was to assess the treatment effect of daily palopegteriparatide on serum calcium levels and therapeutic doses of active vitamin D (i.e. calcitriol or alfacalcidol) and calcium at 26 weeks of treatment.[41]

As shown in Figure 9, the trial consists of a blinded 26-week study period followed by a 156-week OLE period. Participants were randomised 3:1 to receive palopegteriparatide or placebo.[39,41] Details of dosing are given in Table 9.

Data from Weeks 26 (end of the blinded period), 52, 104 and 156 (from the OLE) are used to inform this submission.

**Figure 9: PaTHway trial design**




Abbreviations: ug, microgram
Source: Adapted from PaTHway Clinical Study Protocol v7 2023, data on file[78]

**Table 9: Summary of trial methodology**

| | |
|---|---|
| **Trial name/number** | PaTHway (NCT04701203) |
| **Trial design** | Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group followed by an OLE period.[41] |
| **Duration of trial** | 26 weeks blinded with a 156-week OLE.[41] |
| **Settings and locations where data were collected** | 21 sites across Canada (3), Denmark (2), Germany (1), Hungary (2), Italy (3), Norway (1) and the United States (9).[79] |
| **Patient eligibility criteria (for full details, see Appendix N)** | **Key inclusion criteria[41]**<br>• Men and non-pregnant women (≥18 years of age) with chronic HypoPT of postsurgical, autoimmune, genetic, or idiopathic aetiologies for a duration of at least 26 weeks.<br>• Participants must have been treated with calcitriol ≥0.5 mcg/day or alfacalcidol ≥1.0 mcg/day in addition to elemental calcium ≥800 mg/d for at least 12 weeks before screening.<br>• Stable doses of CT (i.e., active Vitamin D and calcium) were required for at least 5 weeks before screening, not precluding occasional (≤2/week) PRN doses of calcium and/or active Vitamin D.<br>• Urinary calcium excretion ≥125 mg/24 h and eGFR ≥30 mL/min/1.73 $m^2$. |
| | **Key exclusion criteria[41]**<br>• Impaired responsiveness to PTH (pseudohypoparathyroidism), characterised as PTH-resistance, with elevated PTH levels in the setting of hypocalcaemia.<br>• Any disease that might have affected calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HypoPT.<br>• Use of thiazide diuretics within 4 weeks prior to the 24-hour urine collection scheduled to occur within 1 week prior to Visit 1.<br>• Use of PTH-like drugs, including PTH 1-84, PTH 1-34, or other N-terminal fragments or analogues of PTH or PTH-related protein, within 4 weeks prior to Screening.<br>• Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (>0.5 mg/day), |

| | |
|---|---|
| | strontium, or cinacalcet hydrochloride, within 12 weeks prior to Screening.<br>• Use of osteoporosis therapies known to influence calcium and bone metabolism, i.e., bisphosphonate (oral or IV), denosumab, raloxifene, or romosozumab therapies within 2 years prior to screening. |
| **Trial drugs** | • **Blinded 26-week period**<br>– Intervention: All participants started with a fixed dose of palopegteriparatide (18 mcg/day SC), titrated at ≥7 day intervals in increments of 3 mcg/day to an optimal dose over a 10-week period, using a titration algorithm driven by serum calcium.[41]<br>– Comparator: Placebo (mimicking the palopegteriparatide dose).<br>• **Open-label extension period**<br>– Following successful completion of the blinded treatment period, participants from the palopegteriparatide and placebo group were allowed to enter the OLE period when all participants received palopegteriparatide. During the OLE period, all participants receive palopegteriparatide as follows:[78]<br>– If still taking active vitamin D, palopegteriparatide was started at a dose of 18 mcg/day, and was subsequently titrated to an optimal dose by a titration algorithm driven by serum calcium.[78]<br>– If not taking vitamin D and taking trial drug ≥30 mcg/day: palopegteriparatide was started at a dose of 18 mcg/day, and subsequently titrated to an optimal dose following the titration algorithm.[78]<br>– If not taking vitamin D and taking trial drug <30 mcg/day: palopegteriparatide was started at the same dose of trial drug taken at the end of the blinded period, except in cases of an out-of-range serum calcium level at Week 26, when the palopegteriparatide and/or calcium doses were adjusted. [78] |
| **Concomitant medication** | **Permitted concomitant medication:**<br>• CT (active Vitamin D and calcium). Titration of CT was performed according to a protocol-specified algorithm guided by serum calcium values. The algorithm was intended to facilitate independence from CT by discontinuation of active Vitamin D and calcium in response to reestablishment of physiological PTH signalling with palopegteriparatide treatment.[41]<br><br>**Prohibited concomitant medication:**<br>• Loop diuretics, thiazide diuretics, phosphate binders (other than calcium), digoxin, lithium, methotrexate, biotin >30 mcg/day, or systemic corticosteroids (other than as replacement therapy).<br>• PTH-like drugs, including PTH 1-84, PTH 1-34, or other N-terminal fragments or analogues of PTH or PTH-related protein.<br>• Other drugs known to influence calcium and bone metabolism.<br>For the OLE period, these medications are allowed only if deemed necessary by the investigator for patient safety considerations.[78] |

| | |
|---|---|
| **Primary endpoint** | Multi-component efficacy endpoint: the proportion of participants at Week 26 with all of the following:<br>• Albumin-adjusted serum calcium (sCa) measured at the Week 26 visit within the normal range (8.3–10.6 mg/dL)†; and<br>• **Independence from active vitamin D‡** and<br>• **Independence from therapeutic doses of elemental calcium (>600 mg/d)** and<br>• No increase in prescribed trial drug within 4 weeks prior to Week 26 visit. |
| **Other endpoints used in the model/specified in scope** | • Hospital admissions<br>• **Reduction in calcium treatments and Vitamin D analogues**<br>• **Health-related quality of life**<br>• **Adverse effects of treatment**<br>• Healthcare resource utilisation (HCRU)<br>• **Renal function (eGFR)**<br>• Mortality<br>• **Hypercalcaemia**<br>• **Hypocalcaemia**<br>• **Serum calcium**<br>• **Serum phosphate** |
| **Pre-planned subgroups** | Subgroups of interest considered provided that a sufficient number of participants fell in each category (e.g., ≥ 10% of analysis population in all categories) to perform the appropriate statistical analysis:<br>• Age category (<50 versus ≥ 50)<br>• Prior treatment with PTH therapy (yes versus no)<br>• Gender (female versus male)<br>• Aetiology of HypoPT (Post-surgical versus Other [auto-immune, idiopathic, and genetic])<br>• **Duration of HypoPT** (**<5 years**, ≥ 5 and <10 years, ≥ 10 and <20 years, ≥ 20 years)<br>• Region (North America versus Other)<br>• Menopausal status among female (premenopausal versus postmenopausal) |

Outcomes listed in bold are included in the economic model. †Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires two consecutive results outside the normal range within 4 weeks prior to the Week 26 visit. ‡Independence from active Vitamin D will be defined as a daily standing dose equal to zero on all days AND use of any PRN Vitamin D ≤7 days within 4 weeks prior to the Week 26 visit. §Independence from therapeutic calcium will be defined as average daily standing dose ≤600 mg AND use of PRN doses on ≤7 days within 4 weeks prior to the Week 26 visit. ¶Dose decrease permitted for safety reasons.
Abbreviations: CT, conventional therapy; CVD; cardiovascular disease, eGFR, estimated glomerular filtration rate; HCRU, healthcare resource use, HypoPT, hypoparathyroidism; IV, intravenous; m, metre; mcg, microgram; mg, milligram; min, minute; mL, millilitre; OLE, open-label extension; PRN, pro re nata (as needed); PTH, parathyroid hormone; SC, subcutaneous; sCa, serum calcium
Source: PaTHway Clinical Study Protocol v7 2023, data on file[78]

## 2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

### 2.4.1 Statistical analyses

Sample size calculations indicated that 68 participants randomised 3:1 to palopegteriparatide versus placebo would provide 99% statistical power at α=0.05 to demonstrate a statistically significant difference between the groups, assuming a 70% response rate for palopegteriparatide and 15% for placebo for the primary multi-component endpoint.[41] A target total sample size of 76 participants was selected to account for a ~10% dropout rate.[41]

All efficacy analyses were performed based on the ITT population, which consisted of all randomised participants who received at least one dose of the blinded trial drug. Safety analyses were based on the safety analysis population, consisting of all randomised participants who received at least one dose of the trial drug. Participants were analysed based on the actual drug received. Clinical and safety assessments were reported as descriptive statistics. Statistical significance was defined as $p<0.05$ (two-sided).[41]

The primary endpoint was analysed using the Cochran–Mantel Haenszel test stratified by HypoPT aetiology (post-surgical or other).[41] A prespecified sensitivity analysis of the primary composite endpoint was also performed, where pro re nata (PRN, or 'as required') doses of active vitamin D or calcium were not allowed for 4 weeks before the Week 26 visit. Participants without Week 26 albumin-adjusted serum calcium or with >7 days of missing diary data for active vitamin D or calcium during the 4 weeks before Week 26 were reported as non-responders.

Continuous secondary endpoints were analysed using an ANCOVA model with unequal variance, with change from baseline for the respective endpoint as a response variable, treatment assignment and HypoPT aetiology as fixed factors, and baseline variable of the endpoint as a covariate.[41] A prespecified sequential testing procedure was used to control the family-wise, type 1 error rate for the primary and key secondary endpoints.

Only observed data were reported for the primary endpoint (with no missing data imputation). Patients with missing data for key secondary endpoints had post-baseline data imputed using a multiple imputation model stratified by treatment group, under the assumption of missing at random.[39,80]

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, United States [US]).[41]

### 2.4.2 Analysis sets

Five analysis populations are defined (Table 10).[39]

**Table 10: PaTHway – Analysis populations**

| | | Palopeg-teriparatide | Placebo | Total |
|---|---|---|---|---|
| Screened population | All participants who underwent a Screening Visit and received a participant identification number. | NA | NA | 106 |
| Randomised population | All participants who were randomised to a treatment group in the trial. | 63 | 21 | 84 |
| Intent-to-Treat (ITT) population | All participants in the randomised population who received at least one dose of blinded trial drug. | 61 | 21 | 82 |
| Safety analysis population | All participants in the randomised population who received at least one dose of blinded trial drug. Participants were analysed according to actual trial treatment received. If participants took both palopegteriparatide and placebo during the blinded treatment period, they were analysed according to the treatment that was dosed for the majority of time (i.e., ≥ 50% dose days during the Blinded Treatment Period). | 61 | 21 | 82 |
| Pharmacokinetic (PK) population | All participants who received at least one dose of palopegteriparatide and for whom the plasma concentration data were considered sufficient and interpretable (i.e., had at least one non-missing concentration). | 58 | NA | 58 |

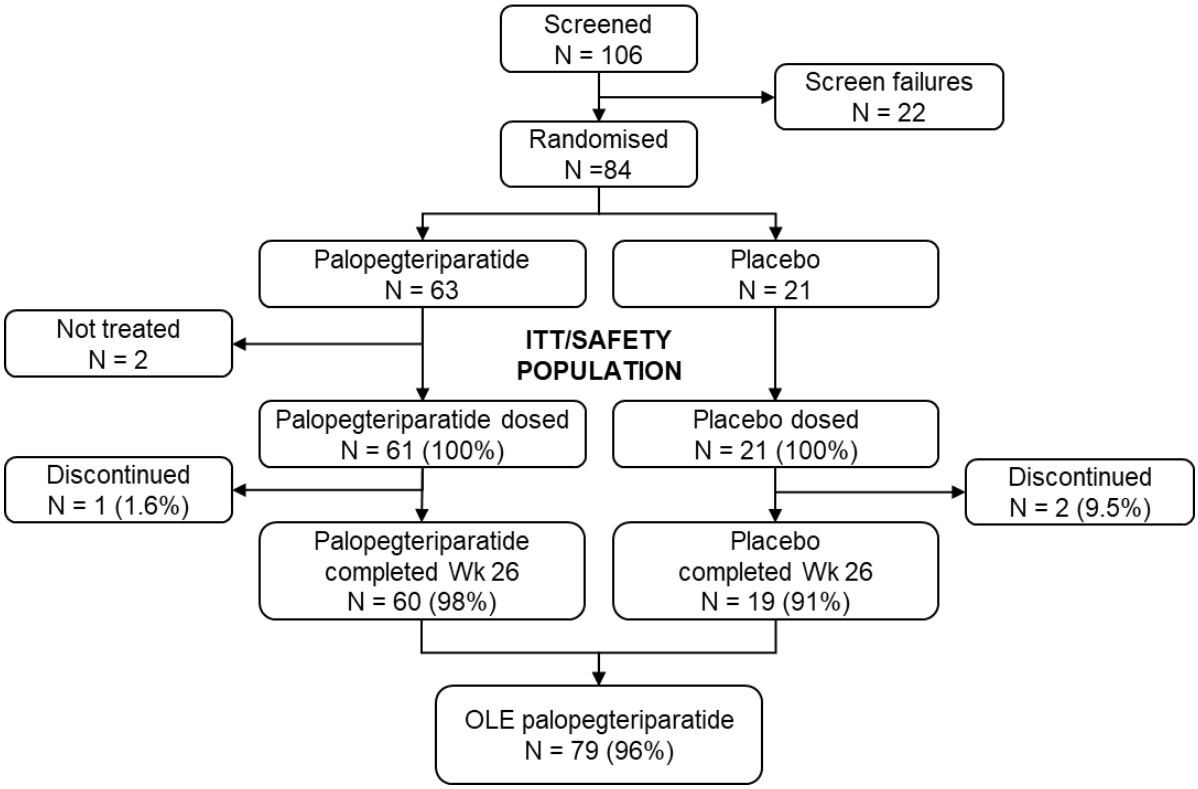
Abbreviations: ITT, intent-to-treat; NA, not available; PK, pharmacokinetic
Source: PaTHway CSR 2022, data on file[39]

### 2.4.3 Participant flow

Participant flow for the PaTHway trial is shown in Figure 10.

A total of 84 participants were randomised to receive palopegteriparatide (n=63) or placebo (n=21); overall 79 patients completed the double-blind period of the trial, 60 in the palopegteriparatide group (two participants were not treated and one participant died [death was unrelated to the trial drug]) and 19 in the placebo group (one adverse event [AE] and one withdrew consent).[39,41]

**Figure 10: PaTHway participant disposition**




Abbreviations: ITT, intent-to-treat; OLE, open-label extension; Wk, week
Source: Khan et al. 2023[41]

### 2.4.4 Participant baseline characteristics

Table 11 presents the baseline demographics, disease characteristics and CT in the PaTHway trial. As mentioned in section 1, the population focussed on in this submission is adult patients with chronic HypoPT whose disease is NAC. This subpopulation represents the patient population in which palopegteriparatide is expected to be used based on clinical guidelines and expert opinion.

PaTHway is considered representative of the NAC population. When applying the criteria from the European Expert Consensus to the PaTHway trial ITT population at baseline, [redacted] patients met the definition of NAC. While using the criteria from

the Second International Workshop [redacted] of the ITT population patients met the definition of NAC (see section 1.3.6.5).[2,3] The methodology used was the same as used in Chen (2019) which assessed clinical burden and HCRU amongst patients with chronic HypoPT, overall and by adequately controlled vs not adequately controlled disease.

Given the high percentage proportion, the clinical characteristics of the trial population, and validation with clinical experts,[16] the trial was considered generalisable to the broader NAC chronic HypoPT population. Consequently, the full data has been used to inform the analysis. Use of the full data set was also considered appropriate to ensure that the robustness of the analysis would not be diluted, given the rare nature of chronic HypoPT and limited patient numbers.

More broadly the trial population was generally representative of the United Kingdom (UK) chronic HypoPT NAC population in terms of demographics and baseline disease characteristics.[81] Baseline demographics were similar between treatment groups.[41] Participants were predominantly female (75.4% of patients in the palopegteriparatide group; 85.7% in the placebo group) and the mean age of the trial population was 49.0 years for the palopegteriparatide group and 47.3 years for the placebo group. Aetiology of HypoPT included neck surgery (85.2% of the palopegteriparatide group; 85.7% of the placebo group), autoimmune disease, intrinsic defects of the parathyroid gland, and idiopathic disease (Table 11).[41]

**Table 11: PaTHway – Baseline demographics, disease characteristics and CT (ITT population)**

| Characteristics | Palopegteriparatide (n=61) | Placebo (n=21) | Total (n=82) |
|---|---|---|---|
| Age (years), mean (SD) | 49.0 (13.1) | 47.3 (11.4) | 48.6 (12.7) |
| **Age group (years) - n (%)** | | | |
| <50 | 28 (45.9) | 14 (66.7) | 42 (51.2) |
| ≥50 | 33 (54.1) | 7 (33.3) | 40 (48.8) |
| Sex at birth, female, n (%) | 46 (75.4) | 18 (85.7) | 64 (78.0) |
| Postmenopausal, n (% of females) | 19 (41.3) | 3 (16.7) | 22 (34.4) |
| Body mass index (kg/m$^2$), mean (SD) | 27.3 (5.8) | 29.5 (5.7) | 27.8 (5.8) |

| Characteristics | Palopegteriparatide (n=61) | Placebo (n=21) | Total (n=82) |
|---|---|---|---|
| **Race - n (%)** | | | |
| Asian | 3 (4.9) | 2 (9.5) | 5 (6.1) |
| White | 57 (93.4) | 19 (90.5) | 76 (92.7) |
| Other | 1 (1.6) | 0 | 1 (1.2) |
| **Geographic region - n (%)** | | | |
| North America | 39 (63.9) | 12 (57.1) | 51 (62.2) |
| Europe | 22 (36.1) | 9 (42.9) | 31 (37.8) |
| **Cause of HypoPT, n (%)** | | | |
| Acquired (neck surgery) | 52 (85.2) | 18 (85.7) | 70 (85.4) |
| Autoimmune disease | 1 (1.6) | 0 | 1 (1.2) |
| Intrinsic genetic defects of the parathyroid glands | 3 (4.9) | 0 | 3 (3.7) |
| Idiopathic disease | 4 (6.6) | 3 (14.3) | 7 (8.5) |
| Other | 1 (1.6) | 0 | 1 (1.2) |
| **Duration of HypoPT (years)** | | | |
| Mean (SD) | 12.0 (11.4) | 11.1 (8.5) | 11.7 (10.7) |
| Min, Max | 1, 56 | 1, 33 | 1, 56 |
| **Participant history, n (%)** | | | |
| Renal insufficiency history | [redacted] | [redacted] | [redacted] |
| Kidney stones history | [redacted] | [redacted] | [redacted] |
| Ectopic calcifications history | [redacted] | [redacted] | [redacted] |
| Vascular calcifications history | [redacted] | [redacted] | [redacted] |
| Brain calcification history | [redacted] | [redacted] | [redacted] |
| Cataract history | [redacted] | [redacted] | [redacted] |
| Seizure history | [redacted] | [redacted] | [redacted] |
| **Baseline CT total daily doses, mean (SD)** | | | |
| Elemental calcium (mg) | 1,748 (904) | 2,105 (1,383) | 1839 (1,050) |
| Active vitamin D: Calcitrol (mcg) | 0.76 (0.34) | 0.69 (0.33) | 0.75 (0.34) |
| Active vitamin D: Alfacalcidol (mcg) | 2.5 (0.9) | 2.0 (0.4) | 2.3 (0.8) |
| **Baseline eGFR** | | | |
| ≥ 60 mL/min/1.73m$^2$ (CKD stage 1-2), (n) | 42 | 17 | 59 |
| ≥ 30[†] to <60 mL/min/1.73m$^2$ (CKD stage 3), (n) | 19 | 4 | 23 |
| **Pill burden[‡]** | | | |

| Characteristics | Palopegteriparatide (n=61) | Placebo (n=21) | Total (n=82) |
|---|---|---|---|
| Pill burden (active vitamin D and calcium), mean (SD) | 6.7 (2.2) | 6.7 (3.0) | NR |
| **24 h urine calcium** | | | |
| 24 h urine calcium (mg/day), mean (SD) | 392 (175) | 329 (140) | 376 (168) |

† PaTHway inclusion criteria specified a lower limit of ≥30 mL/min/1.73m$^2$. ‡ Pill burden was defined as the total daily amount of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches) taken by the participant.
Abbreviations: CKD, chronic kidney disease; CT, conventional therapy; HypoPT, hypoparathyroidism; ITT, intent-to-treat; m, metre; mcg, microgram; mg, milligram; min, minute; min/max, minimum/maximum; mL, millilitre; NR, not reported; SD, standard deviation
Sources: Khan et al 2023[41]; PaTHway CSR 2022, data on file[39]; Rejnmark 2023[82]

## 2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the PaTHway trial is provided in Table 12. Please see Appendix B for further quality assessment of the PaTHway trial.

**Table 12: Quality assessment of the PaTHway trial**

| Questions | PaTHway |
|---|---|
| Was randomisation carried out appropriately? | Yes. Participants were randomised 3:1 to receive palopegteriparatide or placebo during the Blinded Treatment Period. Randomisation was conducted via Interactive Web Randomisation System (IWRS).[83] |
| Was the concealment of treatment allocation adequate? | Yes. The randomisation schedule was developed by an independent party to maintain blinding.[81] |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes. The treatment groups were balanced with respect to age, sex, race, and baseline HypoPT characteristics.[84] |
| Were the care providers, participants, and outcome assessors blind to treatment allocation? | Yes. Both palopegteriparatide and placebo were provided in identical pens by the site pharmacist. It was therefore impossible for the trial staff, caregivers and patients to know which treatment they were assigned to during the Blinded Treatment Period. Additionally, participants were individually and progressively titrated based on a titration algorithm to maintain blinding.[81] |
| Were there any unexpected imbalances in dropouts between groups? | No. |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No. |
| Did the analysis include an intent-to-treat analysis? | Yes. |

| | |
|---|---|
| If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data? | Yes. Missing and incomplete data were identified through the data quality review plan for the trial. Missing and incomplete data were identified for investigation, and possible resolution, by Data Management prior to the trial database lock or snapshot. |

Abbreviations: HypoPT, hypoparathyroidism; ITT, intent-to-treat; IWRS; Interactive Web Randomisation System

## 2.6 Clinical effectiveness results of the relevant trials

### 2.6.1 Primary efficacy outcome

The primary (multi-component) endpoint of the PaTHway trial was met, demonstrating sustained independence from CT while maintaining serum calcium within the normal range for participants treated with palopegteriparatide.[41] Considering the long-term complications that patients with chronic HypoPT are exposed to,[6,38] independence from CT can have a significant impact on the long-term health of patients, while maintaining serum calcium within the normal range for participants treated with palopegteriparatide.[41]

At Week 26, 79% (48/61) of participants in the palopegteriparatide group versus 5% (1/21) in the placebo group achieved normal serum calcium and independence from CT, without an increase in prescribed trial drug over the previous 4 weeks ($p<0.0001$; Table 13).[41] Similar results were observed from a pre-specified sensitivity analysis (where PRN doses of active vitamin D or calcium were not allowed for 4 weeks before the Week 26 visit), where 74% (45/61) of participants in the palopegteriparatide group and 5% (1/21) in the placebo groups met the primary sensitivity analysis endpoint ($p<0.0001$).[41]

By Week 26, 93% (57/61) of participants treated with palopegteriparatide achieved independence from CT (requiring no active vitamin D and independence from therapeutic doses of calcium (defined as ≤600 mg/day of oral calcium)).[41]

**Table 13: PaTHway – Proportion of participants meeting the multi-component primary endpoint at Week 26 (ITT population)**

| | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| Number of participants meeting the primary endpoint criteria at Week 26 (responders) | 48 | 1 |

| | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| Proportion, % (95% CI) | 78.7 (66.3 – 88.1) | 4.8 (0.1 – 23.8) |
| Hypothesis test: p-value (palopegteriparatide versus placebo)† | <0.0001 | |
| **Number of participants meeting each component, n (%)** | | |
| Albumin-adjusted serum calcium within the normal range‡ | 49 (80.3) | 10 (47.6) |
| Independence from active vitamin D§ | 60 (98.4) | 5 (23.8) |
| Independence from therapeutic doses of calcium | 57 (93.4) | 1 (4.8) |
| No increase in prescribed trial drug | 57 (93.4) | 12 (57.1) |

Participants with missing data on one or more of the criteria were considered as non-responders. † Cochran–Mantel–Haenszel test controlling for aetiology of HypoPT (postsurgical versus nonsurgical). ‡ The normal range for albumin-adjusted serum calcium is 8.3–10.6 mg/ dL (2.07–2.64 mmol/L). § Independence from active vitamin D defined as a daily standing dose equal to zero on all days and use of any PRN active vitamin D on no more than 7 days during the 4 weeks prior to the Week 26 visit.
Abbreviations: CI, confidence interval; HypoPT, hypoparathyroidism; ITT; intent-to-treat; PRN, pro re nata (as needed)
Sources: Khan et al 2023[41]

At Week 52, 81% (63/78) of participants (all treated with palopegteriparatide) met the OLE multi-component efficacy endpoint (serum calcium in the normal range and independence from CT),[40] and 95% (74/78) achieved independence from CT (requiring no active vitamin D and ≤600 mg/day of oral calcium).[41]

At Week 104, 97% (74/76) of participants (all treated with palopegteriparatide) achieved independence from CT (requiring no active vitamin D and ≤600 mg/day of oral calcium).[84]

#### 2.6.1.1 Dose evolution

In the palopegteriparatide arm at the end of the 26 weeks of the double-blind phase, 57 (93.4%) participants had no increase in study drug within 4 weeks prior to Week 26 visit (Table 13).[41] Palopegteriparatide doses remained stable throughout the study in participants independent of CT, with a median of [redacted] at Week 2 and [redacted] from Week 4 to the end of the blinded period (Week 26).[39] By Week 26, [redacted] required a daily dose ≥33 mcg, and thus daily concomitant use of two packs of different strength.[85]

### 2.6.2 Secondary efficacy outcomes

#### 2.6.2.1 Patient-reported outcomes

Patient-reported outcomes were assessed by the generic SF-36, EQ-5D and by the disease-specific Hypoparathyroidism Patient Experience Scale (HPES), a 43-item tool used to assess the severity and frequency of symptoms experienced by individuals with chronic HypoPT and the extent to which these symptoms affect their quality of life and daily functioning (see Appendix K for more details).[5,22,86]

Treatment with palopegteriparatide significantly improved disease-specific measures of symptoms, functioning and well-being across HPES-Symptom (physical [p=0.0038] and cognitive [p=0.0055]) and HPES-Impact (physical functioning [p=0.0046] and daily life [p=0.0061]) domains at Week 26, versus placebo (see Table 14 and Figure 11).[22,41] The minimal clinically important difference (MCID) scores for selected HPES domains are as follows: Physical Domain score: -8.7; Cognitive Domain score: -10.0; Physical Functioning score: -15.0; Daily Life domain score: -15.6.

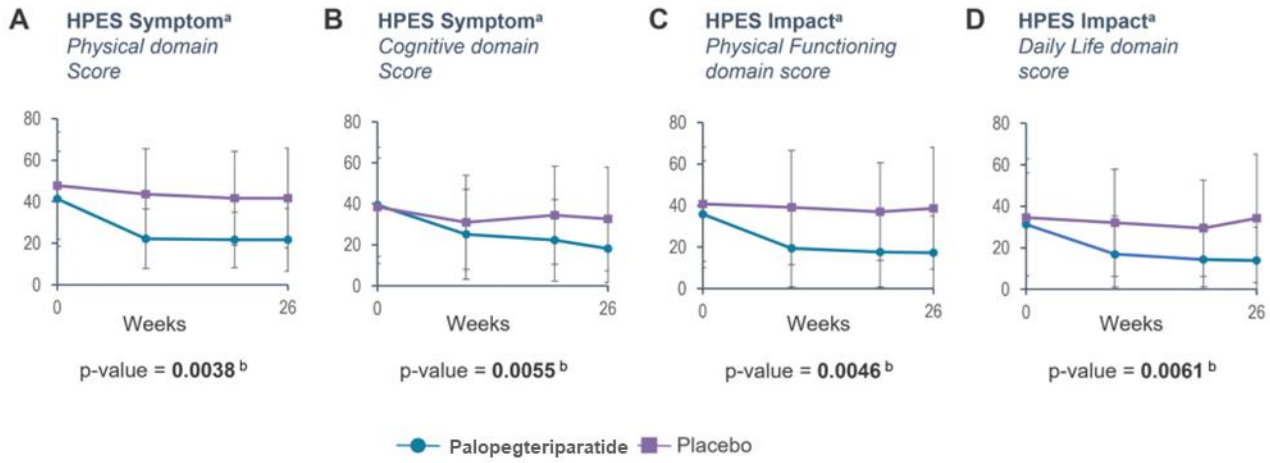
**Table 14: PaTHway – Improvement from baseline to Week 26 in HPES-Impact and Symptom scores (ITT population)**

| HPES scale† | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| **HPES-Impact scale** | | |
| Daily life domain, n | 59 | 19 |
| Mean (SD) | −16.4 (19.6) | −2.9 (21.8) |
| Physical functioning domain, n | 59 | 19 |
| Mean (SD) | −17.7 (20.4) | −5.3 (21.5) |
| Psychological well-being domain, n | 54 | 17 |
| Mean (SD) | −14.2 (19.4) | −0.9 (21.0) |
| Social life and relationship domain, n | 59 | 19 |
| Mean (SD) | −13.5 (20.8) | −3.4 (21.6) |
| Total HPES-Impact score, n | 59 | 19 |
| Mean (SD) | −15.7 (18.0) | −3.9 (19.0) |
| **HPES-Symptom scale** | | |
| Physical domain, n | 59 | 19 |

| HPES scale† | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| Mean (SD) | −19.3 (17.9) | −8.4 (23.7) |
| Cognitive domain, n | 59 | 19 |
| Mean (SD) | −21.0 (24.7) | −7.4 (14.2) |
| Total HPES-Symptom score, n | 59 | 19 |
| Mean (SD) | −20.2 (19.5) | −7.9 (18.0) |

†Lower scores reflect improvement in HypoPT-related symptoms, functioning and well-being.
Abbreviations: HPES, Hypoparathyroidism Patient Experience Scale; HypoPT, hypoparathyroidism; ITT, intent-to-treat; SD, standard deviation
Source: Khan et al 2023[41], Patient reported outcome for PaTHway trial[22,86]

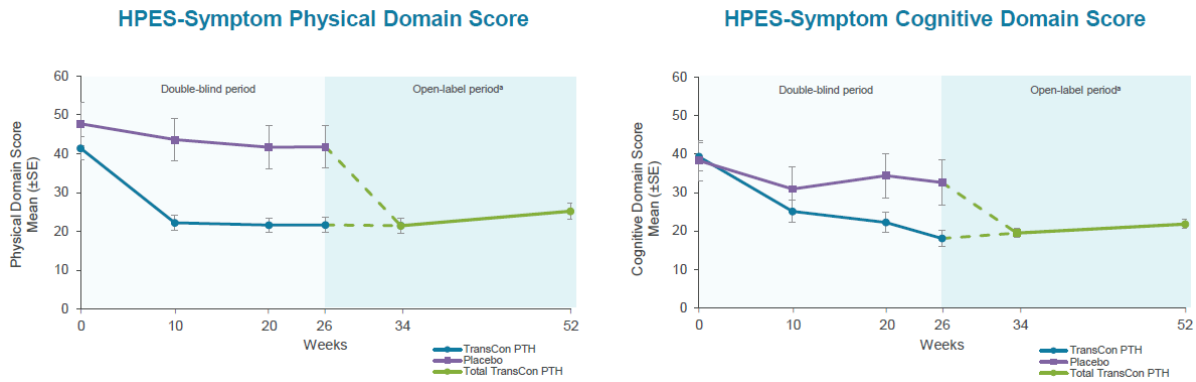
**Figure 11: PaTHway – Treatment effect of palopegteriparatide on HPES scores up to Week 26 (ITT population)**




[a]Lower scores reflect improvement in HypoPT-related symptoms, functioning and well-being; [b]p-values are from the analysis of covariance models assessing change from baseline at Week 26 for palopegteriparatide versus placebo, with aetiology of HypoPT as fixed effects and baseline HPES domain scores as covariates; Negative error bars (SD) are not displayed for values less than zero.
Abbreviations: HPES, Hypoparathyroidism Patient Experience Scale; ITT, intent-to-treat
Source: Khan et al 2023[41]

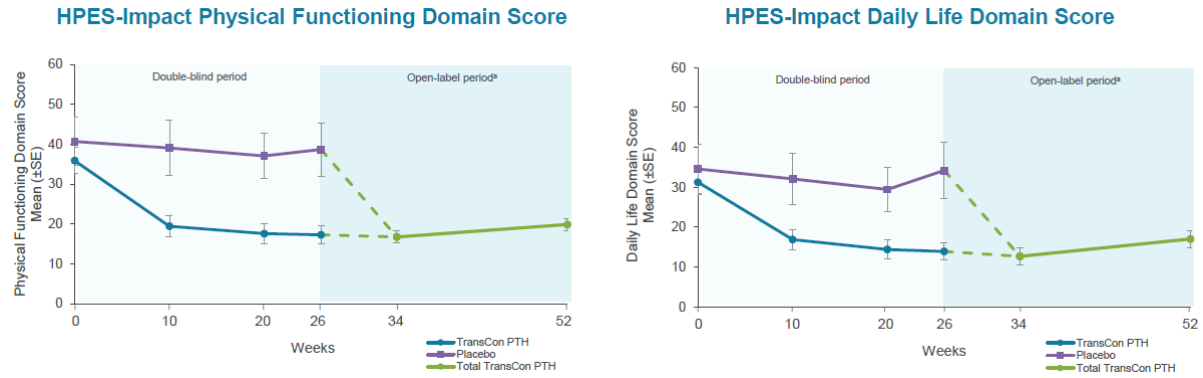
HPES-Symptom (physical and cognitive) and HPES-Impact (physical functioning and daily life) domains showed sustained improvement for participants receiving palopegteriparatide up to Week 52, as shown in Figure 12 and Figure 13, respectively.[40]

**Figure 12: PaTHway – Treatment effect of palopegteriparatide on HPES-Symptom Domains score up to Week 52 (ITT population)**




[a]All particpants received palopegteriparatide during the open-label period
Abbreviations: HPES, Hypoparathyroidism Patient Experience Scale; ITT, intent-to-treat; PTH; parathyroid hormone; SE, standard error
Source: Clarke et al. 2024[40]

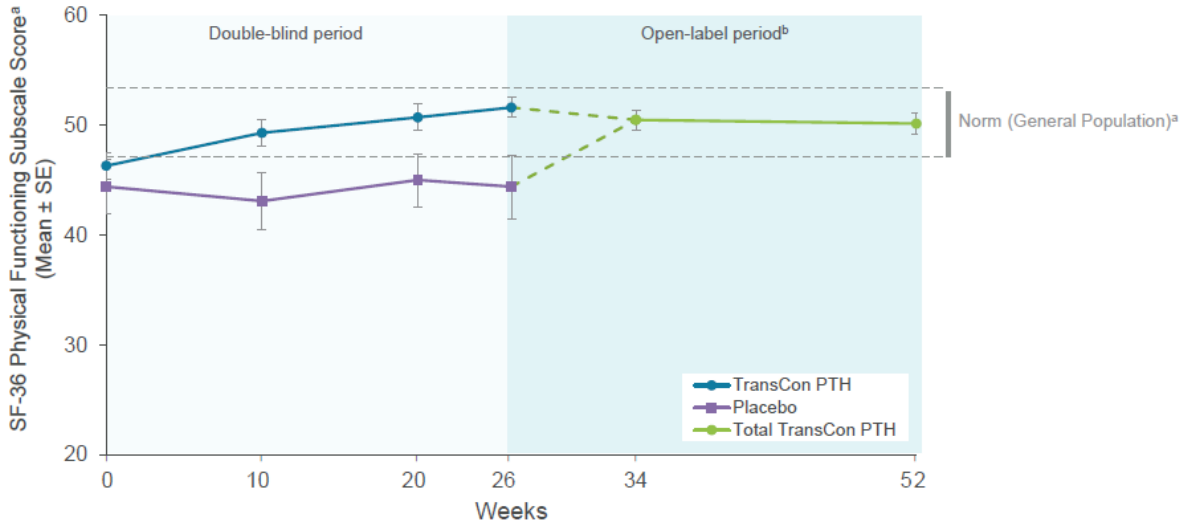
**Figure 13: PaTHway – Treatment effect of palopegteriparatide on HPES-Impact Physical Functioning Domains score up to Week 52 (ITT population)**




[a]All particpants received palopegteriparatide during the open-label period.
Abbreviations: HPES, Hypoparathyroidism Patient Experience Scale; ITT, intent-to-treat; PTH; parathyroid hormone; SE, standard error
Source: Clarke et al. 2024[40]

Health-related quality of life (HRQoL) as measured by the SF-36 also improved significantly in the palopegteriparatide versus placebo group for the physical functioning subscale score (p=0.0347 for between-group differences in change from baseline to Week 26).[41] As shown in Figure 14, mean SF-36 physical functioning subscale scores remained above baseline in OLE period, demonstrating sustained improvement in HRQoL up to Week 52.[40] In participants randomised to placebo, palopegteriparatide treatment in the OLE was associated with improvements in SF-36 scores similar to those observed in the active treatment group during the blinded period.[40]

**Figure 14: PaTHway – Treatment effect of palopegteriparatide on SF-36 physical functioning subscale scores up to Week 52 (ITT population)**




[a]Lower scores are associated with a greater disease burden; increases in scores indicate improvement; [b] Dashed lines indicate the upper (53) and lower (47) T-score bounds for the US general population's average level of functioning, with scores <47 indicating impairment.
Abbreviations: ITT, intent-to-treat; PTH; parathyroid hormone; SE, standard error; SF-36, Short Form 36
Source: Clarke et al. 2023[87]

EQ-5D was assessed for all domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline, Visit 6 (Week 10), Visit 9 (Week 20), and Visit 10 (Week 26).[39]

By Week 26 from baseline, participants treated with palopegteriparatide experienced meaningful improvements across multiple EQ-5D domains, including mobility, usual activities, pain/discomfort, and anxiety/depression. In contrast, while the placebo group saw some reduction in moderate problems, there was no increase in participants reporting no problems, and severe anxiety/depression worsened in some.[39] Improvements in overall health status, measured by the EQ-5D visual analogue scale (VAS), were also observed only in the treatment group.[39]

Results of the EQ-5D domains can be seen in Table 15 below

**Table 15: EQ-5D Domain Outcomes by Week 26**

| Domain | Palopegteriparatide | Placebo |
|---|---|---|
| Mobility | No problem: ↑ from 57.4% to 77.0% | Moderate problem: ↓ from 28.6% to 14.3%; no increase in "no problem" |
| Usual Activities | No problem: ↑ from 42.6% to 62.3% | Moderate problem: ↓ from 23.8% to 9.5%; no increase in "no problem" |

| | | |
|---|---|---|
| Pain/Discomfort | No problem: ↑ from 18.0% to 31.1% | Not specified |
| Anxiety/Depression | No problem: ↑ from 39.3% to 47.5%<br>Slight problems: ↑ from 31.1% to 42.6% | Moderate problem: ↓ from 38.1% to 4.3%<br>Severe problems: ↑ from 4.8% to 19.0% |
| EQ-5D VAS Score | LS mean change: +8.3 (95% CI: 2.9, 13.6) | LS mean change: -0.0 (95% CI: -9.0, 9.0)<br>LS mean difference: 8.3 (p=0.0706) |

Abbreviations: CI, confidence interval; VAS, visual analogue scale; LS, least square

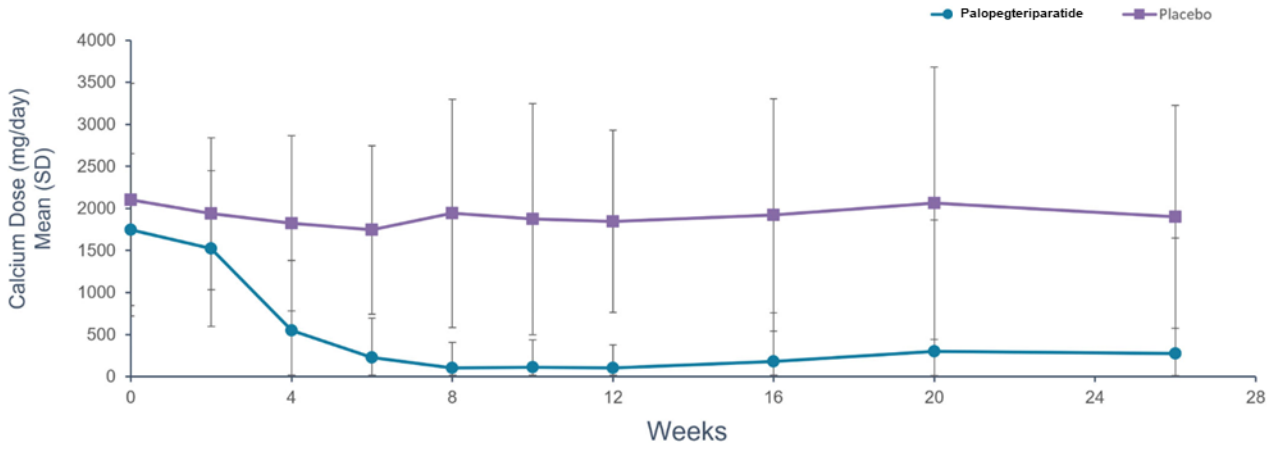
#### 2.6.2.2 Calcium and vitamin D dosage and daily pill burden

Palopegteriparatide enabled rapid and sustained reduction of oral calcium and complete discontinuation of active vitamin D within 8 weeks (Figure 15 and Figure 16).[41]

A significantly greater reduction in mean daily calcium dose versus placebo was observed at 4 weeks (p=0.0003) and up to 26 weeks (p=0.0003; Figure 15). After 4 weeks, mean (standard deviation [SD]) calcium dose decreased from a baseline of 1748.0 (903.9) mg/day to 548.8 (832.7) mg/day, which continued to decrease to 274.2 (1371.8) mg/day at Week 26 in participants treated with palopegteriparatide.

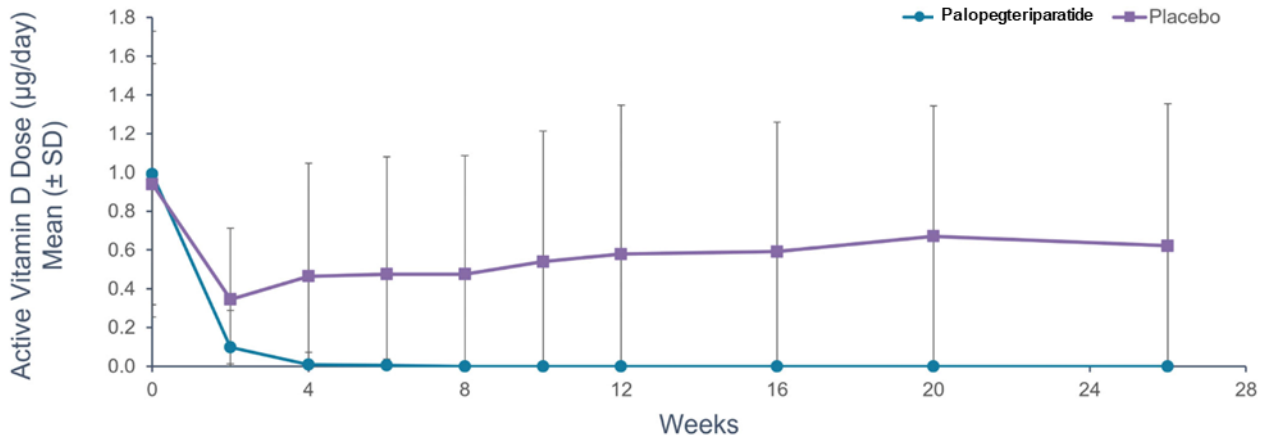
Within 4 weeks, most participants treated with palopegteriparatide discontinued active vitamin D. The difference in least squares (LS) means between the palopegteriparatide and placebo groups was statistically significant at all time points (p<0.0001; Figure 16).

**Figure 15: PaTHway – Elemental calcium treatment dose with palopegteriparatide or placebo (ITT population)**




Per trial protocol, participants were permitted to take calcium ≤600 mg/day as a nutritional supplement, if needed, to meet the recommended dietary intake of calcium. Negative error bars (SD) are not displayed for values less than zero.
Abbreviations: SD, standard deviation; ITT, intent-to-treat
Source: Khan et al 2023[41]

**Figure 16: PaTHway – Active vitamin D treatment dose with palopegteriparatide or placebo (ITT population)**




Per trial protocol, all participants decreased their active vitamin dose by 33% to 50% at the start of the blinded treatment period. Subsequent dose decreases or discontinuations followed a predefined protocol. Mean doses of active vitamin D were calculated from actual mcg prescribed and were not adjusted for relative potency of calcitriol versus alfacalcidol. Negative error bars (SD) are not displayed for values less than zero.
Abbreviations: SD, standard deviation; ITT, intent-to-treat
Source: Khan et al 2023[41]

At Week 26, the mean palopegteriparatide dose was 21.4 mcg/day (median 21 mcg/day, range 9 – 39 mcg/day). Mean (SD) daily pill burden in the palopegteriparatide group decreased from 6.7 (2.2) at baseline to 0.5 (1.7) at Week

26, compared with from 6.7 (3.0) to 5.4 (3.2) in the placebo group (p<0.0001 for LS mean reduction between groups).[41]

#### 2.6.2.3 Bone remodelling markers

Levels of C-terminal telopeptide of type 1 collagen (CTx), measured in the serum, serve as a biomarker for bone resorption, with higher levels associated with increased bone resorption. Together with bone formation marker Procollagen 1 intact N-terminal propeptide (P1NP), higher levels of these biomarkers indicate increased bone turnover.[88] CTx and P1NP increased from the low end of normal at baseline, peaked at Weeks 12 and 26, respectively, and trended progressively downward toward age- and sex-matched norms with 52 weeks of palopegteriparatide treatment.[40]

#### 2.6.2.4 Bone mineral density

Bone mineral density (BMD) is measured using dual X-ray absorptiometry (DXA) of target bone regions. [88,89] A Z-score compares bone density of an individual to the average bone density of people of the same age and sex. A Z-score of zero represents the mean.[89] A Z-score that is positive or negative indicates the data value is higher or lower than the mean, respectively.[90] T-score compares bone density of an individual to the average bone density of a healthy adult (age 30 years). A normal T-score is defined as -1 and above; a low bone mass (osteopenia) is between -1 and -2.5; osteoporosis is defined as a T-score of -2.5 or lower.[90] Mean BMD Z-scores trended toward age- and sex-matched norms at the lumbar spine L1–L4, femoral neck, and total hip, and mean T-scores remained within the normal range for all regions of interest (lumbar spine L1-L4, femoral neck, total hip and distal 1/3 radius) with 52 weeks of palopegteriparatide treatment.[40]

## 2.7 Subgroup analyses

Not applicable.

## 2.8 Meta-analysis

Not applicable.

## 2.9 Indirect and mixed treatment comparisons

Not applicable

## 2.10 Adverse reactions

### 2.10.1 Summary of treatment-emergent adverse events

Safety analyses were performed using the safety analysis population (see Table 10 for a description).

Palopegteriparatide was well tolerated, with most treatment emergent adverse events (TEAEs) being mild (grade 1) to moderate (grade 2) in severity, and no participants discontinued treatment due to treatment-related TEAEs related to the trial drug.[41]

TEAEs were reported in 82% (50/61) of participants treated with palopegteriparatide and in 100% (21/21) of participants treated with placebo at Week 26 (Table 16). The most common TEAEs reported up to Week 26 are presented in Table 17.

By Week 26, 49% (30/61) of participants in the palopegteriparatide group and 38% (8/21) in the placebo group reported a treatment-related TEAE. The most common treatment-related TEAEs in the palopegteriparatide group were injection site reactions (31%; 19/61), hypercalcaemia (10%; 6/61), and headache (10%; 6/61).[41]

Serious TEAEs were reported by five participants (8%) in the palopegteriparatide group, one of which was considered related to treatment (transient hypercalcaemia in the setting of an inadvertent deviation from the titration algorithm that resulted in treatment interruption and hospitalisation), although trial treatment was resumed without incident after supportive therapy.[41] Three participants (14%) in the placebo group reported serious TEAEs. Hypocalcaemia was observed less frequently in the palopegteriparatide (10%, 6/61) versus placebo (43%, 9/21) group at Week 26.

TEAEs related to hypercalcaemia or hypocalcaemia leading to emergency department/urgent care and/or hospitalisation were reported for 7% (4/61) of participants in the palopegteriparatide group and 10% (2/21) of participants in the placebo group at Week 26.

One death of a 74-year-old male with multiple cardiac risk factors occurred during the blinded period of the trial in the palopegteriparatide group due to cardiac arrest; this was deemed unrelated to trial treatment.[41]

**Table 16: PaTHway – Summary of TEAEs at Week 26 (safety population)**

| TEAEs, n (%)† | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| Any TEAE | 50 (82) | 21 (100) |
| Serious TEAE | 5 (8) | 3 (14) |
| Severity‡ | | |
| Grade 1 | 27 (44) | 11 (52) |
| Grade 2 | 21 (34) | 9 (43) |
| Grade 3 | 1 (2) | 1 (5) |
| Grade 4§ | 1 (2) | 0 |
| Treatment-related TEAE | 30 (49) | 8 (38) |
| Serious related TEAE | 1 (2) | 0 |
| TEAE related to hypercalcaemia or hypocalcaemia leading to A&E/urgent care visit and/or hospitalisation | 4 (7) | 2 (10) |
| TEAE leading to trial drug discontinuation§ | 1 (2) | 2 (10) |
| TEAE leading to death§ | 1 (2) | 0 |

† In the severity categories, data are displayed for the highest severity only. TEAEs occurring before the first dose of open-label treatment are included. ‡ Severity as per by the World Health Organization toxicity grading scale. §One participant experienced a fatal cardiac arrest (Grade 4 TEAE; unrelated to the trial drug), which subsequently led to discontinuation of the trial drug and trial.
Abbreviations: A&E, Accidents & Emergency; TEAE, treatment-emergent adverse event
Source: Khan et al 2023[41]

**Table 17: PaTHway – Common (≥5% in any group) TEAEs by preferred term at Week 26 (safety population)**

| TEAEs by preferred term, n (%) | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| Any TEAE | 50 (82) | 21 (100) |
| Injection site reaction | 19 (31) | 0 |
| Headache | 13 (21) | 2 (10) |
| Hypocalcaemia | 6 (10) | 9 (43) |
| Fatigue | 9 (15) | 5 (24) |
| Paresthaesia | 11 (18) | 3 (14) |
| Muscle seizures | 7 (12) | 3 (14) |
| Nausea | 7 (12) | 2 (10) |
| Arthralgia | 6 (10) | 2 (10) |
| Diarrhoea | 6 (10) | 1 (5) |
| Hypercalcaemia | 6 (10) | 0 |
| Constipation | 4 (7) | 1 (5) |
| Insomnia | 4 (6.6) | 1 (5) |

Abbreviations: TEAEs, treatment-emergent adverse event(s)
Source: Khan et al 2023 [41]

TEAEs were reported in 90% (72/80) of participants treated with palopegteriparatide up to Week 52 of the PaTHway trial. Most were mild or moderate (grades 1–2) and none reported during the open label extension led to discontinuation of the trial or palopegteriparatide treatment.[40]

Through Week 104, most TEAEs were mild or moderate, and no new safety signals were reported.[84]

#### 2.10.1.1 Injection site reactions

In most cases, the worst injection site reactions (ISRs) included 0 to <2 cm redness [redacted] or 2 to <5 cm redness [redacted] no itching [redacted] no swelling [redacted] or palpable "firmness only" [redacted]; and no pain [redacted]. No palopegteriparatide treated participant experienced >5 cm redness, moderate or severe itching, or >4 cm swelling. Median duration of ISR was [redacted] hours, ranging from [redacted] to [redacted] hours.[39]

#### 2.10.1.2 Antibody responses

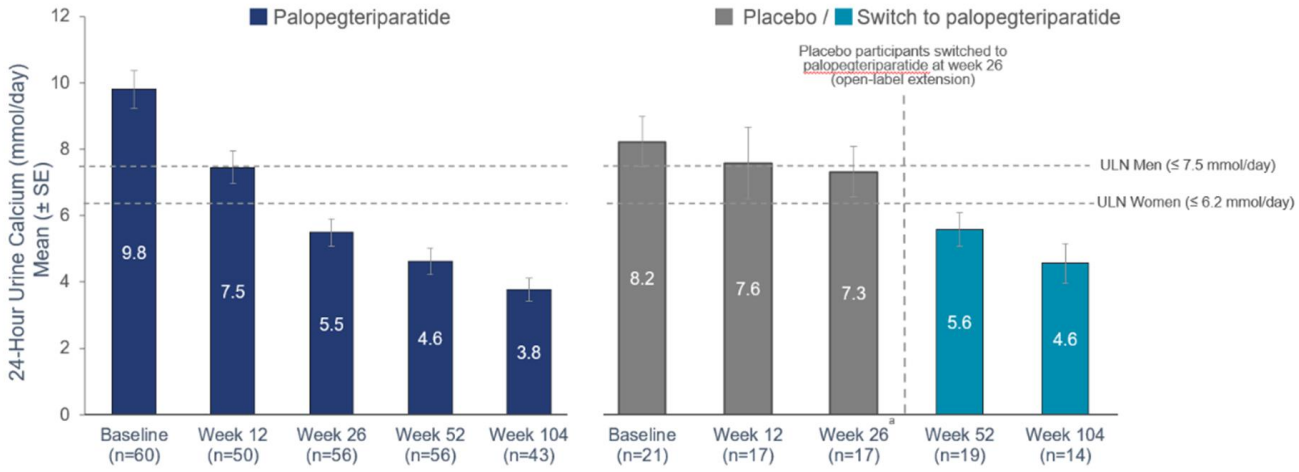
Anti-palopegteriparatide antibodies were detected in 8% of participants at baseline and were treatment-emergent in 5%. [39,41] Antibodies to polyethylene glycol (PEG) were detected in 17% at baseline and were treatment-emergent in 8%. No anti-PTH antibodies were detected at baseline or any time up to Week 26.[39] Anti-PEG antibodies were typically detected in participants with anti-palopegteriparatide antibodies, suggesting that PEG was the epitope. None of the antibodies were neutralising and the presence of antibodies had no evident impact on efficacy or safety.[41]

### 2.10.2 Clinical laboratory evaluation

Palopegteriparatide demonstrated normalisation of mean 24-hour urine calcium at Week 26, improving from a baseline of 392 mg/24 h to 220 mg/24 h ($p<0.0001$ for mean change from baseline), versus 329 mg/24 h to 292 mg/24 h for the placebo group (no significant change from baseline, $p=0.24$; Figure 17).[41] An ANCOVA model, with aetiology of HypoPT as fixed effects and baseline urine calcium excretion value as a covariate, showed a significant difference between groups in change from baseline at Week 26 ($p=0.0085$).[41]

A higher proportion of participants in the palopegteriparatide (60.7%; 37/61) versus placebo (28.6%; 6/21) group had mean 24-hour urine calcium within the normal range (≤250 mg/24h) at Week 26 (p=0.0213).[41] Mean 24-hour urine calcium was maintained within the normal range up to Week 52 (185 mg/24 h)[40] and continued to be maintained below 6.2 mmol/day through Week 104 (4.0 (2.3) mmol/day).[84]

**Figure 17: PaTHway – 24-hour urine calcium (safety population)**




[a]Participants randomized to placebo at baseline initiated palopegteriparatide treatment at Week 26.
Abbreviations: SE, standard error; ULN, upper limit of normal
Source: Schwarz et al. 2024[91]

The analysis of serum calcium levels (incidence and rate) showed that excursions to high calcium levels were mostly observed in palopegteriparatide-treated participants, and that while excursions to low calcium levels were observed in both treatment groups, they were observed more frequently in placebo participants than in palopegteriparatide-treated participants. Excursions to high calcium levels were observed only during the first 3 months of the Blinded Period, likely due to the titration algorithm. Excursions to low calcium levels were observed throughout the entire Blinded Period, but more particularly during the first 3 months. Abnormal serum calcium values were not considered adverse events unless associated with a sign or symptom.[39] A summary of low and high serum calcium incidence for the blinded period is shown in Table 18.

**Table 18: PaTHway - Summary of central clinical laboratory assessments - Low and high serum calcium incidence (%) by period - Blinded Period (Safety Analysis Population)**

| | Serum Calcium Below Normal Range (<8.3 mg/dL) (n/N1, %) | | Serum Calcium <7.5mg/dL (n/N1, %) | | Serum Calcium Above Normal Range (>10.6mg/dL) (n/N1, %) | |
|---|---|---|---|---|---|---|
| | Palopeg-teriparatide (n=61) | Placebo (n=21) | Palopeg-teriparatide (n=61) | Placebo (n=21) | Palopeg-teriparatide (n=61) | Placebo (n=21) |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 0 – Month 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 3 – Month 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: dL, decilitre; mg, milligram;
Source: PaTHway CSR 2022, data on file[39]

### 2.10.3 Safety conclusions

Palopegteriparatide was well tolerated, with most TEAEs being mild (grade 1) to moderate (grade 2) in severity, and no participants discontinued treatment due to treatment-related TEAEs related to the trial drug.[40,41,84]

## 2.11 Ongoing trials

There are two ongoing OLE trials of palopegteriparatide for chronic HypoPT (Table 19).

- PaTH Forward (NCT04009291) is a Phase 2, quadruple arm, multicentre, randomised, double-blind, placebo-controlled, parallel group 4-week trial with an OLE up to 266 weeks.[32]
- PaTHway (NCT04701203) is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group 26-week trial with a 156-week OLE.[41]

**Table 19: Completed and ongoing studies**

| Trial | Description | Dose | Trial population | N† | Status |
|---|---|---|---|---|---|
| PaTH Forward NCT04009291 [32] | Phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel group to evaluate the safety, tolerance, and effectiveness of palopegteriparatide as a replacement therapy for PTH<br>Open-label extension of the Phase 2 PaTH Forward trial up to 266 weeks | 15 mcg, 18 mcg, or 21 mcg daily via SC injection or a placebo, for 4 weeks<br>OLE: Titrated based on serum calcium and CT doses | Adults with chronic HypoPT | 59 | Completed<br>OLE ongoing |
| PaTHway NCT04701203 [79] | Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group trial to investigate the safety and efficacy of palopeg-teriparatide as a replacement therapy for PTH<br>Open-label extension of the Phase 3 PaTHway trial up to 182 weeks | 18 mcg/day (titrated in increments of 3 mcg/day to an optimal dose over a 10-week period) via SC injection or a placebo, for 26 weeks<br>OLE: Titrated to optimal dose | Adults with chronic HypoPT | 82<br>OLE: 79 (60 palopeg-teriparatide, 19 placebo) completed Week 26 and went into the OLE.<br>78 completed Week 52. | Active, not recruiting |

† ITT population.
Abbreviations: CT, conventional therapy; HypoPT, hypoparathyroidism; ITT, intent-to-treat; mcg, microgram; OLE, open-label extension; PTH, parathyroid hormone; SC, subcutaneous

## 2.12 Interpretation of clinical effectiveness and safety evidence

The efficacy, safety, and tolerability results of the PaTHway trial, along with its ongoing OLE, provide robust evidence supporting the use of palopegteriparatide as PTH replacement therapy in adults with chronic HypoPT.

Palopegteriparatide supports sustained independence from CT while maintaining serum calcium within the normal range.[41] (Independence from CT is defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg.)

- At Week 26, 79% (48/61) of participants in the palopegteriparatide group versus 5% (1/21) in the placebo group (p<0.0001) achieved normal serum calcium and independence from CT*, without an increase in prescribed trial drug over the last 4 weeks of the blinded period.[41]

- At Week 52, 81% (63/78) of participants treated with palopegteriparatide met the OLE multi-component efficacy endpoint (serum calcium in the normal range and independence from CT).[40]

- By Week 26, 93% (57/61) of participants treated with palopegteriparatide achieved independence from CT (requiring no active vitamin D and ≤600 mg/day of oral calcium). This proportion was 95% (74/78) at Week 52[40] and 97% at Week 104.[84]

Importantly, palopegteriparatide improves HRQoL in patients with chronic HypoPT, demonstrating significantly improved disease-specific measures of symptoms, functioning and well-being.

Palopegteriparatide demonstrated a favourable safety profile, with no treatment or trial discontinuations due to treatment-related adverse events in the PaTHway trial up to Week 104.

### 2.12.1 Strengths and limitations of the clinical evidence base

The efficacy and safety of palopegteriparatide are demonstrated in a well-designed and robust Phase 3 placebo-controlled trial (PaTHway). Given the rarity of chronic HypoPT as a disease, the pivotal trial enrolled a relatively small sample size (n=84),[41] which may introduce some limitations in the interpretation of the findings.

The double-blinded period followed by the OLE provides a long-term opportunity to examine the sustained efficacy and safety of palopegteriparatide. At the time of submission, efficacy and safety data will be available for 26 weeks of the double-blind phase and 156 weeks of the OLE.

* Defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg.

The randomised treatment groups were balanced with respect to age, sex, race, and baseline chronic HypoPT characteristics, meaning that the outcomes measured can be judged to have started from similar levels in each group.[41] The trial population was generally representative of the UK chronic HypoPT NAC population in terms of demographics and baseline disease characteristics.[81]

The endpoints used in the PaTHway trial are well accepted and validated for use in patients with chronic HypoPT, particularly the primary multi-component endpoint of change in serum calcium levels with a clinically meaningful reduction in calcium and active vitamin D treatments.

The trial examined the effect of palopegteriparatide treatment in participants who were receiving treatment with CT at the start of the trial, meaning that the trial population represents a 'real world' setting with results being transferrable to clinical practice in the UK. Although the trial is conducted at 21 sites in seven countries, none are in the UK, meaning that consideration must be given to whether results from the trial population can be considered transferrable to clinical practice in the UK, however, there are no reasons to consider otherwise, a conclusion that has been further validated by UK clinical experts.

Participant-reported outcomes were assessed by the generic SF-36, EQ-5D and by the disease-specific HPES. HPES is a disease-specific tool for assessing symptoms of HypoPT from a patient perspective.[5] Individuals with HypoPT experience a substantial burden of illness, both with respect to the range and the severity of symptoms. As a disease-specific tool, the HPES should have greater validity, be more responsive to change over time, and be more useful to clinicians and researchers to assess the impact of treatment than more generic tools.[5] The HPES was developed in accordance with Food and Drug Administration (FDA) guidance and best research practices for PRO measure development.[5] It is important to consider the cognitive deficits that are commonly associated with HypoPT,[51] for which the EQ-5D has limitations in this regard and may be insensitive to changes in cognitive impairment.[92]

In summary, the PaTHway Phase 3 trial provides strong evidence for the efficacy and safety of palopegteriparatide in treating chronic HypoPT. Despite a small sample size, the trial was well-designed, with balanced groups and validated endpoints relevant to clinical practice. Long-term data and the use of disease-specific patient-reported outcomes, such as the HPES, further support its benefits. While the trial did not include UK sites, the population was representative, and UK clinical experts consider the findings transferable. These results, together with upcoming ESE guidelines, support the clinical value of palopegteriparatide for chronic HypoPT.

# 3 Cost-effectiveness

## SUMMARY

- HypoPT is a rare endocrine disease, with patients experiencing a range of debilitating symptoms. Chronic HypoPT is associated with complications such as renal impairment, cardiovascular disease, bone fractures, cataracts and increased risk of infection (see section 1.3.4). The objective of the economic analysis was to evaluate the cost-effectiveness of palopegteriparatide compared with CT for adults with chronic HypoPT that is NAC.
- The analysis focused on a subpopulation of the licenced population which reflects the intended positioning of palopegteriparatide as a treatment for patients who have not achieved adequate disease control with CT. The subpopulation represents a clinically relevant population with high unmet need that is aligned to the PaTHway trial population and CPRD analysis (see sections 2.4.4 and 1.3.5.1.3).[10,78]
- As there has been no previous NICE health technology assessment or precedent economic model, a de novo cost-effective model was developed to estimate the costs and health benefits of palopegteriparatide compared to CT as a treatment for adult patients with chronic HypoPT that is NAC in the United Kingdom.

### Model Summary

- The cost-effectiveness partitioned survival model (PSM) was based on clinical and efficacy data and assumptions informed by the pivotal PaTHway trial and the CPRD dataset.
- The model comprised of three health states that were defined by disease control status: adequately controlled AC, NAC, and death. AC and NAC classifications were based on clinical response for the PaTHway trial population and healthcare resource use for the CPRD population, with definitions aligned to capture real-world disease control across both evidence sources.
- The analysis was conducted from an NHS/PSS perspective, with a lifetime time horizon. Costs and outcomes were discounted at 3.5% per annum, in accordance with the NICE reference case.[93]
- Resource use and costs included in the model were taken from the CPRD analysis and appropriate published sources, including the British National Formulary (BNF), National Schedule for NHS, and Personal Social Services Research Unit (PSSRU).[94-96]

### Base-case results

- The results of the base case cost-effectiveness analysis when considering the PAS discount show that, compared with CT, palopegteriparatide is associated with a

quality-adjusted life year (QALY) gain of [redacted], resulting in an incremental cost-effectiveness ratio (ICER) of [redacted].

- Structural and input uncertainty were assessed through scenario analysis. Input uncertainty was further tested using one-way and probabilistic sensitivity analyses. Results were robust to alternative scenarios demonstrating value of treatment even under conservative assumptions.

### 3.1.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify published economic evaluations of potential relevance to this technology appraisal. Electronic database searches were initially conducted on 21 December 2023, with subsequent updates conducted on 8 July 2024, and 27 March 2025.[97]

Following searches, exclusion of duplicates, title and abstract screening, and full-text screening, 41 unique studies from 47 reports were identified and included for data extraction. Full details of the SLR methodology, Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram and included and excluded studies of the SLR are provided in Appendix E.

The SLR identified one United States (US)-based cost-effectiveness model that used a decision analytic approach (Markov disease states) with three health states—usual care, recombinant human parathyroid hormone (rhPTH), and life with side effects—to compare rhPTH with usual care for postsurgical HypoPT patients for a 10-year time horizon.[98]

**Table 20: Overview of published cost effectiveness studies – original and update**

| Trial | Year | Summary of model | Health benefit | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|
| Chomsky-Higgins, 2018[98] | 2017 | Decision analytic model (Markov disease states; Usual care, rhPTH, life with side effects)<br>US healthcare system perspective | Utility values in QALYs:<br>Usual care: 0.778 | Annual cost of rhPTH (total): $139,100<br>Pharmaceutical rhPTH: $137,456 | rhPTH vs. usual care: $804,378/QALY gained |

| | | | | | |
|---|---|---|---|---|---|
| | | 10-year time horizon, 1 year cycle length<br>Intervention: rhPTH<br>Comparator: usual care | rhPTH(1-84): 0.9725<br>Life with side effects (renal): 0.67 | Endocrine office visits (CPT 99213-99215) x 3: $247<br>(Total vitamin D, calcitriol and calcium costs of usual care)/2: $1,398 | |
| | | | | Annual cost of usual care (total): $5,161<br>Endocrine office visits (CPT 99213-99215) x 3: $247<br>Vitamin D (800–1500 IU/day): $247<br>Calcitriol (0.25–2.0 mcg/day): $27<br>Calcium (1–9 g/day) $226 | |

Abbreviations: CPT, current procedural terminology; mcg, microgram; rhPTH, recombinant human parathyroid hormone; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; IU, international unit

## 3.2 Economic analysis

#### 3.2.1.1 Introduction

The economic analysis presented in this submission assesses the cost-effectiveness of palopegteriparatide compared with CT in the treatment of adult patients with chronic HypoPT who are NAC on CT in UK. This subpopulation of chronic HypoPT patients reflect the intended positioning of palopegteriparatide as a treatment for patients who have not achieved adequate disease control with CT and represents a clinically relevant population with high unmet need. The PaTHway trial population and CPRD analysis are aligned to this subpopulation (see sections 2.4.4 and 1.3.5.1.3).

Clinical data were primarily derived from the PaTHway trial. Additional real-world evidence was obtained from the CPRD, which includes linked data from primary care, HES, the ONS, and area-level deprivation indices.[10,78] The CPRD analysis provided information on patient characteristics, healthcare resource use, complication rates, and mortality. These data were used to quantify disease burden

and inform key model parameters and assumptions related to structure, costs, and outcomes.

#### 3.2.1.2 Patient population

The population included in the model is adult patients (18+) with chronic HypoPT who are NAC on CT. The PaTHway clinical trial was determined to be generalisable to this patient population based on baseline characteristics validated by expert clinical input (see section 2.4.4).[16]

#### 3.2.1.3 Model structure

A de-novo partitioned survival model (PSM) was developed with three primary health states. Figure 18 presents the model structure diagram for the three mutually exclusive health states:

- **Adequately controlled (AC):** Patients who respond to treatment with palopegteriparatide enter the model in this state. These patients may transition to NAC over time based on treatment discontinuation.
- **Not adequately controlled (NAC):** Patients receiving CT (meeting the classification of NAC) or who do not respond to palopegteriparatide enter and remain in this state while alive.
- **Death:** All-cause mortality, adjusted by health state mortality risk.

The AC and NAC states were used to differentiate outcomes in HRQoL, costs, complication risk, and mortality.

A linked sub-model captured complications as discrete events. Each event allowed for an assigned cost, disutility, and associated mortality risk where applicable. Complication risks were stratified by health state based on HRs derived from CPRD applied to general population incidence (see section 3.3.2).[99-105] In the base-case, complications were included only as repeatable events with associated disutility; event-level costs and mortality risk were excluded to avoid potential double counting with CPRD-derived health state estimates.[100,105-112]

The model includes functionality to apply treatment-specific reductions in complication risk for AC patients treated with palopegteriparatide. This allows the

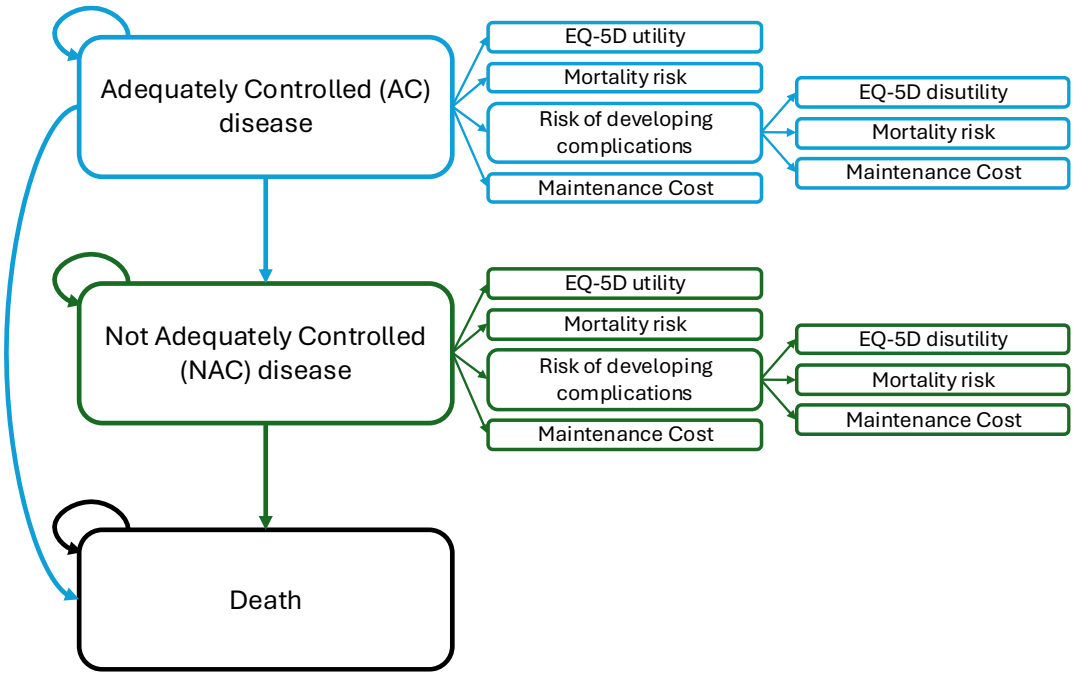
model to account for the physiological benefit of hormone replacement, which may reduce complication risk independently of observable disease control status. Due to the lack of long-term data, this feature was not included within the base-case.

Hypocalcaemia and hypercalcaemia were captured as adverse events (AE) rather than complications, modelled separately by treatment arm using exposure-adjusted rates from the PaTHway trial. Each AE was assigned a cost, disutility, and duration of event. These were treated independently of the complication sub-model to reflect trial-observed treatment differences while avoiding double counting.

A 28-day cycle length was chosen to align with the marketed presentation of palopegteriparatide, which is supplied as two 14-day injection pens per monthly pack, and allowed sufficient granularity to capture the impact of repeatable events. Costs and outcomes were discounted at 3.5% per annum. A half-cycle correction was applied to all costs and outcomes to account for mid-cycle transitions.

The model assumptions and mechanics for health states, transitions, and complications are detailed in sections 3.2.1.4 and 3.3.

**Figure 18: Palopegteriparatide model structure overviews**




Abbreviation: AC = Adequately Controlled; NAC = Not Adequately Controlled; EQ-5D = EuroQol 5-Dimension questionnaire.

#### 3.2.1.4 Model rationale

No previous models have assessed the long-term costs or outcomes associated with chronic HypoPT.[97] A new model was therefore developed to estimate the cost-effectiveness of palopegteriparatide from the perspective of the NHS and PSS.

Classifying patients by disease control (AC vs NAC) was essential to reflect meaningful clinical differences. From engagement with clinical experts, AC patients are expected to have better HRQoL, fewer complications, lower resource use requirements, and reduced mortality, whereas NAC patients experience persistent burden, higher long-term risk and have a higher use of healthcare.[16] Event and outcome differences were therefore modelled based on stratification by control health state.

The model structure was selected based on several key considerations:

- Chronic HypoPT is a rare disease, and data availability is limited, particularly for long-term outcomes and transitions between health states.
- The primary effect of palopegteriparatide is hormone replacement, restoring physiological PTH levels and regulating calcium homeostasis. This is expected to reduce the clinical burden and resource use compared with CT.
- Relevant evidence was available from both the PaTHway clinical trial and CPRD analysis to support differences in utility, costs, and complication risks between AC and NAC health states.
- The partitioned survival model (PSM) structure offered simplicity, transparency, and flexibility while allowing direct use of trial data to estimate time spent in AC and NAC states.

Patients who responded to treatment with palopegteriparatide entered the AC state, while non-responders and all patients receiving CT entered the NAC state. Patients who discontinued or lost treatment response were assumed to move from AC to NAC, reflecting the return to a state of inadequate disease control.

The assumption that patients would remain in the AC state while receiving palopegteriparatide was supported by three key factors:

- In the PaTHway OLE, 97% of patients maintained normal serum calcium levels through 156 weeks, and the frequency of treatment-related AEs(hypocalcaemia and hypercalcaemia) declined over time.[78] Similarly, in the PaTHForward study, by Week 214, 98% of patients maintained normal albumin-adjusted serum calcium, and 93% remained independent from CT.[39] These findings support the assumption that patients who initially respond to palopegteriparatide are likely to sustain biochemical control and treatment benefit with continued long-term use.

- The physiological rationale for sustained benefit is supported by the mechanism of action of palopegteriparatide, which restores the missing PTH. Unlike CT, which supplements calcium and active vitamin D without correcting the hormonal deficiency, palopegteriparatide acts directly on PTH receptors to regulate calcium and phosphate homeostasis, likely leading to better renal calcium handling, more stable serum calcium, and more normal bone turnover. [39] This hormone replacement mechanism is consistent with a durable treatment effect in appropriately selected patients.

- Clinical expert opinion indicated that patients who failed to demonstrate sustained improvement in biochemical control, symptom burden, or quality of life—that is, patients who effectively remained in a NAC state despite treatment—would be discontinued from therapy. This reflects typical clinical practice, in which ongoing treatment is reserved for patients who show continued benefit.[16]

As such, the transition from AC to NAC was applied only for those patients discontinuing therapy, and patients who remained on treatment were assumed to maintain an adequately controlled state unless discontinued. Patients in the NAC state were assumed not to transition to AC without a treatment change, as experts indicated that reversal of inadequate control was highly unlikely in chronic HypoPT without initiating a new therapy.[16]

A linked complication sub-model was included to allow for a more accurate estimate of the clinical and economic burden associated with long-term complications of chronic HypoPT. Capturing complications at the event level allowed the model to reflect the repeatable, non-mutually exclusive nature of these outcomes over the patient's lifetime, while maintaining structural simplicity and transparency.

This approach provided the flexibility to reflect condition-specific variation in clinical burden and cost impact, avoiding the limitations of embedding aggregate assumptions within health state utilities. Complications modelled in this way included CKD, CVD, nephrolithiasis, seizures, infections, and other relevant events identified through literature review, CPRD analysis, and expert validation.[10,16] Rates of complications were stratified by health state, using hazard ratios applied to age- and sex-specific general population rates.

The base case excluded event-level costs and mortality risks for complications, as these elements are already captured within the CPRD-derived health state costs and mortality hazard ratios. Including them directly in the complication event model would risk double counting the burden of disease. However, disutilities were retained, as health state utility values derived from the 26-week double-blind period of PaTHway are unlikely to reflect the long-term HRQoL impact of recurrent or chronic complications.

Clinical experts indicated that long-term treatment with palopegteriparatide may reduce the risk of complications—particularly serious events such as CKD and CVD—due to the restoration of calcium homeostasis and reduced reliance on high-dose CT.[16] While this benefit is considered biologically plausible, reflecting the physiological impact of hormone replacement therapy, the CPRD dataset used to estimate complication incidence includes only patients receiving CT. Because no long-term real-world data exist for patients treated with palopegteriparatide, the base case conservatively assumed equal complication risks across both arms.

Hypocalcaemia and hypercalcaemia were modelled separately as treatment-emergent adverse events to reflect an additional benefit of palopegteriparatide not captured by CPRD-derived inputs. These events reflect episodes of biochemical

instability and occurred at lower frequencies in the treatment arm of the PaTHway trial.[78] By applying exposure-adjusted, treatment-specific event rates within the model, these outcomes were incorporated in a way that preserved comparability while avoiding double counting.

Although HypoPT has various aetiologies (e.g. post-surgical and non-surgical), the model does not stratify by cause. This decision was based on clinical expert input, which indicated that when controlling for duration of disease, the treatment approach, clinical burden, and long-term outcomes are broadly similar across aetiologies.[16] Stratifying by aetiology would have also reduced the sample size for key outcomes—particularly for post-surgical patients—and introduced greater uncertainty without improving relevance to treatment decision-making. Modelling a single combined population based on disease control status (AC or NAC) was therefore considered appropriate and clinically justified.

In summary, the model was designed to reflect the key clinical and economic drivers of chronic HypoPT in UK. Disease control status (AC or NAC) was used as the primary determinant of differences in outcomes, costs, and long-term risk. The inclusion of a linked complication sub-model allowed for broader disease burden to be captured transparently, while the classification of adverse events ensured treatment-specific safety outcomes could be reflected where data allowed. Conservative assumptions were applied where data were limited—such as for complication risk under treatment and stratification by aetiology—with scenario analyses used to explore uncertainty. This framework provides a robust and clinically relevant basis for evaluating the cost-effectiveness of palopegteriparatide in NAC patients receiving CT.

#### 3.2.1.5 Features of the economic analysis

The economic analysis was conducted from the perspective of the NHS and PSS, in accordance with the NICE reference case.[93] All costs were inflated to 2025 values using the consumer price index (CPI).[113]

A lifetime horizon was applied, with a 28-day model cycle length. The modelled population entered at a mean age of 48.56 years, based on the PaTHway trial, and stop at the age of 100 years.[78]

Discontinuation from palopegteriparatide was derived from observed rates in the PaTHway trial and used to model transitions from AC to NAC.[78] Patients discontinuing treatment were assumed to revert to CT. Patients receiving CT were assumed to remain on lifelong therapy.

AC and NAC utility values were derived from an ANCOVA analysis of Week-26 versus baseline mapped EQ-5D data from the PaTHway trial.[114] Complication-related disutilities were sourced from peer-reviewed literature.[100,102,105-112]

Drug costs were sourced from the BNF and confidential PAS assumptions where applicable.[94,95] Health state costs were estimated from CPRD resource use data and costed using NHS tariffs.[10] AE costs were sourced from UK-specific literature.[115]

Complication risks were estimated using hazard ratios from the CPRD dataset, applied to age- and sex-specific general population incidence rates.[99-105] Mortality risk by health state were derived using CPRD-linked mortality data and applied to the 2021–2023 UK life table.[10,116]

Model outputs included total costs, QALYs, and Life Years (LYs). Scenario analyses were conducted to explore structural and parameter uncertainty, including treatment effect on complication rates, discontinuation assumptions, and the inclusion of event-level costs and mortality.

**Table 21: Features of the economic analysis**

| Factor | Chosen value | Justification |
|---|---|---|
| Perspective | NHS and PSS | In line with the NICE reference case.[93] |
| Time horizon | Lifetime horizon | Reflects the chronic nature of HypoPT, where patients may require long-term or lifelong treatment. A lifetime horizon allows the model to capture all relevant differences in costs and outcomes. The baseline age of modelled patients is 48.56 years, based on the PaTHway trial population, with patients simulated up to age 100.[78] |
| Cycle length | 28 days | Consistent with the pack size of the marketed product (palopegteriparatide), which contains two pre-filled 14-day pens. Also allows for sufficient granularity to capture incident events, such as complications, adverse events, and death. |
| Half-cycle correction | Applied | Ensures that events occurring throughout the cycle are appropriately averaged, not assumed at the start or end of each cycle. |
| Clinical rules for treatment continuation | Discontinuation from palopegteriparatide based on observed trial data; CT assumed to continue for life | Discontinuation rates from PaTHway were used to derive an exponential extrapolation for transitions from AC to NAC. Clinical experts confirmed that patients typically discontinue due to lack of response (e.g. no normalisation of calcium, continued use of active vitamin D or calcium, or insufficient symptom relief), or safety/tolerability concerns. CT patients were assumed to remain on lifelong therapy, reflecting the incurable nature of HypoPT.[78] |
| Treatment waning effect | None applied | The biological mechanism of action, as hormone replacement therapy, directly restores physiological regulation of calcium metabolism. Unlike CT, palopegteriparatide addresses the underlying hormonal deficiency, providing a consistent and sustained biochemical effect that supports long-term disease control. This is further supported by PaTHway and PaTHForward OLE trial data demonstrated maintenance of treatment effect through Week 156 and Week 215 respectively.[78,117] Additional observational data for Natpar showed no attenuation over 5 years, supporting long-term durability of benefit.[118] |
| Source of utility values | AC and NAC utility values from ANCOVA analysis of EQ-5D (Week 26 vs baseline) from PaTHway; disutilities for AEs and complications from literature | PaTHway EQ-5D data provided the most relevant source to inform health state utilities. Literature-based values were used for event disutilities not captured in the trial.[114] |

| | | |
|---|---|---|
| Source of costs | - Drug costs: BNF and confidential PAS (for palopegteriparatide)<br>- Health state costs: CPRD-based resource use, costed using NHS reference tariffs<br>- AEs and complications: UK-specific literature | Drug and CT costs reflect UK clinical pricing.[94,95] Health state costs were derived from CPRD analysis and costed using NHS unit costs.[10] AE event costs were sourced from literature.[115] |
| Cost year and inflation | 2025 GBP | All costs were inflated to 2025 using the ONS Consumer Price Inflation index, in accordance with NICE reference case methods.[93,113] |
| Health effect measures | LYs; QALYs | Consistent with the NICE reference case.[93] |
| Discount rate | 3.5% per annum (costs and outcomes) | Applied in line with NICE reference case.[93] |

Abbreviations: AE, adverse event; BNF, British National Formulary; CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; CT, conventional therapy; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EoL, end of life; EQ-5D, EuroQol 5-Dimensions; GBP, British pounds (sterling); HCRU, healthcare resource use; HPES, Hypoparathyroidism Patient Experience Scale; HRQoL, health-related quality of life; HypoPT, hypoparathyroidism; LY, life year; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; ONS, Office for National Statistics; PAS, patient access scheme; PSS, Personal Social Services; PTH, parathyroid hormone; QALY, quality-adjusted life year; SmPC, summary of product characteristics.

#### 3.2.1.6 Intervention technology and comparators

The intervention considered in the analysis is palopegteriparatide, a PTH replacement therapy indicated for the treatment of adults with chronic HypoPT. It is administered as a once-daily subcutaneous injection for self-administration. The recommended UK license starting dosage of palopegteriparatide is 18 mcg daily, with dose adjustments in 3 mcg increments every 7 days to reach the treatment goals stated in the summary of product characteristics (SmPC).[19,85]

The comparator of interest is CT for HypoPT which consists of oral administration of active vitamin D analogues with or without calcium. A simplifying assumption is made whereby alfacalcidol and oral calcium are used to represent CT. It is recognised that alternative active vitamin D are available; this simplifying assumption is not expected to impact the results of the analysis due to the low cost of CT. This has been validated by UK clinical experts.[16]

The intervention (palopegteriparatide) and comparator (CT) included in the model align with the NICE scope and the decision problem described in section 1.1. The model reflects use of palopegteriparatide for adult patients with chronic HypoPT whose disease is not adequately controlled on CT. CT is the only relevant comparator in this population and was therefore selected in accordance with clinical practice and NICE's reference case expectations.

## 3.3 Clinical parameters and variables

The classification of patients into AC and NAC health states was applied consistently across both the PaTHway trial and real-world CPRD data to ensure the model accurately reflected clinical outcomes for each control state. In the trial, AC and NAC were defined based on biochemical, symptomatic, and treatment-specific criteria, while real-world classification required a pragmatic approach informed by healthcare utilisation data (see section 1.3.6.5 for full definitions).

As described in section 1.3.5.1.3, the CPRD dataset was used to assess healthcare resource use and the clinical burden of complications among patients with chronic HypoPT. Since CPRD lacks direct clinical measures such as serum calcium or medication dosing, disease control was inferred from patterns of NHS activity. UK

clinical experts confirmed that hospital-based utilisation—particularly the frequency of outpatient and inpatient encounters—offered a meaningful proxy for disease control status in routine practice.

Based on clinical input and validation, the following thresholds were applied to classify patients in the CPRD dataset:

- AC: ≤5 outpatient visits and <1 inpatient admissions per patient per year
- NAC: >5 outpatient visits and ≥1 inpatient admission per patient per year

These thresholds were applied consistently across the analysis and were reviewed by three UK-based clinical experts to ensure they captured clinically relevant differences in disease burden and patient stability.[16]

### 3.3.1 Efficacy

Efficacy inputs in the model were informed by data from the PaTHway trial.[78]

Patients receiving palopegteriparatide were classified as AC if they met the multi-component primary efficacy endpoint at Week 26, which included independence from active vitamin D and therapeutic doses of calcium, along with biochemical control. In total, [redacted] patients in the treatment arm met these criteria and, therefore, a simplifying assumption that [redacted] of palopegteriparatide patients started the model in the AC health state was used.[78] All patients receiving CT and those not meeting response criteria were classified as NAC and started in that health state. A scenario tested response rates for CT and palopegteriparatide based on the proportion of patients meeting the primary endpoint in the clinical trial.

Disease control was assumed not to persist following discontinuation. Patients were assumed to revert to baseline NAC status without residual benefit. This assumption was validated by clinical experts and reflects the need for continuous treatment to maintain control.[16] Patients who discontinued from palopegteriparatide were assumed to restart CT treatment.

Discontinuation modelling is described further in section 3.3.1.1. Mortality and complications, which were not captured within the trial timeframe, are addressed in sections 3.3.2.3 and 3.3.2.

#### 3.3.1.1 Discontinuation

Discontinuation of palopegteriparatide was based on observed data from the clinical trial. In the OLE phase, [redacted] patients discontinued treatment by Week 156.[39] An annualised discontinuation rate of [redacted] was calculated, which was applied exponentially across the model time horizon.

Patients receiving CT were assumed to remain on treatment for life, reflecting the chronic nature of the condition and the need for ongoing therapy to maintain serum calcium levels.

### 3.3.2 Complications

Complications included in the model were identified through a combination of targeted literature review and validation by UK clinical experts. Expert input supported the inclusion of complications that are both frequent in real-world settings and likely to differ by disease control status (AC vs NAC).[16] This process ensured that clinically relevant and commonly observed complications associated with chronic HypoPT were appropriately captured in the economic analysis. A list of complications included in the model is presented in Table 22.

**Table 22: Complication list**

| Complication |
|---|
| Neurological complications (seizure) |
| Cataract |
| Cardiovascular disease |
| Chronic Kidney Disease |
| Mental health |
| Bone fracture |
| Urinary tract infection |
| Upper respiratory tract infection |
| Lower respiratory tract infection |
| Nephrolithiasis |

| |
|---|
| Nephrocalcinosis |

#### 3.3.2.1 Complication incidence

Incidences for seizure, cataract, fragility fracture, nephrolithiasis, and nephrocalcinosis were sourced from general population controls matched to CT patients in the CPRD analysis.[99] Incidences for CKD, CVD, urinary tract infections (UTI), upper respiratory tract infections (URTI), and lower respiratory tract infections (LRTI) were sourced from the literature (Table 23).[100-105] These were age-gender-stratified where possible, with weighted averages used when age brackets differed. Incidence rates were applied rather than probabilities to allow for the repeatable nature of any single complication for any given patient. Due to the difficulty of classifying mental health and data limitations, it was excluded from the analysis base case.

**Table 23: Complication general population incidence by age category per cycle**

| Complication | 18-29 | 29-39 | 39-49 | 49-59 | 59-69 | 69-79 | 79+ |
|---|---|---|---|---|---|---|---|
| Neurological complications (seizure) [99] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cataract[99] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cardiovascular disease[100] | 0.01% | 0.01% | 0.02% | 0.04% | 0.08% | 0.15% | 0.32% |
| Chronic Kidney Disease[101]* | 0.00% | 0.26% | 0.51% | 1.03% | 1.28% | 2.18% | 2.57% |
| Mental health | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Bone fracture[99] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Urinary tract infection[102] | 0.68% | 0.68% | 0.91% | 0.91% | 0.91% | 1.09% | 1.27% |
| Upper respiratory tract infection[104] | 0.01% | 0.16% | 0.16% | 0.16% | 0.05% | 0.06% | 0.07% |
| Lower respiratory tract infection[103] | 0.25% | 0.25% | 1.25% | 6.26% | 0.47% | 0.47% | 0.47% |
| Nephrolithiasis[99] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Nephrocalcinosis[38] | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.01% | 0.02% |

*Notes: Prevalence data adjusted by estimated duration of disease of 10-years.

To reflect the differential burden associated with disease control, relative risks for complications were adjusted using hazard ratios stratified by health state from the CPRD analysis.[10] Table 24 presents, for each complication, the hazard ratio for AC versus general population, and hazard ratio for NAC versus general population.

**Table 24: Complication risk**

| Complication | AC vs Gen pop | NAC vs Gen pop |
|---|---|---|
| Neurological complications (seizure) | [redacted] | [redacted] |
| Cataract | [redacted] | [redacted] |
| Cardiovascular disease | [redacted] | [redacted] |
| Chronic Kidney Disease | [redacted] | [redacted] |
| Mental health | [redacted] | [redacted] |
| Bone fracture | [redacted] | [redacted] |
| Urinary tract infection | [redacted] | [redacted] |
| Upper respiratory tract infection | [redacted] | [redacted] |
| Lower respiratory tract infection | [redacted] | [redacted] |
| Nephrolithiasis | [redacted] | [redacted] |
| Nephrocalcinosis | [redacted] | [redacted] |

Source: CPRD analysis[10]

#### 3.3.2.2 Adverse events

Hypocalcaemia and hypercalcaemia events were captured as treatment emergent adverse events using treatment exposure-adjusted event rates from the PaTHway trial double blinded phase (Table 25).[78] The model included only hypocalcaemia and hypercalcaemia as adverse events, as these were considered to capture impactful, treatment-emergent events that occur repeatedly throughout a patient's life and contribute significantly to patient burden and healthcare utilisation. The model then assumes hypercalcaemia and hypocalcaemia continue to occur over the lifespan as complications, with palopegteriparatide attenuating the disease-attributable excess incidence.

**Table 25: Adverse event incident rate per cycle**

| Adverse event | Palopegteriparatide | CT |
|---|---|---|
| Hypercalcaemia | [redacted] | [redacted] |
| Hypocalcaemia | [redacted] | [redacted] |

Source: PaTHway clinical trial[78]

#### 3.3.2.3 Mortality

Mortality was modelled using general population life tables, with adjustments applied by health state to reflect elevated mortality risk among HypoPT patients. Mortality risk in the model was informed by real-world evidence from the CPRD.[10]

Hazard ratios were estimated by comparing mortality in patients with chronic HypoPT against matched general population controls and were stratified by AC and NAC status.[10] These hazard ratios were applied to UK general population life tables to generate age-sex-specific mortality rates for each health state.[116]

**Table 26: Hazard ratios for mortality**

| Mortality | Hazard ratio |
|---|---|
| AC | [redacted] |
| NAC | [redacted] |

Abbreviations: AC, adequately controlled disease; NAC, not adequately controlled disease; Source: CPRD analysis[10]

Additional mortality risk for complications were not included within the base case analysis due to the potential risk of double counting mortality risk. Given the CPRD analysis excluded patients who had a prior diagnosis of CKD or CVD event, there is a potential risk of underestimating long-term mortality from these complications.

## 3.4 Measurement and valuation of health effects

### 3.4.1 Health-related quality-of-life data from clinical trials

In the PaTHway trial, patient-reported outcomes were assessed by the generic SF-36, EQ-5D and by the disease-specific Hypoparathyroidism Patient Experience Scale (HPES) tool. EQ-5D data was deemed the most appropriate for informing the model.

The EQ-5D-5L data collected during the PaTHway clinical trial was mapped to the EQ-5D-3L descriptive system to calculate utility values by health state. The base case analyses utilised the mapping function created by Hernandez-Alava et al. (2023) in line with the NICE reference case.[93,114] This model applies the ANCOVA-adjusted treatment difference in EQ--5D-3L utility (UK value set) calculable from EQ-5D-5L responses collected during the double-blind phase of the PaTHway trial to the

baseline utility for the ITT to represent the utility of the palopegteriparatide-treated arm (Table 27).

**Table 27: Baseline EQ-5D-3L values for the ITT**

| Baseline subgroup | Palopegteriparatide | | | Placebo | | | All participants | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SE | N | Mean | SE | N | Mean | SE |
| ITT population | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: EQ-5D-3L, EuroQoL 5 Dimensions 3 Levels; ITT, intent-to-treat; SE, standard error
Source: PaTHway CSR 2022, data on file, using the mapping function created by Hernandez-Alava et al. 2023.[29,119]

The Week 26 EQ-5D-3L change-from-baseline was estimated using the ANCOVA-adjusted least squares (LS) mean between-treatment difference for the ITT population of PaTHway (palopegteriparatide vs placebo: [redacted](Table 28).

**Table 28: EQ-5D-3L utility score at Baseline versus Week 26 (ITT)**

| Baseline | Treatment group (palopegteriparatide) | Control group (placebo) |
|---|---|---|
| Baseline | | |
| N | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] |
| SD, SE | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] |
| Observed at week 26 | | |
| N | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] |
| SD, SE | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] |
| ANCOVA model | | |
| N | [redacted] | [redacted] |
| LS Mean (SE) | [redacted] | [redacted] |
| 95% CI for LS mean | [redacted] | [redacted] |
| Difference in LS means (SE) | [redacted] | [redacted] |
| 95% CI for Difference in LS Means | [redacted] | [redacted] |
| P-value (Treatment vs control) | [redacted] | [redacted] |

Abbreviation: ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-3L, EuroQoL 5 Dimensions 3 Levels; ITT, intent-to-treat; LS, least squares; Max, maximum; Min, minimum; SD, standard deviation; SE, standard error
Source: Ascendis utility data analysis 2024, data on file[114]

### 3.4.2 Health-related quality-of-life studies

An SLR was conducted to identify relevant HRQoL data to inform the model. Electronic database searches were conducted on 21 December 2023, 08 July 2024, and 27 March 2025.[120] Following searches, exclusion of duplicates, title and abstract screening, and full-text screening, 73 unique studies from 104 reports were identified and included for data extraction. From these, 19 were clinical trials and 54 were real-world evidence (RWE) studies.

Full details of the SLR methodology, PRISMA diagram and included and excluded studies of the SLR are provided in Appendix F.

The SLR found substantial humanistic burden associated with chronic HypoPT. Patients reported persistent symptoms despite CT, with HRQoL scores substantially lower than in the general population. Greater symptom severity was associated with lower utility values and poorer HRQoL outcomes. Use of PTH therapy—including TransCon PTH (palopegteriparatide)—was consistently associated with improvement in HRQoL across SF-36, RAND-36, EQ-5D VAS, the HPES, and fatigue-specific instruments. These improvements were consistently greater than those observed with CT across trials and real-world studies. However, only two studies were identified that reported preference-based utility values, and neither aligned with the NICE reference case requirements:

- Weycker et al 2016, a post hoc analysis of the REPLACE trial of rhPTH 1-84 mapped observations from SF-36 to health utilities index-2 (HUI2) to determine health state utility change from baseline between responders and non-responders.[121] As the HUI2 instrument is not admissible within the NICE reference case, no data relevant to the current submission was reported.[93]

- Siggelkow 2020, the EQ-5D-5L index instrument was administered to patients with HypoPT and the UK value set reported by Devlin (2018).[12,122] Despite demonstrating a sensible correlation with symptom severity, the explicit

exclusion of the Devlin (2018) value set from the NICE reference case precludes the direct use of utility values from this source.[93]

Therefore, the model base case applied mapped EQ-5D-3L values observed directly in the PaTHway trial. These were used to estimate the mean utility difference between treatment arms (palopegteriparatide vs CT) and are consistent with the NICE reference case in terms of instrument, valuation set, and trial-relevant population.

While broader evidence of mental and cognitive improvement was captured across a range of non-utility instruments, no suitable preference-based study was identified to quantify this benefit. As such, any additional cognitive utility gain associated with palopegteriparatide is likely to be conservatively represented in the model.

### 3.4.3 Health-related quality-of-life data used in the cost-effectiveness analysis

As described in section 3.4.1, the model utilises PaTHway EQ-5D-5L data to inform the health state utilities for the AC and NAC states.[114] Age-gender adjustments were made to health state utilities to ensure demographic adjustment over the lifetime horizon of the model were captured using Hérnandez Alava et al. (2022) (Table 30).[123]

**Table 29: Health state utilities**

| Baseline utility | Utility |
|---|---|
| AC | [redacted] |
| NAC | [redacted] |

Abbreviations: AC, adequately controlled disease; NAC, not adequately controlled disease; Source: PaTHway trial[114]

**Table 30: General population utility age-adjustment**

| General population utility | | Female | Male |
|---|---|---|---|
| Age | Fixed | [redacted] | [redacted] |
| | Age | [redacted] | [redacted] |
| | Age^2 | [redacted] | [redacted] |

Source: M Hernández Alava, S Pudney, A Wailoo (2022)[123]

#### 3.4.3.1 Event-based acute disutility

##### *3.4.3.1.1 End-of-life (EoL)*

No relevant sources for EoL disutility were identified in the HRQoL SLR (Appendix F). However, patient HRQoL is independently linked to mortality.[124] To represent this, an EoL acute disutility was calculated using a recent study by Hatswell et al. (2023) which studied change in EQ-5D-3L utility (UK value set) versus time to death.[125] The preferred log (TTD) model utility at Day 28 (0.530) and Day 1 (0.265) prior to death, enabled a proportional EoL disutility of 0.500 for each cycle in which death occurred to be estimated. This source was applied based on the long-term follow-up and quantity of data analysed, with 5-years of follow-up and over 4,000 EQ-5D observations recorded.

##### *3.4.3.1.2 Complications*

Complication disutilities were assumed to apply for a duration of one cycle. The applied disutilities and source for each complication is provided in Table 31.

**Table 31: Complication disutility**

| Complication | Details |
|---|---|
| Neurological complications (seizure) | The parameter estimates of adult patients with epilepsy having one seizure daily (0.130) versus those seizure free (0.800) were combined.[126] |
| Cataract | From Andayani 2022, the weighted disutility of cataract patients (-0.346) with moderate or worse visual acuity was compared to those with mild visual acuity impairment (0.926).[106] |
| Cardiovascular disease | (0.337) calculated from composite events disutilities from Dyer 2010 (Myocardial Infarction and Heart Failure) and Golicki 2015 (Stroke) weighted by incidence from Conrad 2024 (expanded below).[100,107,108] |
| Chronic Kidney Disease | The EQ-5D utility score of all CKD stages combined (0.74) versus the stage G1/G2 utility score (0.85) from Jesky 2016.[109] |
| Mental health | Excluded from base case |
| Bone fracture | From the catalogue of EQ-5D scores in chronic disease assembled by Van Wilder et al., the disutility of those with vertebral fracture (-0.490) was compared to the healthy age-matched population norm (0.810).[110] |

| | |
|---|---|
| Urinary tract infection | The TTO utility decrement of mild to moderate UTI in type 2 diabetes (T2DM, 0.090) was compared to the mean utility score for uncomplicated T2DM of 0.920.[111] |
| Upper respiratory tract infection | From the Van Wilder catalogue the utility of any respiratory tract disease (0.71) was compared with age-matched population norm of 0.85 to derive disutility.[110] |
| Lower respiratory tract infection including pneumonia | |
| Nephrolithiasis | From Eryildrim 2015, the mean EQ-5D index of 0.72 was compared against the age-gender population norm of 0.910 to calculate disutility.[112] |
| Nephrocalcinosis | |

Abbreviations: EQ-5D, EuroQoL 5 Dimensions; T2DM, type 2 diabetes mellitus; TTO, timed trade-off; UTI, urinary tract infection; VAS, visual analogue scale.

No relevant sources for CVD disutility were identified in the HRQoL SLR (Appendix F).[120] Therefore, alternative sources were identified to model CVD disutility. Dyer (2010) reports a structured literature search for CVD that includes 66 papers and provides utility estimates across a range of CV subgroups.[107] Due to the systematic approach applied, this source has useful applications for modelling of utilities and QALYs in economic evaluations. Golicki (2015) provides a comprehensive assessment of the validity of EQ-5D in stroke. The study included a large sample size (n=408) with a range of aetiologies.[108]

An incidence-weighted composite acute disutility for CVD was calculated using the difference between best (denominator) and worst (numerator) health state utilities for each of myocardial infarction (MI), heart failure (HF), and stroke (Table 44).

- For MI, this was the utility for Canadian Cardiovascular Society (CCS) grade IV (0.36) versus CCS grade 0 (0.81).[107]
- For HF, this was the utility of moderate to severe states (New York Heart Association Functional Classification [NYHA] Class III/IV, 0.51) versus mild states (NYHA Class II/I, 0.78).[107]

- For stroke, this was the mean utility of hospitalised stroke patients (0.528) versus that for patients with a modified Rankin Scale of zero (i.e. no stroke-related impairments, 0.884).[108]

Numerators and denominators were weighted by the relative UK incidence of each CVD component.[100]

**Table 44: Derivation of composite CVD event acute disutility**

| | Incidence†[100] | Numerator | Denominator | Absolute | Proportional | Source |
|---|---|---|---|---|---|---|
| MI | 190 | 0.360 | 0.810 | -0.450 | -0.556 | Dyer 2010[107] |
| HF | 367 | 0.510 | 0.780 | -0.270 | -0.346 | |
| Stroke | 181 | 0.528 | 0.884 | -0.356 | -0.403 | Golicki 2015[108] |
| CVD | 738 | 0.370 | 0.813 | -0.337 | -0.414 | |

†Per 100,000 person years
Abbreviations: CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction

### 3.4.4 Adverse events

The duration of hypocalcaemia and hypercalcaemia events were taken from the observed period that serum calcium initially increased during study drug titration before returning to within baseline levels during the phase of palopegteriparatide dose titration, with an assumed 7-day duration for hypercalcaemia and hypocalcaemia (Table 32). The disutility for both hypocalcaemia and hypercalcaemia were estimated from an assumed requirement for emergency hospital admission. From Lin (2020), median EQ-5D utility on admission (0.440) was compared against that at discharge (0.648) to derive disutility (Table 32).[127]

**Table 32: Adverse event disutility**

| Adverse event | Disutility (Lin 2020)[127] | Duration |
|---|---|---|
| Hypercalcaemia | 0.21 | 7.00 |
| Hypocalcaemia | 0.21 | 7.00 |

## 3.5 Cost and healthcare resource use identification, measurement and valuation

This section describes the costing options included in the model. Direct costs included in the base case analysis were drug costs, drug administration costs,

routine care costs, complication costs, adverse event costs, and mortality costs. All costs in this section are shown in their inflated Great British pound (GBP) year according to price and index year.

An SLR was conducted to identify evidence regarding HCRU/costs or economic analyses associated with the management of adult patients with HypoPT. The SLR was conducted based on the reporting standards of the PRISMA and general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions as well as general methodological requirements outlined by key HTA bodies, such as the NICE, Canada's Drug Agency, and European Network for Health Technology Assessment.[71-75,128,129]

The searches were conducted on July 8, 2024, with an update on March 27, 2025; the searches returned 2,071 records. In total, 101 reports were screened at the full-text level, 61 of which were excluded. Additional reports were identified through other sources and assessed for eligibility. Overall, 41 unique studies from 47 reports were identified for the economic SLR.[120]

Full details of the SLR methodology, PRISMA diagram and included and excluded studies of the SLR are provided in Appendix G.

None of the available HCRU estimates in the literature adequately described the relationship between HypoPT disease control and HCRU. The model base case therefore imputed aggregated annual HCRU costs for AC and NAC patients by combining the observed distribution of total healthcare costs in CPRD.[10]

For the costs of adverse events, the SLR was not informative and thus a targeted literature review of cost studies focusing on these elements was conducted.[97] Historical factors were mitigated by adjusting the origin cost to GBP2025 using the ONS CPI as specified in the NICE reference case.[93,113]

### 3.5.1 Intervention and comparators' costs and resource use

#### 3.5.1.1 Drug acquisition costs

Palopegteriparatide costs consist of the drug cost of palopegteriparatide plus the cost of oral calcium at the dose observed in PaTHway at Week 26 (assumed to be

constant thereafter).[78,85] See section 2.3.1 for information on the PaTHway trial design.

Palopegteriparatide costs were based on an initial dose per administration of 18 mcg, accounting for titration to stable dose in accordance with the PaTHway clinical trial and SmPC.[78,85] All patients treated with palopegteriparatide are concomitantly treated with CT within the first year of the model, as per the Week 26 multi-component endpoint in the PaTHway trial.

The base-case analysis reflects the mean titrated dose observed up to Week 156 in the PaTHway OLE and is assumed to be constant thereafter.[78] Accordingly, the palopegteriparatide cost calculations reflect the proportion of patients requiring a dose>33mcg (and therefore two pens per administration). The observed proportion of palopegteriparatide patients requiring two pens per administration (those randomised to trial drug only) at each study visit of the randomised portion of the PaTHway trial was aligned to each 28-day model cycle using a last observation carried forward approach. Compliance was incorporated, with [redacted] compliance rate for palopegteriparatide incorporated from the PaTHway clinical trial.[39]

CT costs are assumed to include the cost of alfacalcidol and oral calcium at the respective mean doses observed at Week 26 in the placebo arm of PaTHway (see section 3.2.1.6).[78] The costs of CT were applied on a per cycle basis for both the CT comparator arm and patients who discontinued from palopegteriparatide (Table 33). As there are multiple CT products available, for simplicity the model assumes the use of alfacalcidol and calcium carbonate to represent CT. Table 33 presents the acquisition costs for palopegteriparatide and CT.

**Table 33: Drug costs of palopegteriparatide, calcium and alfacalcidol**

| Drug | Source | Pack price | Size | Strength | Unit price | Price per unit |
|---|---|---|---|---|---|---|
| Calcium carbonate pack | BNF[95] | £9.33 | 100 tablets | 500 mg | £ 0.09 per tablet | £ 0.0002 per mg |
| Alfacalcidol pack | BNF[94] | £4.56 | 30 capsules | 0.25 mcg | £ 0.15 per capsule | £ 0.61 per mcg |
| Palopgeteriparatide pack price | Ascendis | List price: £7,406.00 | 28-day pack | | | |

| | | | |
|---|---|---|---|
| | | PAS Price: [redacted] | |

Abbreviations: BNF, British National Formulary; mcg, micrograms; mg, milligrams, mL, millilitre; PAS, patient access scheme

#### 3.5.1.2 Drug administration cost

Administration fees for palopegteriparatide included a one-off cost accounting for additional costs of administration for the initial titration period.

An initial administration cost is applied to palopegteriparatide patients to represent the 4-week titration phase for palopegteriparatide (based on the observation that the majority of dose titration took place within the first 4-weeks of the 10-week dose titration period in the double-blind phase of PaTHway). The initial titration period is assumed to incur a consultant-led OP appointment at initiation then two Band 7 specialist-nurse-led appointments for serum-calcium monitoring and dose adjustment lasting 30 minutes each based on clinical input; costed at NHS reference tariffs (Table 34).[96,130,131] Thereafter, palopegteriparatide is expected to be delivered directly to patients for self-administration (at zero cost to NHS) though ongoing prescribed calcium is supplied in primary care incurring dispensing costs and 3-monthly repeat prescription general practitioner (GP) consultation (Table 34).

Administration fees for CT were assumed to accrue from supply in primary care (for which continuity of care responsibility lies), for which monthly pharmacy dispensing fees per drug item supplied apply, as do 3-monthly costs for GPs issuing repeat prescriptions for the same (Table 34).[96,130]

**Table 34: Drug administration costs associated with palopegteriparatide titration phase and CT**

| Setting | Item | Source | Cost | Year | In Use |
|---|---|---|---|---|---|
| Community Pharmacy | Dispensing | Drug Tariff[130] | £1.27 per item | 2024 | £1.27 |
| | Duration | Assumption | Every 28 days | | |
| General Practitioner | Repeat script | Unit Costs of Health & Social Care[96] | £44.56 per consultation | 2023 | £44.56 |
| | Duration | Assumption | Every 84 days | | |
| Specialist Care† | Calcium assay | NHS Reference Costs[131] | £1.55 | 2022 | £1.69 |
| | Endocrine OP visit‡ | | £206 | 2022 | £224.89 |

| | | | | | |
|---|---|---|---|---|---|
| | Specialist nurse visit‡ | Unit Costs of Health & Social Care[96] | £34 | 2023 | £34.65 |

†Costs are adjusted to 2024 values using the ONS Consumer Price Index; One-off cost applied at treatment initiation. ‡The 4-week titration phase for palopegteriparatide is assumed to incur a consultant-led OP appointment at initiation then two Band 7 specialist-nurse-led appointments for serum-calcium monitoring and dose adjustment lasting 30 minutes each.
Abbreviations: CT, conventional therapy; NHS, National Health Service; OP, outpatient

**Table 35: Summary of annual drug acquisition and administration costs for palopegteriparatide and CT (with PAS)**

| | Palopeg' cost | Calcium carbonate | Alfa-calcidol | Administration (initial year) | Administration (subsequent years) | Total (initial year) | Total (subsequent years) |
|---|---|---|---|---|---|---|---|
| Palopegteriparatide | £[redacted] | £[redacted] (initial year) | £[redacted] (initial year) | £ 525.11 | £ 0 | £[redacted] | £[redacted] |
| CT | | £125.88 | £137.24 | £ 226.11 | £ 226.11 | £ 489.24 | £ 489.24 |

Abbreviation: CT, conventional therapy; palopeg', palopegteriparatide.

### 3.5.1.3 Health-state unit costs and resource use

Health state maintenance costs for AC and NAC patients as shown in Table 35 were derived from analysis of CPRD data. This analysis quantified HCRU for patients with chronic HypoPT, stratified by disease control status (AC or NAC), and included primary care consultations, outpatient attendances, inpatient admissions, emergency visits, and kidney replacement therapy.

**Table 36: Health state maintenance costs**

| Health state | Cost per annum (£2025 indexed) | Origin cost Health state maintenance costs per patient per annum | Source | Origin year |
|---|---|---|---|---|
| AC | [redacted] | [redacted] | CPRD analysis[10] | 2021 |
| NAC | [redacted] | [redacted] | | 2021 |

Abbreviations: AC, adequately controlled disease; NAC, not adequately controlled disease; NHS, National Healthcare Services; NICE, National Institute of Health and Care Excellence

### 3.5.1.4 Adverse reaction unit costs and resource use

The AEs of symptomatic hypocalcaemia and hypercalcaemia are each assumed to incur an emergency hospital admission cost per event (Table 36).

**Table 37: Adverse event costs**

| Health state | Cost per annum (£2025 indexed) | Origin cost Health state maintenance costs per event | Source | Origin year |
|---|---|---|---|---|
| Hypocalcaemia | £3,315.25 | £2,650.41 | Ward 2023[115] | 2020 |
| Hypercalcaemia | £3,315.25 | £2,650.41 | | 2020 |

### 3.5.1.5 End of Life

Healthcare resource costs have been shown to escalate rapidly in the year prior to death. The model applied the EoL cost from the PSSRU *Unit Costs* 2024 report for the category “any chronic condition” as shown in Table 38

**Table 38: End of life costs**

| Health state | Cost per annum (£2025 indexed) | Origin cost Health state maintenance costs per event | Source | Origin year |
|---|---|---|---|---|
| End of life | £14,245.52 | £ 14,029 | PSSRU[96] | 2024 |

## 3.6 Severity

There has been no previous NICE health technology assessment in this indication and therefore there is no precedent for severity weighting. The summary features of the QALY shortfall analysis are presented in Table 39. Although the threshold was not met for the severity weighting, the results are presented to highlight the absolute QALY shortfall in this population (Table 40).

**Table 39: Summary features of QALY shortfall analysis**

| Factor | Value | Reference to section in submission |
|---|---|---|
| Sex distribution | [redacted] | Section 3.2.1.5 |
| Starting age | [redacted] | Section 3.2.1.5 |

Abbreviations: QALY, quality adjusted life year

**Table 40: Summary of QALY shortfall analysis**

| Expected total QALYs for the general population | Total QALYs that people living with a condition would be expected to have with current treatment | Deterministic analysis QALY shortfall |
|---|---|---|
| [redacted] | [redacted] | [redacted] (absolute)<br>[redacted] (proportional) |

Abbreviations: QALY, quality adjusted life year

## 3.7 Uncertainty

To assess uncertainty in the extrapolation of long-term effects and inputs, the model explores a range of sensitivity analyses and the face validity of the model over the time horizon is assessed, including deterministic one-way sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenarios to test key assumptions and sensitive parameters.

Key uncertainties explored include:

- Limited long-term data for patients receiving palopegteriparatide, including whether improved disease control reduces complication risk beyond what is observed in CT-treated patients
- Limited trial duration for capturing sustained HRQoL improvements
- Exclusion of long-term mortality risk from serious complications such as CKD and CVD

## 3.8 Summary of base-case analysis inputs

A summary of the variables applied in the economic model are presented in Table 41.

**Table 41: Summary of variables applied in the economic model**

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Baseline age (mean years) | [redacted] | [redacted] | Section 3.2.1.5 |
| Male gender (%) | [redacted] | [redacted] | Section 3.2.1.5 |
| Palopeg responder patients | [redacted] | [redacted] | Section 3.3.1 |
| CT responder patients | [redacted] | [redacted] | Section 3.3.1 |
| Cycle discontinuation rate | [redacted] | [redacted] | Section 3.3.1.1 |
| Baseline utility: AC | [redacted] | [redacted] | Section 3.4 |
| Baseline utility: NAC | [redacted] | [redacted] | Section 3.4 |
| Female General population utility: Age Fixed | [redacted] | [redacted] | Section 3.4 |
| Female General population utility: Age Age | [redacted] | [redacted] | Section 3.4 |
| Female General population utility: Age Age^2 | [redacted] | [redacted] | Section 3.4 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Male General population utility: Age Fixed | [redacted] | [redacted] | Section 3.4 |
| Male General population utility: Age Age | [redacted] | [redacted] | Section 3.4 |
| Male General population utility: Age Age^2 | [redacted] | [redacted] | Section 3.4 |
| Event disutility Utility: End of life | [redacted] | [redacted] | Section 3.4.3.1.1 |
| Disutility value - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Cataract | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Cardiovascular disease | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Chronic Kidney disease | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Mental health | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Bone fracture | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Urinary tract infection | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Nephrolithiasis | [redacted] | [redacted] | Section 3.4.3.1.2 |
| Disutility value - Nephrocalcinosis | [redacted] | [redacted] | Section 3.4.3.1.2 |
| AC vs Gen pop - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| AC vs Gen pop - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| AC vs Gen pop - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| NAC vs Gen pop - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle Incidence Rate - General population 18-29 - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 18-29 - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle Incidence Rate - General population 29-39 - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 29-39 - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle Incidence Rate - General population 39-49 - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 39-49 - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 49-59 - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle Incidence Rate - General population 59-69 - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 59-69 - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle Incidence Rate - General population 69-79 - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 69-79 - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Neurological complications (seizure) | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Cataract | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Cardiovascular disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Chronic Kidney disease | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Mental health | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Bone fracture | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Urinary tract infection | [redacted] | [redacted] | Section 3.3.2.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle Incidence Rate - General population 79+ - Upper respiratory tract infection | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Lower respiratory tract infection including pneumonia | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Nephrolithiasis | [redacted] | [redacted] | Section 3.3.2.1 |
| Cycle Incidence Rate - General population 79+ - Nephrocalcinosis | [redacted] | [redacted] | Section 3.3.2.1 |
| CT arm: Ca carbonate Pack price | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Ca carbonate Pack size | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Ca carbonate Strength | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Ca carbonate Dose strength | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Ca carbonate Doses per cycle | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Alfacalcidol Pack price | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Alfacalcidol Pack size | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Alfacalcidol Strength | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Alfacalcidol Dose strength | [redacted] | [redacted] | Section 3.5.1.1 |
| CT arm: Alfacalcidol Doses per cycle | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Ca carbonate Pack price | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Ca carbonate Pack size | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Ca carbonate Strength | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Ca carbonate Dose strength | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Ca carbonate Doses per cycle | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Alfacalcidol Pack price | [redacted] | [redacted] | Section 3.5.1.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Palopeg arm: Alfacalcidol Pack size | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Alfacalcidol Strength | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Alfacalcidol Dose strength | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Alfacalcidol Doses per cycle | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg Pack price | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg Pack size | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg Strength | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg Dose strength | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg Doses per cycle | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg RDI | [redacted] | [redacted] | Section 3.5.1.1 |
| Palopeg arm: Palopeg Discount | [redacted] | [redacted] | Section 3.5.1.1 |
| Administration cost - on initiation: Ca carbonate | [redacted] | [redacted] | Section 3.5.1.2 |
| Administration cost - on initiation: Alfacalcidol | [redacted] | [redacted] | Section 3.5.1.2 |
| Administration cost - on initiation: Palopeg | [redacted] | [redacted] | Section 3.5.1.2 |
| Administration cost - ongoing: Ca carbonate | [redacted] | [redacted] | Section 3.5.1.2 |
| Administration cost - ongoing: Alfacalcidol | [redacted] | [redacted] | Section 3.5.1.2 |
| Administration cost - ongoing: Palopeg | [redacted] | [redacted] | Section 3.5.1.2 |
| Percentage of double pen patients at Week - 0 | [redacted] | [redacted] | Section 3.5.1.1 |
| Percentage of double pen patients at Week - 26 | [redacted] | [redacted] | Section 3.5.1.1 |
| Percentage of double pen patients at Week - 52 | [redacted] | [redacted] | Section 3.5.1.1 |
| Percentage of double pen patients at Week - 104 | [redacted] | [redacted] | Section 3.5.1.1 |
| Percentage of double pen patients at Week - 156 | [redacted] | [redacted] | Section 3.5.1.1 |

| Variable | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Event costs: End-of-life cost | [redacted] | [redacted] | Section 3.5.1.5 |
| Health state maintenance costs: AC | [redacted] | [redacted] | Section 3.5.1.3 |
| Health state maintenance costs: NAC | [redacted] | [redacted] | Section 3.5.1.3 |
| Palopeg Adverse event (person years): Symptomatic hypercalcemia | [redacted] | [redacted] | Section 3.3.2.2 |
| Palopeg Adverse event (person years): Symptomatic hypocalcaemia | [redacted] | [redacted] | Section 3.3.2.2 |
| CT Adverse event (person years): Symptomatic hypercalcemia | [redacted] | [redacted] | Section 3.3.2.2 |
| CT Adverse event (person years): Symptomatic hypocalcaemia | [redacted] | [redacted] | Section 3.3.2.2 |
| Adverse event Cost per event: Hypercalcemia | [redacted] | [redacted] | Section 3.5.1.4 |
| Adverse event Cost per event: Hypocalcaemia | [redacted] | [redacted] | Section 3.5.1.4 |
| Adverse event Disutility: Hypercalcaemia | [redacted] | [redacted] | Section 3.4.4 |
| Adverse event Disutility: Hypocalcaemia | [redacted] | [redacted] | Section 3.4.4 |
| Adverse event Duration: Hypercalcemia | [redacted] | [redacted] | Section 3.5.1.4 |
| Adverse event Duration: Hypocalcaemia | [redacted] | [redacted] | Section 3.5.1.4 |
| Mortality: Health state AC | [redacted] | [redacted] | Section 3.3.2.3 |
| Mortality: Health state NAC | [redacted] | [redacted] | Section 3.3.2.3 |

### 3.8.1 Assumptions

Model assumptions along with respective details and sources are described in Table 42.

**Table 42: Model assumptions**

| Model Assumption | Value / Approach | Justification |
|---|---|---|
| Costs and clinical outcomes | Extrapolated over a lifetime horizon | The clinical trial captured outcomes over 26 weeks, whereas HypoPT is a lifelong condition. A lifetime horizon reflects the chronic nature of the disease and |

| | | |
|---|---|---|
| | | was validated by clinical experts.[16] Discontinuation is the main mechanism for movement from AC to NAC, |
| Response | Patients cannot regain AC status after discontinuation | Patients discontinuing palopegteriparatide due to loss of response or adverse events are assumed to revert to CT and enter the NAC state, with no subsequent improvement. Patients in the NAC state are assumed to remain NAC for the remainder of the model unless a treatment change occurs. This reflects expert validation that disease control is not maintained following discontinuation and is consistent with trial data.[78] |
| Efficacy | Treatment benefit sustained until discontinuation | The proportion of patients achieving AC at Week 26 is assumed to persist while on treatment. No additional treatment effect or waning is applied. This was validated through expert input and is consistent with the open-label extension.[78] |
| Complications | Risk modelled using CPRD incidence rates and health state–adjusted hazard ratios | Age-specific incidence rates for complications were derived from CPRD analysis and adjusted using AC and NAC-specific hazard ratios. These risks were applied across the model time horizon. |
| Utility | Health state utilities derived from EQ-5D-3L data for treatment options. | Utility values were derived from EQ-5D-3L data from the trial, consistent with the NICE reference case. The palopegteriparatide and CT utilities were assumed representative of the AC and NAC health states respectively given the majority of palopegteriparatide patients meeting the primary endpoint, and therefore could be approximated to the AC group, while the majority CT patients were considered NAC (section 3.4.3). |
| Routine care | Varies by health state | Resource use differs between AC and NAC based on clinical expert input and real-world data. This variation is used to inform differential costs by health state.[16] |
| Adverse events and complications | Continuous incident events | Treatment emergent adverse events and complications were assumed to occur throughout the time horizon based on clinical expert opinion.[16] The events were captured as incident events to avoid the potential overcomplication of accounting for long-term outcomes from singular events which would require model memory. |

Abbreviations: CT, conventional therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year

## 3.9 Base-case results

### 3.9.1 Base-case incremental cost-effectiveness analysis results

Palopegteriparatide was expected to have a small improvement in life-years, with undiscounted life years of [redacted] versus [redacted] for palopegteriparatide and CT respectively. Palopegteriparatide patients were estimated to remain on treatment for an average of [redacted] years across this time.

At list price, treatment with palopegteriparatide was associated with a total cost of [redacted], a total QALY gain of [redacted], and an incremental QALY gain of [redacted] compared with CT. The corresponding incremental cost was [redacted], resulting in an ICER of £682,280 per QALY gained (Table 43).

When considering the confidential PAS price for palopegteriparatide, the total cost is reduced to [redacted], with an incremental cost of [redacted]. Total QALYs remain at [redacted], resulting in an incremental QALY gain of [redacted]. The ICER using the PAS scenario is £20,731per QALY gained (Table 44). At the £20,000 and £30,000 thresholds, the NHBs are [redacted] and [redacted], respectively, with corresponding NMBs of [redacted] and [redacted] (Table 46).

**Table 43: Base case results (list price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £682,280 | £682,280 |
| CT | [redacted] | [redacted] | [redacted] | [redacted] | | | | |

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year

**Table 44: Base case results (PAS price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,731 | £20,731 |
| CT | [redacted] | [redacted] | [redacted] | | | | | |

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year; PAS, patient access scheme

**Table 45: Net health benefit (list price)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | NHB at £20,000 | NHB at £30,000 | NMB at £20,000 | NMB at £30,000 |
|---|---|---|---|---|---|---|---|---|
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| CT | [redacted] | [redacted] | [redacted] | | | | | |

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year; NHB, net health benefit, NMB, net monetary benefit

**Table 46: Net health benefit (PAS price)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | NHB at £20,000 | NHB at £30,000 | NMB at £20,000 | NMB at £30,000 |
|---|---|---|---|---|---|---|---|---|
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| CT | [redacted] | [redacted] | | | | | | |

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year; NHB, net health benefit, NMB, net monetary benefit, PAS, patient access scheme

## 3.10 Exploring uncertainty

### B.1.1.1 Probabilistic sensitivity analysis (with PAS)

Probabilistic sensitivity analysis was conducted by simultaneous random sampling of all input variables between the lower and upper bounds of their respective confidence intervals and recording the model output for 10,000 Monte Carlo simulations.

When considering the PAS price for palopegteriparatide, the probabilistic analysis showed that the average total cost was [redacted] and the average total QALYs were [redacted]. Compared with CT, this corresponded to an incremental cost of [redacted] and an incremental QALY gain of [redacted], resulting in a mean probabilistic ICER of £19,623 per QALY gained (Table 47).

The resulting NHB was [redacted] at a threshold of £20,000 per QALY gained and [redacted] at £30,000. The associated NMB values were [redacted] and [redacted], respectively (Table 48). These findings are consistent with the deterministic base-case PAS analysis, supporting the robustness of the model results to input uncertainty.

**Table 47: Probabilistic results (PAS price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,623 | £19,623 |
| CT | [redacted] | [redacted] | [redacted] | | | | | |

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year

**Table 48: Probabilistic net health benefit (list price)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | NHB at £20,000 | NHB at £30,000 | NMB at £20,000 | NMB at £30,000 |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| CT | [redacted] | [redacted] | | | | | | |

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year; NHB, net health benefit, NMB, net monetary benefit

Plotting the incremental cost and incremental QALYs from each simulation on a cost-effectiveness plane (Figure 19) shows most model simulation results ([redacted]) occupy the North-East quadrant i.e. palopegteriparatide was more effective but also more costly than CT; [redacted] of simulations occupied the South-East quadrant i.e. palopegteriparatide was more effective and less costly than CT.

**Figure 19: Cost-effectiveness plane for base case analysis of palopegteriparatide versus CT**

Abbreviations: CT, conventional therapy; QALY, quality-adjusted life year; WTP, willingness to pay

Interpreting the Monte Carlo model simulations on a cost-effectiveness acceptability curve (Figure 20) palopegteriparatide has a [redacted] chance of being cost-effective at a willingness to pay (WTP) threshold of £20,000 per QALY gained and a [redacted] chance of being cost effective at a WTP of £30,000 per QALY gained.

**Figure 20: Cost-effectiveness acceptability curve for base case analysis of palopegteriparatide versus CT**

Abbreviation: CT, conventional therapy; QALY, quality-adjusted life year

### 3.10.1 Deterministic sensitivity analysis (with PAS)

One-way deterministic sensitivity analysis was conducted to understand the impact of individual parameter uncertainties on the base case ICER. This analysis is presented in the form of a Tornado diagram showing the top 10 parameters in descending order

of their magnitude of ICER difference between the lower and upper bounds of their respective confidence intervals (Figure 21). The most influential parameters were baseline utility values for AC and NAC, followed by NAC health state maintenance costs, incidence of symptomatic hypocalcaemia on CT, and cost per hypocalcaemia event. Parameters related to mortality and AEs had comparatively smaller impacts on the ICER. The lower bound scenario for the baseline utility for AC becomes lower than the NAC utility value, hence, the ICER becomes negative.

**Figure 21: Tornado diagram showing the top 10 parameters impacting the base-case ICER**

Abbreviations: AC, adequately controlled; NAC, not adequately controlled; CT, conventional therapy [for HypoPT]; AE, adverse event; ICER, incremental cost-effectiveness ratio.

### 3.10.2 Scenario analysis

To explore the robustness of the model to key structural and parameter uncertainties, a series of deterministic scenario analyses were conducted. These scenarios tested plausible variations in assumptions relating to discontinuation, mortality, utilities, adverse events, dosing, and costs, reflecting clinical uncertainty or alternative plausible inputs. Table 49 presents the rationale for the scenarios tested.

**Table 49: Scenario rationale**

| Scenario | Base case value | Scenario value | Rationale |
|---|---|---|---|
| Undiscounted | Discount (costs): 3.5%<br>Discount (outcomes): 3.5% | Discount (costs): 0%<br>Discount (outcomes): 0% | Illustrates total health and cost outcomes without applying discounting. |
| Trial primary endpoint response (discontinue immediately) | Palopeg responders: [redacted]<br>CT responders: [redacted]<br>Palopeg initial non-responders: discontinue immediately | Palopeg responders: [redacted]<br>CT responders: [redacted]<br>Palopeg initial non-responders: discontinue immediately | Reflects only patients who met the primary endpoint (79%) per PaTHway trial, assuming non-responders discontinue immediately. |
| Trial primary endpoint response (discontinue rate) | | Palopeg responders: [redacted]<br>CT responders: [redacted]<br>Palopeg initial non-responders: discontinue at annual rate | Reflects only patients who met the primary endpoint (79%) per PaTHway trial, assuming non-responders discontinue at the usual rate. |
| Half discontinuation | Discontinuation rate (cycle): [redacted] | Discontinuation rate (cycle): [redacted] | Halves discontinuation rate to test lower treatment discontinuation. |
| Double discontinuation | | Discontinuation rate (cycle): [redacted] | Doubles discontinuation rate to test increased treatment discontinuation. |
| Utility analysis for patients meeting primary endpoint | AC baseline utility: [redacted]<br>NAC baseline utility: [redacted] | AC baseline utility: [redacted]<br>NAC baseline utility: [redacted] | Tests utilities values observed for change-from baseline among responders only, reflecting a more conservative scenario. |
| Complication costs | Costs excluded | Neurological complications (seizure): £170<br>Cataract: £1,221 | Applies increased cost of complications to test resource-use impact. |

| | | | |
|---|---|---|---|
| | | Cardiovascular disease: £7,741<br>Bone fracture: £1,257<br>Urinary tract infection: £117<br>Upper respiratory tract infection: £4,924<br>Lower respiratory tract infection: £4,924<br>Nephrolithiasis: £4,598<br>Nephrocalcinosis: £1,551 | |
| Dose distribution: none | Week 0: [redacted]<br>Week 26: [redacted]<br>Week 52: [redacted]<br>Week 104: [redacted]<br>Week 156+: [redacted] | Week 0+: [redacted] | Tests no dose escalation. |
| Dose distribution: 26 weeks | | Week 0: [redacted]<br>Week 26+: [redacted] | Tests dose distribution based on week 26 data from PaTHway. |
| Dose distribution: 52 weeks | | Week 0: [redacted]<br>Week 26: [redacted]<br>Week 52+: [redacted] | Tests dose distribution based on week 52 data from PaTHway. |
| Dose distribution: 104 weeks | | Week 0: [redacted]<br>Week 26: [redacted]<br>Week 52: [redacted]<br>Week 104+: [redacted] | Tests dose distribution based on week 104 data from PaTHway. |
| No mortality benefit | AC vs Gen pop HR: [redacted]<br>NAC vs Gen pop HR: [redacted] | AC vs Gen pop HR: [redacted]<br>NAC vs Gen pop HR: [redacted] | Removes mortality benefit from AC patients. |
| Lower bound mortality | | AC vs Gen pop HR: [redacted]<br>NAC vs Gen pop HR: [redacted] | Applies lower 95% CI for mortality estimates (both arms), testing optimistic survival outcomes. |
| Upper bound mortality | | AC vs Gen pop HR: [redacted]<br>NAC vs Gen pop HR: [redacted] | Applies upper 95% CI for mortality estimates (both arms), testing conservative survival outcomes. |
| Complications excluded | Complication utility impact included | Complication utility impact excluded | Removes impact of complications. |

| | | | |
|---|---|---|---|
| AEs – half cost impact | AE cost: £3,315.25 | AE cost: £1,657.63 | Halves cost impact of adverse events to reflect lower AE severity or cost. |
| AEs – half utility impact | AE disutility: 0.208 | AE disutility: 0.104 | Halves disutility impact of adverse events to reflect uncertainty in HRQoL decrement. |
| End-of-life excluded | End of life impact included | End of life impact excluded | Removes terminal care costs to test effect on cost outcomes. |
| Price erosion due to commercial context | PAS discount: [redacted] | PAS discount year 0-10: [redacted]<br>PAS discount year 10+: [redacted] | Further 35% discount on pack price assumed from year 10 onwards to account for higher rebate rates for older medicines under VPAG and potential generic competition when majority of patients are still on treatment. Discount applied from year 10 in model to represent 12 years post marketing authorisation in practice. |

AE, adverse event; CT, conventional therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality-adjusted life year.

Several scenarios had a notable impact on the ICER, particularly those relating to treatment discontinuation, mortality benefit, and adverse event assumptions:

- Discontinuation assumptions: Varying the long-term discontinuation rate had a limited impact on cost-effectiveness. In the half discontinuation scenario, where patients remained on treatment for longer, total QALYs increased to [redacted], with an ICER of £16,531/QALY (–20.3% vs. base case). Doubling the discontinuation rate reduced total QALYs to [redacted] but still yielded an ICER of £19,830/QALY (–4.3%).

- Mortality assumptions: The model assumed a mortality benefit associated with achieving AC. Removing this assumption reduced QALYs to [redacted] and produced an ICER of £18,076/QALY (–12.8%). Using the lower and upper bounds of the health state–specific hazard ratios resulted in ICERs of £20,415/QALY (–1.5%) and £20,849/QALY (+0.6%), respectively.

- Utility assumptions: Using utility values derived only from responder patients in the PaTHway trial increased the ICER to £23,690/QALY (+14.3%). Halving the disutility impact of adverse events increased the ICER to £47,171/QALY (+127.5%).

- Cost assumptions: Excluding end-of-life costs had a minor impact (ICER: £21,797/QALY, +5.1%). Reducing the cost of adverse events by half had no effect (ICER unchanged). Including complication-specific costs resulted in a lower ICER of £11,966/QALY (–42.3%), confirming that complications contribute substantially to the overall economic burden of chronic HypoPT. Excluding complications altogether produced a modest ICER increase to £22,149/QALY (+6.8%).

- Dose distribution assumptions: Alternative assumptions for the average dose used over time were tested. The most conservative assumption (no variation in dose distribution) reduced the ICER to –£3,199/QALY (dominant vs. CT), while assumptions based on observed data at 26, 52, and 104 weeks resulted in ICERs of –£700/QALY, £13,559/QALY, and £16,803/QALY, respectively.

- Trial primary endpoint response: Applying the treatment effect only to patients meeting the PaTHway primary endpoint and assuming discontinuation after response increased the ICER to £28,576/QALY (+37.8%), representing a conservative assumption. When these patients were assumed to discontinue at the observed rate, the ICER was £23,097/QALY (+11.4%).

Additionally, a scenario has been included to illustrate the changing commercial context that is an important consideration for medicines treating chronic conditions such as palopegteriparatide, which have a significant estimated time-on-treatment beyond the patent protection period. The modelled mean and median time-on-treatment are greater than this time period, therefore the total costs accounted for in the model are considerably higher than they would be. The scenario incorporates the Voluntary Scheme for Branded Medicines Pricing and Access (VPAG) mechanism whereby companies repay a percentage of revenue from sales of

branded medicines to the NHS (in addition to the PAS already applied). This scenario remains conservative as it only includes the rebate rate for older medicines from 12 years post marketing authorisation (year 10 in the model) and not the rebates payable up to this point. However, it arguably more accurately reflects the true costs that are likely to occur, and reduces the uncertainty of some assumptions, reinforcing that palopegteriparatide is a cost-effective intervention for the treatment of chronic HypoPT.

**Table 50: Scenario results (PAS price)**

| Scenarios | Palopegteriparatide | | CT | ICER (£Cost/QALY) (% difference) | |
|---|---|---|---|---|---|
| | Total Cost | Total QALYs | Total Cost | Total QALYs | |
| Base case | [redacted] | [redacted] | [redacted] | [redacted] | £20,731 (+0.0%) |
| Undiscounted | [redacted] | [redacted] | [redacted] | [redacted] | £23,368 (+12.7%) |
| Trial primary endpoint response (discontinue immediately) | [redacted] | [redacted] | [redacted] | [redacted] | £28,576 (+37.8%) |
| Trial primary endpoint response (discontinue rate) | [redacted] | [redacted] | [redacted] | [redacted] | £23,097 (+11.4%) |
| Half discontinuation | [redacted] | [redacted] | [redacted] | [redacted] | £16,531 (-20.3%) |
| Double discontinuation | [redacted] | [redacted] | [redacted] | [redacted] | £19,830 (-4.3%) |
| Responder patients utility | [redacted] | [redacted] | [redacted] | [redacted] | £23,690 (+14.3%) |
| Complication costs | [redacted] | [redacted] | [redacted] | [redacted] | £11,966 (-42.3%) |
| Dose distribution none | [redacted] | [redacted] | [redacted] | [redacted] | -£3,199 (-115.4%) |

| | | | | | |
|---|---|---|---|---|---|
| Dose distribution 26-weeks | [redacted] | [redacted] | [redacted] | [redacted] | -£700 (-103.4%) |
| Dose distribution 52-weeks | [redacted] | [redacted] | [redacted] | [redacted] | £13,559 (-34.6%) |
| Dose distribution 104-weeks | [redacted] | [redacted] | [redacted] | [redacted] | £16,803 (-18.9%) |
| No mortality benefit | [redacted] | [redacted] | [redacted] | [redacted] | £18,076 (-12.8%) |
| Use lower bound mortality (both) | [redacted] | [redacted] | [redacted] | [redacted] | £20,415 (-1.5%) |
| Use upper bound mortality (both) | [redacted] | [redacted] | [redacted] | [redacted] | £20,849 (+0.6%) |
| Complications excluded | [redacted] | [redacted] | [redacted] | [redacted] | £22,149 (+6.8%) |
| Adverse events - half the impact of costs | [redacted] | [redacted] | [redacted] | [redacted] | £20,731 (+0.0%) |
| Adverse events - half the impact of utilities | [redacted] | [redacted] | [redacted] | [redacted] | £47,171 (+127.5%) |
| End of life costs excluded | [redacted] | [redacted] | [redacted] | [redacted] | £21,797 (+5.1%) |
| Palopegteriparatide price erosion | [redacted] | [redacted] | [redacted] | [redacted] | £982 (-95.3%) |

## 3.11 Benefits not captured in the QALY calculation

There are arguably a number of benefits associated with the use of palopegteriparatide in the treatment of chronic HypoPT that are not currently captured in the economic model and QALY calculation:

- **Reduction in pill burden:** Managing HypoPT effectively often means that patients have a high number of pills to take on a daily basis – 27% take three to five pills every day.[132] More than a quarter of patients find the number of pills they are required to take challenging.[132] Moreover, managing blood calcium levels effectively can require patients to change the number of calcium pills and active vitamin D capsules that they take daily: 21% of patients find the regular changes to the number of calcium pills to be challenging, and the figure is 16% of patients for active vitamin D capsules.[132]

- **Cognitive burden:** HypoPT is associated with cognitive symptoms, such as brain fog, which can cause QoL burden for patients. Trial analyses have shown EQ-5D to be insensitive to change in cognitive status, in line with other clinical domains, therefore suggesting that the impact of cognitive burden is not fully captured within the health state utilities.

- **Treatment benefit beyond disease control classification:** The model assumes that all patients in the AC health state experience the same risks of complications and mortality, regardless of whether disease control is achieved through CT or palopegteriparatide. However, clinical experts indicated that patients achieving disease control with physiological PTH replacement may experience lower long-term risks of complications such as CKD and CVD compared with those on CT. These potential treatment-specific benefits are not captured in the model, as complication and mortality risks were derived from the CPRD dataset, which only includes patients treated with CT. Therefore, the model may underestimate the true long-term clinical and economic value of disease control achieved with palopegteriparatide.

- **Complication-related mortality risk:** The model does not attribute additional mortality risk directly to individual complications. Instead, health state–level

mortality risk was estimated from CPRD data. However, this dataset excluded patients with a history of CKD or CVD at baseline, meaning the long-term mortality impact of these serious complications is not fully reflected. As a result, the potential for progressive CKD or CVD to increase mortality risk over time is not captured. This limitation may lead to an underestimation of the long-term survival and economic burden of poorly controlled disease, particularly in NAC patients at higher risk of developing these complications.

- **Caregiver burden:** In line with assessment guidelines, the model focuses only on the patient burden in terms of quality of life and costs incurred by the NHS from their treatments and care. However, caregivers of patients with HypoPT also experience considerable burden[12] proportional to disease severity, which is not included in the model, therefore in this regard the economic analysis can be said to be an underestimate of the true value of palopegteriparatide, which significantly reduces disease severity.[41]

- **Work impairment**: HypoPT also has a significant impact on both patient and caregiver employment and productivity proportional to disease severity.[12] The economic impact of this phenomenon on patients, their caregivers, or society is not included in the model. Therefore, in this regard, the economic analysis can further be said to be an underestimate of the true value of palopegteriparatide.

## 3.12 Subgroup analysis

Given chronic HypoPT is a rare disease with limited trial size and that the PaTHway trial represents a subpopulation of the licenced population, it was not appropriate to undertake further subgroup analysis.

## 3.13 Validation

### 3.13.1 Validation of cost-effectiveness analysis

Key clinical assumptions and structural elements of the cost-effectiveness model were validated through targeted consultation with UK-based clinical experts experienced in the management of chronic HypoPT. Experts reviewed the definitions of AC and NAC, the assumed natural history of disease progression, and the clinical

plausibility of treatment effects over time. The approach to classifying patients using healthcare resource use in real-world data and treatment response in the clinical trial was confirmed to be appropriate and reflective of current clinical practice. Experts also validated assumptions related to treatment discontinuation, the relationship between disease control and complications, and the relevance of included health outcomes. Feedback was used iteratively throughout model development to ensure that the analysis aligned with clinical expectations and captured the relevant aspects of patient management in the UK setting.

Technical validation was undertaken to ensure the model performed as intended and aligned with good practice in health economic modelling. Internal quality control processes included independent cross-checking of formulas, review of logic and flow, and audit of data inputs against source references. Stress testing of model outputs was performed through scenario and sensitivity analyses to assess the internal consistency and parameter responsiveness of the model. An independent external modeller conducted a full technical review of the model to verify transparency, structural logic, and appropriateness of implementation.

## 3.14 Interpretation and conclusions of economic evidence

This analysis evaluated the cost-effectiveness of palopegteriparatide compared with CT in adult patients with chronic HypoPT whose disease is NAC on CT. The analysis adopts the NHS and PSS perspectives over a lifetime horizon. The model incorporates a straightforward structure based on AC and NAC disease states and captures the main clinical and economic drivers of burden, including AEs, complications, and HRQoL.

The model population is based on the PaTHway trial and is considered broadly generalisable to the NAC population in UK, comprising predominantly post-surgical patients, with a mean age of around 50 years and a higher proportion of females. As all patients with chronic HypoPT will initially be treated with CT, this population is consistent with the decision problem and expected treatment pathway.

The economic model results suggest that palopegteriparatide is cost-effective, with a base-case probabilistic ICER of £20,731 per QALY gained. Deterministic scenario

analyses showed that the model is robust to alternative assumptions regarding discontinuation, mortality benefit, and AEs.

The model required assumptions around long-term treatment duration, sustainability of effect, mortality benefit, and the clinical and economic burden of AEs—each representing key structural uncertainties due to limited long-term data. Discontinuation was varied to test uncertainty around persistence on treatment, with scenarios applying both halved and doubled discontinuation rates. Mortality benefit associated with achieving AC status was tested by removing it entirely and by applying lower and upper bounds from available mortality estimates. AE assumptions were tested by reducing either their cost or disutility impact by 50%.

These scenarios showed that changes in discontinuation influenced QALY gains due to variation in time on treatment, with modest impact on costs. Mortality scenarios produced consistent results regardless of whether benefit was excluded or varied. Adjustments to AE cost and disutility inputs affected total costs and QALYs respectively, but did not substantially alter the direction or magnitude of model outcomes.

A limitation of the CPRD dataset used to characterise real-world NAC patients is the higher proportion of non-surgical patients compared with clinical practice. However, based on expert input, differences in disease burden and management between post-surgical and non-surgical patients are expected to diminish once adjusted for time since diagnosis, supporting the generalisability of the analysis.

In summary, palopegteriparatide provides a clinically and cost-effective treatment option for adults with chronic HypoPT whose disease is not adequately controlled with CT. By restoring physiological PTH activity, palopegteriparatide addresses the underlying hormonal deficiency, leading to improved disease control, reduced risk of complications, and enhanced quality of life. The economic model demonstrates that these clinical benefits translate into meaningful health gains for the chronic HypoPT population who are NAC on CT.

Finally, it should be noted that this submission arguably represents a conservative assessment of the cost effectiveness of palopegteriparatide as it does not take into

account the implications of VPAG or generic entry, which are significant considerations given the length of time-on-treatment estimated for palopegteriparatide with [redacted] of patients predicted to still be on treatment after [redacted] years. Ascendis strongly believes this scenario should be considered for decision making as it adversely effects interventions that are intended for chronic treatments as well as small pharmaceutical companies that have one indication products and a small portfolio.

# 4 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality of life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: Checklist of confidential information

Appendix K: Hypoparathyroidism Patient Experience Scale (HPES)

Appendix L: PaTHway study inclusion and exclusion criteria

# 5 References


1. Sinnott B. Hypoparathyroidism – Review of the Literature 2018. *Rare Disord Diagn Ther.* 2018;4(12).
2. Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. *J Bone Miner Res.* 2022;37(12):2568–2585.
3. Bollerslev J, Rejnmark L, Zahn A, et al. European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders. *Eur J Endocrinol.* 2022;186(2):R33–r63.
4. Bjornsdottir S, Ing S, Mitchell DM, et al. Epidemiology and Financial Burden of Adult Chronic Hypoparathyroidism. *J Bone Miner Res.* 2022;37(12):2602–2614.
5. Brod M, Waldman LT, Smith A, Karpf D. Assessing the Patient Experience of Hypoparathyroidism Symptoms: Development of the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom). *Patient.* 2020;13(2):151–162.
6. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nat Rev Dis Primers.* 2017;3:17080.
7. Sardella A, Bellone F, Morabito N, et al. The association between hypoparathyroidism and cognitive impairment: a systematic review. *J Endocrinol Invest.* 2021;44(5):905–919.
8. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract.* 2014;20(7):671–679.
9. Shoback DM, Bilezikian JP, Costa AG, et al. Presentation of Hypoparathyroidism: Etiologies and Clinical Features. *The Journal of Clinical Endocrinology & Metabolism.* 2016;101(6):2300–2312.
10. Ascendis Pharma. Retrospective analysis of healthcare resource utilization and cost associated with chronic hypoparathyroidism in England. (CPRD study). Version 8. Data on File. 2025.
11. Brod M, Waldman L, Smith A, Karpf D. MON-LB092 Understanding the Patient-Centered Impact of Hypoparathyroidism on Functioning and Well-Being. *J Endrocr Soc.* 2019;3(1).
12. Siggelkow H, Clarke BL, Germak J, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. *Clin Endocrinol (Oxf).* 2020;92(2):159–168.
13. Gafni RI CM. Hypoparathyroidism. *N Engl J Med.* 2019;380(18):1738-1747.
14. Gronemeyer K, Fuss C, Hermes F, et al. Renal complications in chronic hypoparathyroidism – a systematic cross-sectional assessment. *Sec. Thyroid Endocrinology.* 2023;14.
15. Waldman LT BM, Smith A, Karpf D. PDB115 Impacts of hypoparathyroidism on patient work productivity and out-of-pocket costs. *Value in Health.* 2019 May;22:S159.
16. Ascendis Pharma. KOL Summary Report. Data on File. 2025.
17. Kiam JS SV, Glenister L, Fraser WD, Turner JJO. UK national chronic hypoparathyroidism audit. *Clin Endocrinol (Oxf).* 2022;97(5):562–567.
18. Ascendis Pharma. Hypoparathyroidism HCP ATU. UK report. Data on File. 2024. 2024.
19. GOV.UK. Ascendis Pharma.Yorvipath SmPC. 2024; https://products.mhra.gov.uk/substance/?substance=PALOPEGTERIPARATIDE.
20. Takeda. Takeda to Discontinue Manufacturing of NATPAR® / NATPARA® for Patients with hypoparathyroidism at the End of 2024. 2022;

https://www.takeda.com/en-us/newsroom/statements/2022/takeda-to-discontinue-manufacturing-of-natpar-natpara/.
21. Takeda. Direct Healthcare Professional Communication (DHPC) ||Natpar (parathyroid hormone (rDNA)) 100/75/50/25 micrograms/dose powder and solvent for solution for injection: Discontinuation of manufacturing at the end of 2024 and update on 100mcg shortage. 2022; https://assets.publishing.service.gov.uk/media/638358738fa8f56ea9d462e3/Natpar.pdf.
22. Ascendis Pharma. Ascendis Pharma. Briefing Book for Patient Reported Outcome Instruments Included in the Phase 3 Clinical Trial of Palopegteriparatide in Adults with Hypoparathyroidism. Data on File. .
23. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *Bmj.* 2013;346:f324.
24. Karpf DB, Pihl S, Mourya S, et al. A Randomized Double-Blind Placebo-Controlled First-In-Human Phase 1 Trial of TransCon PTH in Healthy Adults. *J Bone Miner Res.* 2020;35(8):1430–1440.
25. Ascendis Pharma. United Kingdom's MHRA Approves YORVIPATH® (palopegteriparatide) in Great Britain for the Treatment of Adults with Chronic Hypoparathyroidism. 2024; https://investors.ascendispharma.com/news-releases/news-release-details/united-kingdoms-mhra-approves-yorvipathr-palopegteriparatide.
26. GOV.UK. Orphan Register. 2025; https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register.
27. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *J Bone Miner Res.* 2013;28(12):2570–2576.
28. Vivien Lim BLC. Hypocalcemia. *Endocrinology and Diabetes: A Problem Oriented Approach: Second Edition.* 2022.
29. Ascendis Pharma. BluePrint Orphan, Ascendis Chronic Hypoparathyroidism Report. 2024.
30. Brandi ML, Bilezikian JP, Shoback D, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab.* 2016;101(6):2273–2283.
31. Khan AA, Koch CA, Van Uum S, et al. Standards of care for hypoparathyroidism in adults: a Canadian and International Consensus. *Eur J Endocrinol.* 2019;180(3):P1–p22.
32. Khan AA, Rejnmark L, Rubin M, 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–e385.
33. Bilezikian JP, Khan A, Potts JT, Jr., et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. *J Bone Miner Res.* 2011;26(10):2317–2337.
34. Khan AA AH, Ali DS, Al Kassem Z, Almoulia A, Afifi H, Braga M, Cheng A, Malhem J, Millar A, Morgante E, Muhammad P, Paul TL, Prebtani A, Punthakee Z, Khan T, Khan S, Shrayyef M, Van Uum S, Young JEM, Brandi ML, Ovize M, Weiss B. . Skeletal health status among patients with chronic hypoparathyroidism: results from the Canadian National Hypoparathyroidism Registry (CNHR). *Osteoporos Int.* 2025(36(4):673-684).
35. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine CM. Low health-related quality of life in hypoparathyroidism and need for PTH analog. *Endocr Connect.* 2022;11(1).

36. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. *J Bone Miner Res.* 2013;28(11):2277–2285.
37. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. *Circulation.* 2021;143(11):1157–1172.
38. Gosmanova EO, Chen K, Rejnmark L, et al. Risk of Chronic Kidney Disease and Estimated Glomerular Filtration Rate Decline in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. *Adv Ther.* 2021;38(4):1876–1888.
39. Ascendis Pharma. Clinical Study Report. TransCon PTH TCP-304 (Palopegteriparatide; PaTHway). Data on File. 2022.
40. Clarke BL, Khan AA, Rubin MR, 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):951–960.
41. Khan AA, Rubin MR, Schwarz P, 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.
42. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296–1305.
43. Gosmanova EO, Houillier P, Rejnmark L, Marelli C, Bilezikian JP. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: a systematic literature review : Renal disease in chronic hypoparathyroidism. *Rev Endocr Metab Disord.* 2021;22(2):297–316.
44. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab.* 2012;97(12):4507–4514.
45. Ayodele O, Rejnmark L, Mu F, et al. Five-Year Estimated Glomerular Filtration Rate in Adults with Chronic Hypoparathyroidism Treated with rhPTH(1-84): A Retrospective Cohort Study. *Adv Ther.* 2022;39(11):5013–5024.
46. Kaul S, Ayodele O, Chen K, et al. Association of Serum Calcium and Phosphate With Incident Cardiovascular Disease in Patients With Hypoparathyroidism. *Am J Cardiol.* 2023;194:60–70.
47. Fletcher BR, Damery S, Aiyegbusi OL, et al. Symptom burden and health-related quality of life in chronic kidney disease: A global systematic review and meta-analysis. *PLoS Med.* 2022;19(4):e1003954.
48. Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med.* 2008;359(4):391–403.
49. Cleveland Clinic. Estimated Globemerular Filtration Rate (eGFR). 2021; https://my.clevelandclinic.org/health/diagnostics/21593-estimated-glomerular-filtration-rate-egfr.
50. Astolfi D, Murphy D, Sanders B, et al. The Voices of Hypopara Survey: Journey of patients living with hypoparathyroidism. 2020.
51. Sikjaer T, Eskildsen SF, Underbjerg L, Østergaard L, Rejnmark L, Evald L. Hypoparathyroidism: changes in brain structure, cognitive impairment, and reduced quality of life. *J Bone Miner Res.* 2024;39(7):855–866.
52. Ware JE SC. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Medical Care.* 1992;30(6):473–483.
53. Brod M, Waldman LT, Smith A, Karpf D. Living with hypoparathyroidism: development of the Hypoparathyroidism Patient Experience Scale-Impact (HPES-Impact). *Qual Life Res.* 2021;30(1):277–291.
54. Ascendis Pharma. People with Hypoparathyroidism (hypoPT): Treatment Burden Survey (Data on File). 2024.

55. Büttner M, Krogh D, Siggelkow H, Singer S. Impairments in quality of life and predictors of symptom burden in patients with hypoparathyroidism: results from a population-based survey. *Endocrine.* 2023;82(2):419–426.
56. Rubin MR, Tabacco G, Omeragic B, Majeed R, Hale C, Brickman AM. A Pilot Study of Cognition Among Hypoparathyroid Adults. *J Endocr Soc.* 2022;6(3):bvac002.
57. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Postsurgical hypoparathyroidism--risk of fractures, psychiatric diseases, cancer, cataract, and infections. *J Bone Miner Res.* 2014;29(11):2504–2510.
58. Kaul S, Gosmanova EO, Castriota F, et al. Recent Trends in Hypoparathyroidism-Related Inpatient and Emergency Department Admissions and Costs in the United States. *J Endocr Soc.* 2023;7(5):bvad050.
59. Herteux J, Geiger SJ, Starchl C, et al. Hospitalizations, emergency room visits and causes of death in 198 patients with permanent hypoparathyroidism: a retrospective Austrian study (2005-2022). *Endocr Connect.* 2023;12(5).
60. Gandjourl A, Armsen W, Wehmeyer W, Multmeierl J, Ulrich Tschulena U. Costs of patients with chronic kidney disease in Germany. *PloS ONE.* 2020;15(4).
61. Chen K, Krasner A, Li N, Xiang CQ, Totev T, Xie J. Clinical burden and healthcare resource utilization among patients with chronic hypoparathyroidism, overall and by adequately vs not adequately controlled disease: a multi-country chart review. *J Med Econ.* 2019;22(11):1141–1152.
62. Orloff LA, Wiseman SM, Bernet VJ, et al. American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. *Thyroid.* 2018;28(7):830–841.
63. Stack BC, Jr., Bimston DN, Bodenner DL, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY DISEASE STATE CLINICAL REVIEW: POSTOPERATIVE HYPOPARATHYROIDISM--DEFINITIONS AND MANAGEMENT. *Endocr Pract.* 2015;21(6):674–685.
64. Büttner M, Musholt TJ, Singer S. Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review. *Endocrine.* 2017;58(1):14–20.
65. Abate EG, Clarke BL. Review of Hypoparathyroidism. *Front Endocrinol (Lausanne).* 2016;7:172.
66. Tay D, Cremers S, Bilezikian JP. Optimal dosing and delivery of parathyroid hormone and its analogues for osteoporosis and hypoparathyroidism - translating the pharmacology. *Br J Clin Pharmacol.* 2018;84(2):252–267.
67. Marcucci G, Masi L, Cianferotti L, et al. Chronic hypoparathyroidism and treatment with teriparatide. *Endocrine.* 2021;72(1):249–259.
68. Underbjerg L, Sikjaer T, Rejnmark L. Long-Term Complications in Patients With Hypoparathyroidism Evaluated by Biochemical Findings: A Case-Control Study. *J Bone Miner Res.* 2018;33(5):822–831.
69. Vadiveloo T, Donnan PT, Leese CJ, Abraham KJ, Leese GP. Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study. *Clin Endocrinol (Oxf).* 2019;90(2):285–292.
70. Matsushita K, Kaptoge S, Hageman SHJ, et al. Including measures of chronic kidney disease to improve cardiovascular risk prediction by SCORE2 and SCORE2-OP. *Eur J Prev Cardiol.* 2023;30(1):8–16.
71. Page M, McKenzie J, Bossuyt P, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372.
72. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions (Version 6.5). 2024; https://training.cochrane.org/handbook.
73. National Institute for Health and Care Excellence (NICE). The social care guidance manual. 2016; https://www.nice.org.uk/process/pmg10/chapter/appendix-b-methodology-checklist-systematic-reviews-and-meta-analyses.

74. Canadian Drug Agency. Guidelines for the Economic Evaluation of Health Technologies: Canada. 2021; https://www.cda-amc.ca/guidelines-economic-evaluation-health-technologies-canada-0.
75. Canadian Drug Agency. Procedures for Reimbursement Reviews. 2023; https://www.cda-amc.ca/procedures-reimbursement-reviews.
76. European Commission. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 2024; https://health.ec.europa.eu/document/download/1f6b8a70-5ce0-404e-9066-120dc9a8df75_en?filename=hta_practical-guideline_direct-and-indirect-comparisons_en.pdf.
77. European Commission. Guideance on Validity of Clinical Studies. 2024; https://health.ec.europa.eu/document/download/9f9dbfe4-078b-4959-9a07-df9167258772_en?filename=hta_clinical-studies-validity_guidance_en.pdf.
78. Ascendis Pharma. PaTHway (TCP-304) Clinical Study Protocol v7.0. Data on File. 2023.
79. ClinicalTrials.gov. (NCT04701203) A Trial Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Daily in Adults With Hypoparathyroidism (PaTHway). 2025; https://clinicaltrials.gov/study/NCT04701203.
80. Ascendis Pharma. PaTHway trial Statistical Methods and Interim Analysis Plan. Version 2.0. 2021.
81. Iqbal K, Dass N, Gip C, Vila J, Rylands AJ, Marelli C. Defining the Characteristics of Chronic Hypoparathyroidism Not Adequately Controlled on Conventional Therapy: Consensus Findings of Three European Delphi Panels. *Adv Ther.* 2019;36(11):3007–3016.
82. Rejnmark L, Ayodele O, Lax A, Mu F, Swallow E, Gosmanova EO. The risk of chronic kidney disease development in adult patients with chronic hypoparathyroidism treated with rhPTH(1-84): A retrospective cohort study. *Clin Endocrinol (Oxf).* 2023;98(4):496–504.
83. Rejnmark L, Gosmanova EO, Khan AA, et al. Palopegteriparatide Treatment Improves Renal Function in Adults with Chronic Hypoparathyroidism: 1-Year Results from the Phase 3 PaTHway Trial. *Adv Ther.* 2024;41(6):2500–2518.
84. Schwarz P, Rejnmark L, Gosmanova E, et al. Sustained improvement in renal function with palopegteriparatide in adults with chronic hypoparathyroidism: 2-year results from the phase 3 PaTHway trial. *Endocrine Abstracts.* 2024;99.
85. Ascendis Pharma. PaTHway dosing data. Data on File.
86. Ascendis Pharma. Distribution of domain scores for the Hypoparathyroidism Patient Experience Scale (HPES) in the PaTHway clinical trial. Data on File. 2024.
87. Ascendis Pharma. [Oral presentation] Endocrine Society Annual Meeting. 2023.
88. Song L. *Calcium and Bone Metabolism Indices. In: Advances in Clinical Chemistry [Internet].* 2017.
89. Carey JJ, Delaney MF, Love TE, et al. DXA-generated Z-scores and T-scores may differ substantially and significantly in young adults. *J Clin Densitom.* 2007;10(4):351–358.
90. Kanis JobotWHOSG, ,. *Assessment of osteoporosis at the primary health-care level. Technical Report.* University of Sheffield;2007.
91. Schwarz P GE, et al.,. Oral Presentation. 26th European Congress of Endocrinology 2024. 2024.
92. Krabbe PF, Stouthard ME, Essink-Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. *J Clin Epidemiol.* 1999;52(4):293–301.
93. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. 2023; https://www.nice.org.uk/process/pmg36.
94. BNF. Alfacalcidiol. 2024; https://bnf.nice.org.uk/drugs/alfacalcidol/.

95. BNF. Calcium carbonate medicinal forms. 2024.
96. PSSRU. Unit Costs of Heath and Social Care 2023 Manual. 2023; https://kar.kent.ac.uk/105685/.
97. Ascendis Pharma. *Systematic literature review and knowledge book of economic evidence to support TransCon PTH in hypoparathyroidism* 2025.
98. Chomsky-Higgins KH, Rochefort HM, Seib CD, et al. Recombinant Parathyroid Hormone Versus Usual Care: Do the Outcomes Justify the Cost? *World J Surg.* 2018;42(2):431–436.
99. Ascendis Pharma. Economic and clinical outcomes for hypoparathyroidism and general population sub-cohorts without specified complications and stratified by controlled and uncontrolled hypoparathyroidism. Data on File. 2025.
100. Conrad N, Molenberghs G, Verbeke G, et al. Trends in cardiovascular disease incidence among 22 million people in the UK over 20 years: population based study. *Bmj.* 2024;385:e078523.
101. Rethemiotaki I. Global prevalence of cardiovascular diseases by gender and age during 2010-2019. *Arch Med Sci Atheroscler Dis.* 2023;8:e196–e205.
102. van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. Public health impact of adverse bone effects of oral corticosteroids. *Br J Clin Pharmacol.* 2001;51(6):601–607.
103. Al Rajeh AM, Naser AY, Siraj R, et al. Acute upper respiratory infections admissions in England and Wales. *Medicine (Baltimore).* 2023;102(21):e33616.
104. Safiri S, Mahmoodpoor A, Kolahi AA, et al. Global burden of lower respiratory infections during the last three decades. *Front Public Health.* 2022;10:1028525.
105. Ketteler M, Chen K, Gosmanova EO, et al. Risk of Nephrolithiasis and Nephrocalcinosis in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. *Adv Ther.* 2021;38(4):1946–1957.
106. Andayani T, Kristina S, Hidayaturahmah R. Comparison and validation of EuroQol-5 Dimension level and Short Form-6 Dimension in cataract patients. *Pharmacy Education.* 2022;22(2).
107. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes.* 2010;8:13.
108. Golicki D, Niewada M, Buczek J, et al. Validity of EQ-5D-5L in stroke. *Qual Life Res.* 2015;24(4):845–850.
109. Jesky MD, Dutton M, Dasgupta I, et al. Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. *PLoS One.* 2016;11(11):e0165675.
110. Van Wilder L, Rammant E, Clays E, Devleesschauwer B, Pauwels N, De Smedt D. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. *Qual Life Res.* 2019;28(12):3153–3161.
111. Shingler S, Fordham B, Evans M, et al. Utilities for treatment-related adverse events in type 2 diabetes. *J Med Econ.* 2015;18(1):45–55.
112. Eryildirim B, Sahin C, Tuncer M, et al. Effect of medical expulsive therapy on the health-related quality of life of patients with ureteral stones: a critical evaluation. *Int Urol Nephrol.* 2015;47(8):1271–1275.
113. Statistics OfN. Consumer price inflation tables. 2025; https://www.ons.gov.uk/economy/inflationandpriceindices/datasets/consumerpriceinflation.
114. Ascendis Pharma. Analysis of Utility Data from a Clinical Trial for Hypoparathyroidism Technical Report.; 2024. Data on File. 2024.
115. Ward T, Lewis RD, Brown T, Baxter G, de Arellano AR. A cost-effectiveness analysis of patiromer in the UK: evaluation of hyperkalaemia treatment and lifelong RAASi

maintenance in chronic kidney disease patients with and without heart failure. *BMC Nephrol.* 2023;24(1):47.
116. Office for National Statistics. National life tables: UK. 2025; https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
117. New 4-Year Data Shows Sustained Response to TransCon® PTH (Palopegteriparatide) Therapy in Adults with Hypoparathyroidism [press release]. 2025.
118. Abouzid M, Riad M, Singh J, Yadav R, Rendón M, Dueñas J. Three Cases of Hypoparathyroidism Treated Successfully with Daily Recombinant Human Parathyroid Hormone rhPTH (1-84; Natpara) Subcutaneous Injections, with Improvement in the Quality of Life and Reduction in Daily Calcium and Vitamin D Requirements. *Endocrine Practice.* 2021;27(6).
119. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics.* 2023;41(2):199–207.
120. Ascendis Pharma. *Health-related quality of life systematic literature review to support TransCon PTH in hypoparathyroidism.* 2025.
121. Weycker D, Chen K, Vera-Llonch M, Bornheimer R, Oster G. PDB72 - Phase III Trial of Recombinant Human Parathyroid Hormone in Hypoparathyroidism: A Post-HOC Analysis of Change in Health-State Utility Among Responders. *Value in Health.* 2016;19(7).
122. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ.* 2018;27(1):7–22.
123. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. 2022.
124. Lorem G, Cook S, Leon DA, Emaus N, Schirmer H. Self-reported health as a predictor of mortality: A cohort study of its relation to other health measurements and observation time. *Scientific Reports.* 2020;10(1):4886.
125. Hatswell AJ, Chaudhary MA, Monnickendam G, et al. Modelling Health State Utilities as a Transformation of Time to Death in Patients with Non-Small Cell Lung Cancer. *Pharmacoeconomics.* 2024;42(1):109–116.
126. Wester V, de Groot S, Versteegh M, et al. Good Days and Bad Days: Measuring Health-Related Quality of Life in People With Epilepsy. *Value Health.* 2021;24(10):1470–1475.
127. Lin CF, Huang YH, Ju LY, et al. Health-Related Quality of Life Measured by EQ-5D in Relation to Hospital Stay and Readmission in Elderly Patients Hospitalized for Acute Illness. *Int J Environ Res Public Health.* 2020;17(15).
128. European Network for Health Technology Assessment. Guideline: Levels of evidence - Internal validity of randomised controlled trials. 2015; https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf. Accessed 13/05/2025.
129. European Network for Health Technology Assessment. D4.3 Direct and Indirect Comparisons. . 2020; https://www.eunethta.eu/d4-3/. Accessed 13/05/2025.
130. NHS Business Services Authority. Drug Tariff. 2020; https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff.
131. NHS England. National Cost Collection for the NHS. 2025.
132. Parathyroid UK. Living with chronic hypoparathyroidism. 2017; https://www.parathyroiduk.org/wp-content/uploads/2018/05/Living-with-chronic-hypoparathyroidism-final-report.pdf.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

# Summary of Information for Patients (SIP)

**May 2025**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6380_palopegteriparatide hypoparathyroidism _SIP | 1.0 | No | 16 May 2025 |

# Summary of Information for Patients (SIP):

## The pharmaceutical company perspective

### What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

### SECTION 1: Submission summary

**1a) Name of the medicine** (generic and brand name):

**Generic name:** Palopegteriparatide

**Brand name:** Yorvipath® ▼

**1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

This submission focuses on part of the population covered by the technology's marketing authorisation, specifically adults with chronic HypoPT whose disease is not adequately controlled on conventional therapy.

This proposed population is narrower than the marketing authorisation because these are the patients by which palopegteriparatide is deemed to be most clinically suitable, whom would benefit from a second-line treatment of parathyroid hormone replacement therapy following conventional therapy.

**1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 24 April 2024, the UK Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisation for palopegteriparatide as a parathyroid hormone replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism. [1],[2]

Palopegteriparatide has been granted a GB orphan designation (this is a special status given to certain drugs called orphan drugs, which show promise in the treatment, prevention or diagnosis of a rare disease).

GB orphan designation number: PLGB 51127/0001-0003/OD1[3]

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

| |
|---|
| Ascendis collaborated with the charity Parathyroid UK to survey their members about their experiences of living with hypoparathyroidism. Parathyroid UK received a grant of £5,000 for their support in recruiting respondents. The survey was undertaken by a third party which was paid for by Ascendis. Each survey respondent also received a £10 Amazon voucher for their time. |

## SECTION 2: Current landscape

### 2a) The condition – clinical presentation and impact

| |
|---|
| Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.<br><br>Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained. |
| Hypoparathyroidism (HypoPT) is a rare endocrine condition caused by having too little parathyroid hormone (PTH), which is produced in the parathyroid glands located in the neck.[4],[5]The role of PTH is to help regulate the levels of calcium, phosphate and active vitamin D in the bones and blood.[5] This is important for the health of the nervous system, muscles and bones.[6]<br><br>HypoPT most commonly (75% of cases) occurs due to the removal of, or damage to, the parathyroid glands during neck surgery, with the remainder attributed to autoimmune, genetic, or idiopathic conditions (i.e., conditions with an unknown cause).[7] HypoPT is considered to be chronic if it lasts for more than six months. [8]<br><br>The reported prevalence of chronic HypoPT ranges from 6.4–37 per 100,000, with reported incidence of 0.8–2.3 per 100,000 per year.[9] A recent search of published information about HypoPT in the UK estimated that approximately 14,100 people in the UK are living with chronic HypoPT.[10]<br><br>When levels of PTH are too low, blood calcium levels fall (hypocalcaemia) and blood phosphate levels rise (hyperphosphataemia).[4] As a result, people with HypoPT can suffer a range of symptoms including muscle cramps, tiredness, paraesthesia (a tingling sensation or 'pins and needles'), impaired memory and concentration, depression and anxiety.[4],[5],[7] In severe cases, patients may experience throat spasms and seizures, which can be life-threatening.[4]<br><br>The symptoms associated with HypoPT often mean that quality of life is impacted for those living with the condition. This can mean finding it hard to work or socialise with friends and family, or even perform typical daily activities such as driving or preparing a meal.[5] Caregivers can be affected also: caring for someone with HypoPT has been shown to affect the ability to work and engage in everyday activities.[11]<br><br>There is currently no cure for HypoPT, and treatment typically involves daily active vitamin D with/without oral calcium to try and keep calcium levels in the blood within the normal range.[5],[12] However, this does not fully replace the functions of PTH itself and requires careful monitoring and frequent adjustments to the number of pills to be taken.[5],[13] Some patients are unable to take oral treatments and therefore require time-consuming hospitalisations for calcium infusions to |

take place instead, with healthcare staff needed to monitor the patient during these procedures. For some patients, it is also the case that vitamin D and/or calcium treatments do not adequately control their disease, and they subsequently experience further symptoms and poorer quality of life. More seriously, long-term treatment with calcium and vitamin D can lead to irreversible damage to the kidneys and the cardiovascular system.[4],[14],[15]

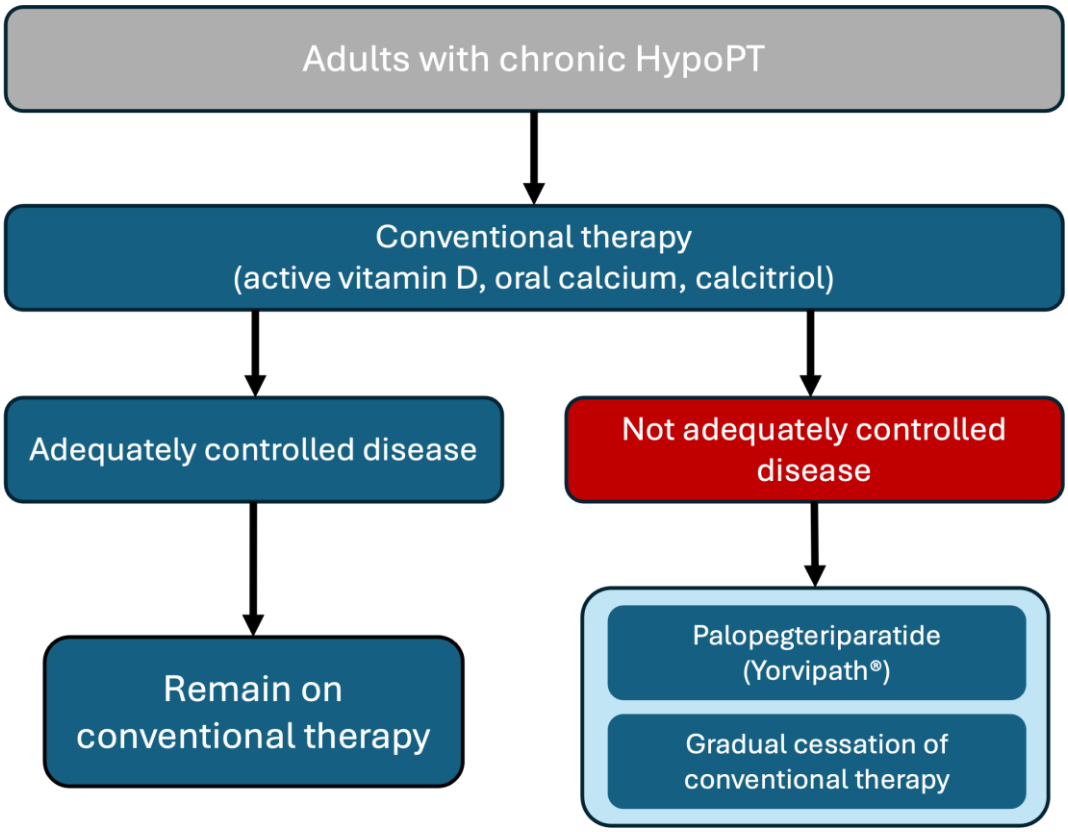
**2b) Diagnosis of the condition (in relation to the medicine being evaluated)**

| Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment? |
| --- |
| HypoPT is diagnosed based on the detection of low PTH and calcium levels on two occasions at least two weeks apart.[12] It is considered to be chronic if it lasts for more than six months.[8] |

**2c) Current treatment options:**

| The purpose of this section is to set the scene on how the condition is currently managed:<br>• What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.<br>• Please also consider:<br>o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.<br>o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are. |
| --- |
| Treatment for HypoPT aims to relieve symptoms and bring the levels of calcium and other minerals in the blood back within health ranges.[12]<br><br>Current (conventional) treatment is typically active vitamin D with/without calcium to increase calcium levels in the blood (and thereby reduce the symptoms of hypocalcaemia).[8]<br><br>Palopegteriparatide is expected to be used in patients whose disease is not adequately controlled with conventional therapy as illustrated in Error! Reference source not found.. |

***Figure 1: Proposed position of palopegteriparatide in the treatment pathway***




*People with HypoPT may remain on calcium and active vitamin D when starting palopegteriparatide but the requirement for these treatments is expected to decline as palopegteriparatide treatment is established, with many people receiving the drug no longer requiring these supplements in line with trial results. Doses of active forms of vitamin D with/without calcium will need to be adjusted prior to initiating and during treatment with palopegteriparatide based on serum calcium value. The optimal dose of palopegteriparatide after titration is the minimum dose required to prevent hypocalcaemia. This is the dose that maintains serum calcium within the normal range without the need for active forms of vitamin D or calcium beyond recommended nutritional action for the general population (generally less than 600 mg per day). At Week 104 of the Phase 3 PaTHway trial, 97% (74/76) of participants achieved independence from CT (defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg). Patients receiving the maximum palopegteriparatide dose of 60 mcg per day who experience ongoing hypocalcaemia may require co-administration of therapeutic calcium and/or active forms of vitamin D.
Abbreviations: CT, conventional therapy; HypoPT, hypoparathyroidism.
Sources: Adapted from SmPC[16]

Clinical guidelines outline the patients for whom conventional therapy is not adequate and would benefit from PTH replacement therapy. These guidelines have been translated into specific quantifiable criteria that could be used to identify patients and operationalise the definition of not adequately controlled (NAC) in clinical practice. The definition was reviewed and validated by three UK-based clinical experts. [17]

Patients with chronic HypoPT may be classified as having NAC disease if they meet ANY one of the below criteria. Patients who do not meet any of the criteria are considered to have adequately controlled disease.

- **High-dose conventional therapy:**
    - Calcitriol (active vitamin D) ≥ 1.0 mcg/day
    - Alfacalcidol ≥ 2.0 mcg/day

- Calcium supplementation ≥ 2000 mg/day

- **Severe symptoms and/or healthcare use:**
  - Emergency room or urgent care visits related to HypoPT (within 6 months)
  - Hospitalisations related to HypoPT (within 6 months)
  - Poor quality of life (SF-36 Physical Functioning score < 40)

- **Renal impairment and/or history of renal complications:**
  - Documented renal insufficiency
  - History of kidney stones (nephrolithiasis)
  - eGFR < 60 mL/min/1.73m²

**2d) Patient-based evidence (PBE) about living with the condition**

**Context:**

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

HypoPT has a considerable negative impact on health-related quality of life (HRQoL), impacting the ability to work and perform daily activities.[18] People with HypoPT have a lower quality of life than the general population as determined by surveys, questionnaires and visual tools.[19],[20],[21],[22],[23],[11]

People with HypoPT have expressed their concern about the long-term health implications of the condition, particularly cardiovascular health, kidney stones/function and calcium build-up in organs.[12] Members of Parathyroid UK who took part in an online survey had the following to say about the burden of HypoPT on their lives:[24]

*"I feel like my life revolves around this illness I never have days where I feel good or normal I am always tired or fatigued, days with sore bones and cramps and aches."*

*"I was a confident self-reliant woman with a great job I am now reliant on family to support me I no longer feel confident to travel alone and have had to reduce my hours and lose my old job"*

*"I feel a lot of frustration as a parent that I get tired and can't do as much with my kids. People don't understand the impact on me both physically and mentally both at home and work, and I'm scared of the long-term impact on my health and kidneys."*

*"I had to close my business…I have severe brain fog and can't get words out, or even spell. I don't drive anymore as I get lost on journeys."*

Whilst a survey conducted in multiple countries reported that the proportion of people with HypoPT in full-time work decreased from 58% (232 out of 397 respondents) before HypoPT diagnosis to 34% (135 out of 397 respondents).[11] In addition, other research has shown that 90% of those with HypoPT report symptoms that interfered with work productivity;[25] 30% were not able to work;[25] 45% needed unpaid time off. [7] Work and activity impairment was greater in people whose HypoPT symptoms were more severe.[7]

Caregivers of those with HypoPT also experience considerable burden, including detrimental effects on their ability to work and perform daily activities.[11] Caregivers also reported overall work impairment (20.8%) and negative impact on personal relationships (28% reported major impact on spousal/partner relationship).[11]

## SECTION 3: The treatment

### 3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Palopegteriparatide is what is known as a "prodrug" of PTH.[26] A prodrug is an inactive medication or compound that needs to be activated inside the body before it can work. Palopegteriparatide is made up of a type of PTH that is linked to a "carrier" molecule that keeps the PTH inactive.[26] Following injection under the skin, palopegteriparatide travels around the body in the bloodstream until the conditions are correct for the carrier to unlink from the PTH molecule, freeing the PTH to bind to receptors such as those on the kidneys and bones where it is needed.[26] The linker and the carrier molecule then pass harmlessly out of the body in the urine. [26]

Palopegteriparatide works by replacing the 'missing' PTH in the body. The goal of treatment is to raise serum calcium to the target/normal range,[12] while achieving independence from calcium and active vitamin D treatments. This will mean people with HypoPT will have fewer tablets to take to control the disease, while also benefitting from reduced risk of long-term harms that are associated with conventional therapies.

### 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of**

| **life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.** |
|---|
| No. |

### 3c) Administration and dosing

| How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.<br><br>How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments? |
|---|
| Palopegteriparatide is given as a self-administered injection under the skin (subcutaneous injection) once a day using a pre-filled pen.[16]<br><br>After a minimum of seven days a blood sample will be taken to test how well the treatment is controlling blood calcium levels. Based on the results of the test the dose of palopegteriparatide may be adjusted; however, whatever the dose, the treatment will continue to be administered daily. If the dose is changed at any time, the blood test will be repeated within 7-14 days of the change so that the doctor can check how well the treatment is working and decide if any further dose adjustment is needed.<br><br>Palopegteriparatide treats the underlying cause of HypoPT but does not cure the disease, so will continue to be given by daily injection for as long as it is needed to control calcium levels in the blood.<br><br>People with HypoPT may remain on calcium and active vitamin D when starting palopegteriparatide but the requirement for these treatments is expected to decline as palopegteriparatide treatment is established, with many people receiving the drug no longer requiring the prior treatments in line with trial results. This will reduce the number of tablets that people with HypoPT need to take and reduce the risk of long-term harm associated with the current treatment. |

### 3d) Current clinical trials

| Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials. |
|---|
| Two clinical trials have investigated the efficacy (how well a treatment works) and safety of palopegteriparatide in adults with chronic HypoPT:<br><br>• PaTH Forward (NCT04009291) is a Phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel group 4-week trial (now completed) with an ongoing open-label extension (OLE) up to 266 weeks.[27],[28]<br><br>• PaTHway (NCT04701203) is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group 26-week trial (now completed) followed by an ongoing 156 -week OLE.[29]<br><br>This submission focuses on evidence from the Phase 3 PaTHway study. |

**PaTHway**

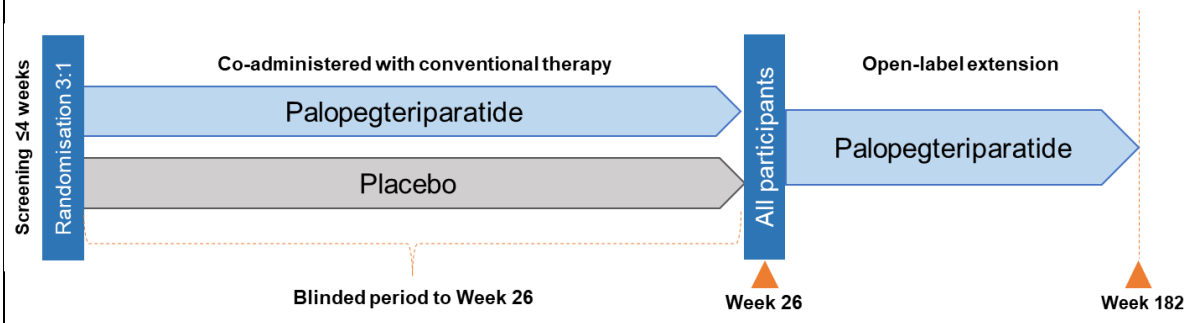
PaTHway is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group trial, investigating the safety and efficacy of palopegteriparatide in adults with chronic HypoPT, with an ongoing OLE (as of May 2025).

The primary objective of the PaTHway trial is to assess the treatment effect of daily palopegteriparatide on the amount of calcium in the blood, and the impact on therapeutic doses of active vitamin D and calcium after 26 weeks of treatment.

Participants were divided randomly into two groups in a ratio of 3:1. For the first 26 weeks of the study one group was given palopegteriparatide (61 participants) while the other group received a placebo (a substance with no medicinal activity that is given in an identical way to the medicine under investigation) (21 participants). The trial was 'double-blinded' meaning that neither the researchers nor the participants knew who was receiving palopegteriparatide and who was receiving placebo. The palopegteriparatide and placebo treatments were co-administered with conventional therapy (active vitamin D and calcium) which was given to treat the symptoms of hypocalcaemia.[30] A main aim of the study was to reduce the dose of conventional therapy if possible.

At Week 26 the trial changed to what is known as 'open label', meaning it became 'unblinded' allowing participants and researchers to know which treatment the participants were receiving. At this point, all the participants in the placebo group who continued into the OLE period were switched from placebo to palopegteriparatide, meaning that all participants in the OLE were receiving palopegteriparatide.

**Figure 1 PaTHway trial design**




Source: Adapted from the PaTHway Clinical Study Report.[30]

## 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The PaTHway study showed that **palopegteriparatide was effective at keeping blood calcium levels within the normal range and providing independence from therapeutic doses of calcium and active vitamin D, compared with placebo.** ('Independence' was defined as no longer needing active vitamin D and taking no more than 600 mg per day of calcium, an amount judged to be sufficient to meet the recommended intake for general health rather than a 'therapeutic' dose for treating HypoPT).[30]

- Around 79% (48 out of 61) of participants given palopegteriparatide for 26 weeks achieved normal blood calcium levels, no longer needed conventional therapy (active vitamin D and high-dose calcium) and were on a stable dose of the medicine. This compared with 5% (1 out of 21) of participants given placebo.[29]
- This effect was sustained: at 52 weeks 81% (63 out of 78) of participants treated with palopegteriparatide had normal blood calcium levels and no longer needed calcium and active vitamin D treatment.[31]

### 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Two generic tools were used to measure health related quality of life (HRQoL) in the PaTHway trial as well as a disease-specific tool called the Hypoparathyroidism Patient Experience Scale (HPES).

Treatment with **palopegteriparatide significantly improved HRQoL** in adults with chronic HypoPT:

- Disease-specific measures of symptoms, functioning and well-being across HPES-Symptom (physical [p=0.0038] and cognitive [p=0.0055]) and HPES-Impact (physical functioning [p=0.0046] and daily life [p=0.0061]) domains were significantly improved at Week 26, versus placebo.[29]
- Quality of life was also shown to be significantly improved when measured using the SF-36 physical functioning sub-scale. These improvements were sustained through one year of treatment (up to Week 52). [29],[31]

### 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

**Palopegteriparatide was well tolerated in the PaTHway trial, with most side effects being mild to moderate in severity**. No trial participants had to stop treatment due to side effects related to

palopegteriparatide.[29] The only serious side effect judged to be related to palopegteriparatide treatment was temporary and resulted from an inadvertent treatment interruption; palopegteriparatide treatment was later resumed in this individual without incident.

By Week 26, the most common side effects reported in the palopegteriparatide group were injection site reactions (31%; 19/61), headache (13%; 13/61) and paraesthesia (18%; 11/61).[29] The most common side effects in the placebo group were hypocalcaemia (low blood calcium [43%; 9/21]), fatigue (24%; 5/21) and paraesthesia and muscle spasms (14%; 3/21), each.[29]

By Week 52, side effects had been reported in 90% (72/80) of participants treated with palopegteriparatide. Most were mild or moderate (grades 1–2) and none reported during the open-label extension led to discontinuation of the trial or palopegteriparatide treatment.[31]

At Week 104, most side effects were mild or moderate, and no new safety signals were reported.[32]

**3h) Summary of key benefits of treatment for patients**

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Palopegteriparatide maintains PTH within the normal physiological range over 24 hours, and trial evidence showed that treatment with palopegteriparatide lead to maintained blood calcium levels within the normal range in the majority of individuals treated,[29],[31] reducing the risk of the debilitating symptoms that can result from hypocalcaemia.
    - Palopegteriparatide maintains PTH within physiological range over 24 hours, while having little or no effect on renal function.
- Treatment with palopegteriparatide resulted in independence from conventional therapy (defined as taking no active vitamin D and no more calcium than required for general good health) in the majority of individuals treated,[29],[31] reducing the risk of long-term complications associated with conventional therapy and also reducing the number of pills to be taken each day.
- Treatment with palopegteriparatide significantly improved HRQoL.[29],[31]

**3i) Summary of key disadvantages of treatment for patients**

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

- Patients treated with palopegteriparatide may experience injection site reactions, however these are predominantly mild and short-lasting, and in the trials did not lead to discontinuation of treatment

**3i) Value and economic considerations**

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

**Cost-effectiveness modelling approach**

A health economic model was developed to compare the cost and health benefits of palopegteriparatide against conventional therapy (active vitamin D and calcium) in patients with chronic HypoPT whose disease is not adequately controlled on conventional therapy.

Patients who were not adequately controlled on conventional therapy are assumed to be adequately controlled on palopegteriparatide. Patients with adequately controlled disease experience improved quality of life, reduced symptoms and risk of developing complications and death in comparison to patients with not adequately controlled disease based on data from the clinical trial and real-world evidence.

**Costs**

The costs considered within the analysis include drug costs, administration costs, disease management costs, and the costs associated with managing adverse events (AEs) and complications.

**Uncertainty**

Whilst the best available evidence was used to inform the economic modelling, it did require some assumptions particularly as patients with chronic HypoPT are expected to remain on treatment for a long period of time, potentially the rest of their life. A key assumption that underpins the submission is that the evidence from PaTHway is generalisable to UK patients whose disease is not adequately controlled on conventional therapy. This was considered appropriate as patients in PaTHway met the definition of not adequately controlled outlined in section 2c. Clinical experts also validated that the patients in the trial were comparable to patients in the UK with not adequately controlled disease and that the trial is reflective of UK clinical practice.

**Benefits not captured in the economic model**

There were benefits associated with palopegteriparatide that it was not possible to capture either due to the NICE methods for economic modelling or to ensure there was no risk of overestimating the benefit.

- **Cognitive impairment :** HypoPT is associated with many cognitive symptoms, such as brain fog, which can cause high levels of quality of life burden for patients. Trial analyses have shown EQ-5D to be insensitive to change in cognitive status, in line with other clinical domains, therefore suggesting that the impact of cognitive burden is not fully captured within the health state utilities

- **Reduction in pill burden:** Patients have a high number of pills to take on a daily basis – 27% take three to five pills every day to manage their HypoPT – and more than a quarter find the number of pills they are required to take challenging. [5]Palopegteriparatide could reduce the number of pills that patients need to take to manage their disease.

- **Impact of the disease on caregivers:** In line with NICE methods, the model focuses only on the patient burden in terms of quality of life and costs incurred by the NHS from their treatments and care. However, caregivers of patients with HypoPT also experience considerable burden[11] proportional to disease severity, which is not included in the model. In this regard the economic analysis can be said to be an underestimate of the true value of palopegteriparatide, which significantly reduces disease severity.[29]

- **Work impairment:** HypoPT also has a significant impact on both patient and caregiver employment and productivity proportional to disease severity.[11] The economic impact of this phenomenon on patients, their caregivers, or society is not included in the model. Therefore, in this regard, the economic analysis can further be said to be an underestimate of the true value of palopegteriparatide.

## 3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Palopegteriparatide utilises Ascendis' innovative Transcon technology platform. Transcon or "transient conjugation," refers to the unique ability to temporarily (transiently) link an inert carrier to a parent drug with known biology. HypoPT is the last remaining endocrine condition without a replacement therapy and the Transcon technology has made this possible.

Palopegteriparatide is the first replacement therapy for PTH and has been designed to provide stable PTH levels within the physiological range (the 'normal' range in a healthy person) for 24 hours, comparable to providing PTH by continuous infusion.[26]

## 3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

| Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here |
|---|
| It is expected that more women than men will be treated with palopegteriparatide; this is because post-surgical HypoPT is more common in women than men as women are more likely to have thyroid disease and hence undergo thyroidectomy.[33] |

## **SECTION 4:** Further information, glossary and references

### 4a) Further information

| Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.<br>Where possible, please provide open access materials or provide copies that patients can access. |
|---|
| **Further information on NICE and the role of patients:**<br><br>• Public Involvement at NICE Public involvement \| NICE and the public \| NICE Communities \| About \| NICE<br>• NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance \| Help us develop guidance \| Support for voluntary and community sector (VCS) organisations \| Public involvement \| NICE and the public \| NICE Communities \| About \| NICE<br>• EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/<br>• EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf<br>• National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/<br>• INAHTA: http://www.inahta.org/<br>• European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf<br><br>**Further information on HypoPT and palopegteriparatide:**<br><br>• NHS information on HypoPT: NHS Health A to Z: Hypoparathyroidism<br>• Patient organisation providing information about HypoPT and its treatment: Parathyroid UK<br>• Document used by healthcare professionals that explains how to use and prescribe palopegteriparatide: Yorvipath Summary of Product Characteristics |

- Package leaflet: Information for the patient about palopegteriparatide: Yorvipath Patient Information Leaflet

**4b) Glossary of terms**

| | |
|---|---|
| **Cardiovascular system** | Comprises the heart, arteries, veins and capillaries. |
| **Double-blind** | A design often used in clinical trials meaning that neither the researchers nor the participants knew which treatment group (e.g. a particular drug or placebo) a participant was assigned to. A double-blind approach is used so that knowledge of which treatment (or placebo) is being received doesn't affect (bias) the assessment of the drug. |
| **Efficacy** | How well a treatment works (this term is usually used when reporting clinical trial data). |
| **Endocrine** | Relating to or denoting glands which secrete hormones or other products directly into the blood. |
| **EQ-5D** | Health-related quality of life assessment tool that comprises a short descriptive questionnaire and a visual measurement scale that assess five HRQoL areas (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). |
| **European Medicines Agency (EMA)** | The regulatory body that evaluates medicines to see if they should be licensed for use in the European Union. |
| **Health-related quality of life (HRQoL)** | An individual's or a group's perceived physical and mental health over time. |
| **Hyperphosphataemia** | High level of phosphorus in the blood. |
| **Hypocalcaemia** | Low level of calcium in the blood. |
| **Hypoparathyroidism Patient Experience Scale (HPES)** | A disease-specific patient-reported outcome measure used to capture the HypoPT-specific burden of symptoms and the impact experienced by individuals with HypoPT. |
| **Incremental cost-effectiveness ratio (ICER)** | Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition. |
| **Injection site reaction** | A local adverse event that can occur after receiving a shot of medicine; can include pain, itching, swelling or redness around the site of injection. |
| **Marketing authorisation** | Approval from a regulatory body to market a medicine in a specified country (e.g. Great Britain) or region (e.g. European Union). |
| **Medicines and Healthcare products Regulatory Agency (MHRA)** | The regulatory body that regulates medicines, medical devices and blood components for transfusion in the UK. |
| **Orphan designation** | A status given to certain drugs called orphan drugs, which show promise in the treatment, prevention or diagnosis of an orphan disease. |
| **Orphan disease** | A rare disease or condition that affects no more than five per 10,000 individuals in the UK.[34] |
| **Phase 3 trial** | A late-stage clinical trial that is often used as the primary source of data for applications for marketing authorisation of a drug. |
| **Placebo** | A 'dummy drug' given to participants in the placebo control group of a clinical trial. A placebo is designed to look the same as the drug being |

| | |
|---|---|
| | investigated so that people do not know if they received the actual drug or the placebo. A placebo is given to compare the effects of receiving the drug being investigated versus no drug (over and above any 'placebo effect'). |
| **Quality-adjusted life year (QALY)** | A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines. |
| **Randomised** | When participants in a clinical study are randomly assigned to a group in the trial (e.g. the group being given the medicine, or the group being given a placebo). |
| **Hormone receptor** | A molecule on the surface of or inside a cell that binds to a specific hormone molecule. |
| **SF-36** | Patient questionnaire that covers a range of areas (domains) of HRQoL. |
| **Side effect** | An effect, whether therapeutic or adverse, that is unintended; although the term is predominantly used to describe adverse effects, it can also apply to beneficial, but unintended, consequences of the use of a drug. |
| **Subcutaneous injection** | An injection given just under the skin (into the fatty layer of tissue) using a short needle. |

**4c) References**

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:


1. Ascendis Pharma. United Kingdom's MHRA Approves YORVIPATH® (palopegteriparatide) in Great Britain for the Treatment of Adults with Chronic Hypoparathyroidism. 2024; https://investors.ascendispharma.com/news-releases/news-release-details/united-kingdoms-mhra-approves-yorvipathr-palopegteriparatide.
2. GOV.UK. Medicines & Healthcare products Regulatory Agency. Marketing authorisations granted 15 to 30 April 2024. 2024; https://assets.publishing.service.gov.uk/media/663df12eae748c43d37938de/marketing-authorisations-granted-15-to_30-april-2024.pdf.
3. GOV.UK. Orphan Register. 2025; https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register.
4. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nat Rev Dis Primers.* 2017;3:17080.
5. Parathyroid UK. Living with chronic hypoparathyroidism. 2017; https://www.parathyroiduk.org/wp-content/uploads/2018/05/Living-with-chronic-hypoparathyroidism-final-report.pdf.
6. Endocrinology Sf. You and your Hormones: Parathyroid glands. 2022; https://www.yourhormones.info/glands/parathyroid-glands/.
7. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract.* 2014;20(7):671–679.
8. Brandi ML, Bilezikian JP, Shoback D, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab.* 2016;101(6):2273–2283.
9. Bjornsdottir S, Ing S, Mitchell DM, et al. Epidemiology and Financial Burden of Adult Chronic Hypoparathyroidism. *J Bone Miner Res.* 2022;37(12):2602–2614.
10. Ascendis Pharma. Chronic Hypoparathyroidism Report. Data on File. 2024.
11. Siggelkow H, Clarke BL, Germak J, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. *Clin Endocrinol (Oxf).* 2020;92(2):159–168.

12. Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. *J Bone Miner Res.* 2022;37(12):2568–2585.
13. Sinnott B. Hypoparathyroidism – Review of the Literature 2018. *Rare Disord Diagn Ther.* 2018;4(12).
14. Astolfi D, Murphy D, Sanders B, et al. The Voices of Hypopara Survey: Journey of patients living with hypoparathyroidism. 2020.
15. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. *J Bone Miner Res.* 2013;28(11):2277–2285.
16. GOV.UK. Ascendis Pharma.Yorvipath SmPC. 2024; https://products.mhra.gov.uk/substance/?substance=PALOPEGTERIPARATIDE.
17. Ascendis Pharma. KOL Summary Report. Data on File. 2025.
18. Brod M, Waldman L, Smith A, Karpf D. MON-LB092 Understanding the Patient-Centered Impact of Hypoparathyroidism on Functioning and Well-Being. *J Endrocr Soc.* 2019;3(1).
19. Bilezikian JP, Khan A, Potts JT, Jr., et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. *J Bone Miner Res.* 2011;26(10):2317–2337.
20. Büttner M, Musholt TJ, Singer S. Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review. *Endocrine.* 2017;58(1):14–20.
21. Arlt W FC, Callies F, Reincke M, Schneider P, Timmermann W, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. *Eur J Endocrinol.* 2002 Feb;146(2):215–22.
22. Hillary SL CJ, Wadsley J, Newell-Price JD, Brown NJ, Balasubramanian SP. Quality of Life in Post-Surgical Hypoparathyroidism (PoSH) in Thyroid and Parathyroid Surgery. *World J Surg.* 2022 Dec;46(12):3025–33.
23. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine CM. Low health-related quality of life in hypoparathyroidism and need for PTH analog. *Endocr Connect.* 2022;11(1).
24. Ascendis Pharma. People with Hypoparathyroidism (hypoPT): Treatment Burden Survey (Data on File). 2024.
25. Waldman LT BM, Smith A, Karpf D. PDB115 Impacts of hypoparathyroidism on patient work productivity and out-of-pocket costs. *Value in Health.* 2019 May;22:S159.
26. Karpf DB, Pihl S, Mourya S, et al. A Randomized Double-Blind Placebo-Controlled First-In-Human Phase 1 Trial of TransCon PTH in Healthy Adults. *J Bone Miner Res.* 2020;35(8):1430–1440.
27. Khan AA, Rejnmark L, Rubin M, 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–e385.
28. ClinicalTrials.gov. (NCT04701203) A Trial Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Daily in Adults With Hypoparathyroidism (PaTHway). 2025; https://clinicaltrials.gov/study/NCT04701203.
29. Khan AA, Rubin MR, Schwarz P, 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.
30. Ascendis Pharma. PaTHway (TCP-304) Clinical Study Protocol v7.0. Data on File. 2023.
31. Clarke BL, Khan AA, Rubin MR, 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):951–960.

32. Schwarz P, Rejnmark L, Gosmanova E, et al. Sustained improvement in renal function with palopegteriparatide in adults with chronic hypoparathyroidism: 2-year results from the phase 3 PaTHway trial. *Endocrine Abstracts.* 2024;99.
33. Ascendis Pharma. Clinical Study Report. TransCon PTH TCP-304 (Palopegteriparatide; PaTHway). Data on File. 2022.
34. GOV.UK. Medicines & Healthcare products Regulatory Agency.Orphan medicinal products. 2021; https://www.gov.uk/guidance/orphan-medicinal-products-in-great-britain.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

# Clarification questions

**June 2025**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6380 palopegteriparatide clarification questions | V1.0 | Yes | June 2025 |

**Notes for company**

**Highlighting in the template**

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

**To delete grey highlighted text, click anywhere within the text and press DELETE.**

# Section A: Clarification on effectiveness data

## *Decision Problem*

**A1. Priority question: Please supply data and/or analyses for all outcomes listed in the decision problem and scope (CS Table 1) that were analysed in PaTHway. Please note that potential double counting is not grounds for not presenting the evidence. In particular, please supply data for:**

a. **Physical and cognitive symptoms**

b. **Renal function (eGFR)**

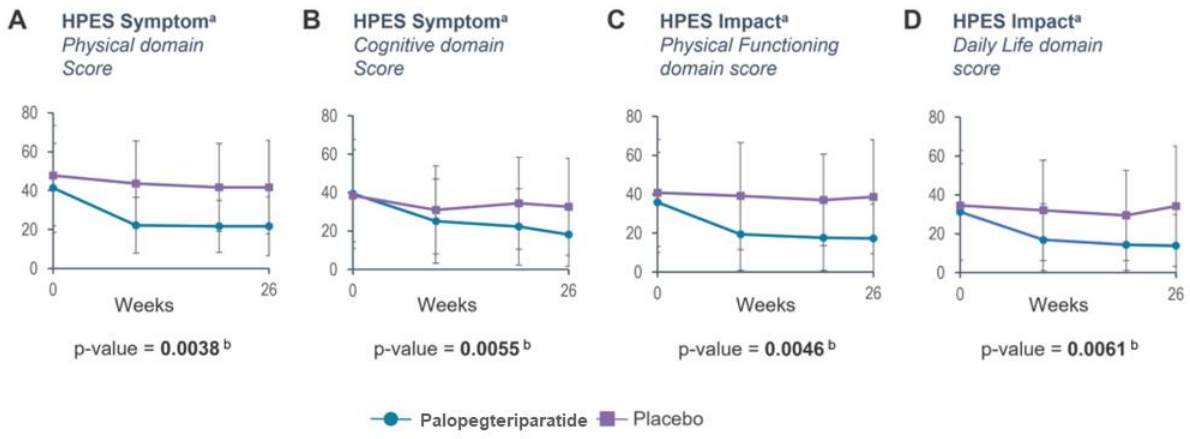
**Response:** In the PaTHway trial, change in physical and cognitive symptoms is measured using the disease specific quality of life tool, HPES. Section 2.6.2.1 of the company submission presents these results, demonstrating that treatment with palopegteriparatide significantly improved disease-specific measures of symptoms, functioning and well-being across HPES-Symptom (physical [p=0.0038] and cognitive [p=0.0055]) and HPES-Impact (physical functioning [p=0.0046] and daily life [p=0.0061]) domains at Week 26, versus placebo (see Table 1 and Figure 1

below which represent Table 14 and Figure 11 in the CS).[1,2] The minimal clinically important difference (MCID) scores for selected HPES domains are as follows: Physical Domain score: -8.7; Cognitive Domain score: -10.0; Physical Functioning score: -15.0; Daily Life domain score: -15.6.

**Table 1: PaTHway - improvement from baseline to Week 26 in HPES-Impact and Symptom scores (ITT population)**

| HPES scale† | Palopegteriparatide (n=61) | Placebo (n=21) |
|---|---|---|
| **HPES-Impact scale** | | |
| Daily life domain, n | 59 | 19 |
| Mean (SD) | −16.4 (19.6) | −2.9 (21.8) |
| Physical functioning domain, n | 59 | 19 |
| Mean (SD) | −17.7 (20.4) | −5.3 (21.5) |
| Psychological well-being domain, n | 54 | 17 |
| Mean (SD) | −14.2 (19.4) | −0.9 (21.0) |
| Social life and relationship domain, n | 59 | 19 |
| Mean (SD) | −13.5 (20.8) | −3.4 (21.6) |
| Total HPES-Impact score, n | 59 | 19 |
| Mean (SD) | −15.7 (18.0) | −3.9 (19.0) |
| **HPES-Symptom scale** | | |
| Physical domain, n | 59 | 19 |
| Mean (SD) | −19.3 (17.9) | −8.4 (23.7) |
| Cognitive domain, n | 59 | 19 |
| Mean (SD) | −21.0 (24.7) | −7.4 (14.2) |
| Total HPES-Symptom score, n | 59 | 19 |
| Mean (SD) | −20.2 (19.5) | −7.9 (18.0) |

**Figure 1: PaTHway - Treatment effecr of palopegteriparatide on HPES scores up to Week 26**




[a]Lower scores reflect improvement in HypoPT-related symptoms, functioning and well-being; [b]p-values are from the analysis of covariance models assessing change from baseline at Week 26 for palopegteriparatide versus placebo, with aetiology of HypoPT as fixed effects and baseline HPES domain scores as covariates; Negative error bars (SD) are not displayed for values less than zero.
Abbreviations: HPES, Hypoparathyroidism Patient Experience Scale; ITT, intent-to-treat
Source: Khan et al 2023[2]

With regard to renal function (A1b), a *post-hoc* analysis was conducted to examine the impact of palopegteriparatide treatment on renal function in adults with chronic HypoPT in PaTHway.[3]

At baseline, mean eGFR was numerically lower in participants randomised to receive palopegteriparatide (67.3 mL/min/1.73m$^2$) versus placebo (72.7 mL/min/1.73m$^2$) and the proportion of participants with eGFR <60 mL/min/1.73m$^2$ (impaired renal function) was numerically higher in the palopegteriparatide (31.1%) versus placebo (19.1%) group.[3]

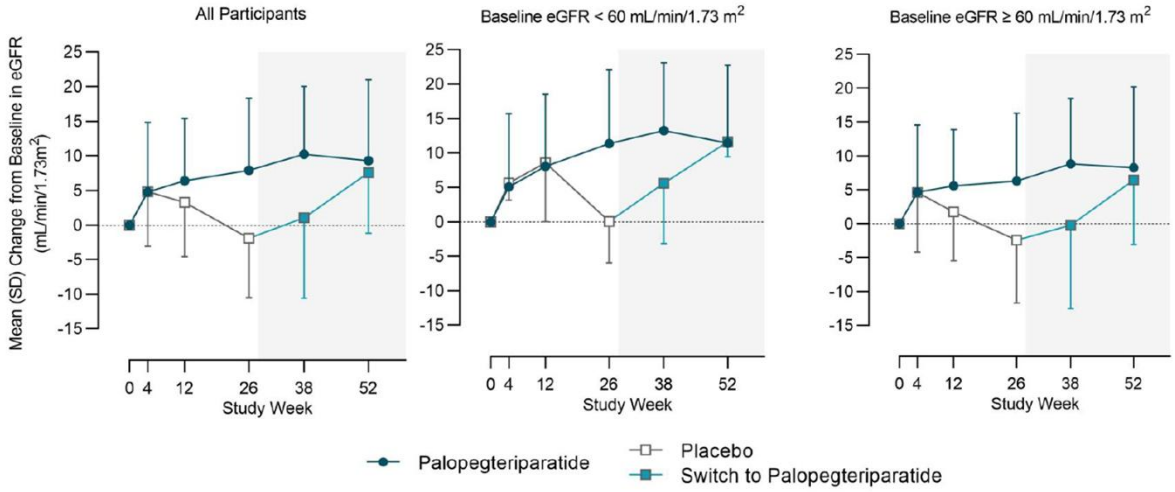
Palopegteriparatide treatment resulted in significant and sustained improvement in renal function:

- From baseline to Week 26, mean (SD) eGFR increased by 7.9 (10.4) mL/min/1.73m$^2$ in the palopegteriparatide group and decreased by -1.9 (8.6) mL/min/1.73 m$^2$ in the placebo group (P<.001 for the difference between groups).

- Treatment with palopegteriparatide over 52 weeks resulted in a mean (SD) increase in eGFR of 9.3 (11.7) mL/min/1.73m$^2$ from baseline (P<0.0001). The mean (SD) eGFR increased by 7.6 (8.7) mL/min/1.73m$^2$ (P<0.01) from

baseline to Week 52 for participants who switched from placebo to palopegteriparatide treatment at Week 26.

**Figure 2: PaTHway- Mead (SD) changes from baseline in eGFR through Week 52 for the overall popuation and by baseline eGFR sub-group**




eGFR, estimated glomerular filtration rate; SD, standard deviation
Source: Rejnmark *et al.* 2024[3]

At Week 52, 64% (39 of 61) of participants randomised to palopegteriparatide had a clinically meaningful change in eGFR of ≥5 mL/min/1.73 $m^2$ and 43% (26 of 61) had an increase in eGFR of ≥10 mL/min/1.73 $m^2$ from baseline (Figure 2).[3] eGFR response rates in participants randomised to placebo increased from 26% at Week 26 (end of the blinded period) to 57% at Week 52 after switching to palopegteriparatide.

**A2. Priority question: Subgroup data is not reported in the submission, but has been presented in PaTHway CSR. Please discuss the subgroup analysis findings for subgroups set out in the decision problem (CS Table 1):**

a. **By eGFR level**

b. **By disease severity**

c. **If feasible, please present subgroup analyses by gender, given statement on equality issues**

**Response:** The pre-specified subgroups analysed in PaTHway and reported in the CSR were age, prior treatment with PTH therapy, gender, aetiology, duration of HypoPT, region and menopausal status among females. The subgroup analysis by gender is presented in Appendix A.

Disease severity and eGFR level were not pre-specified subgroups in the trial however it is appreciated that they were identified as subgroups of interest in the appraisal final scope. Analysis of patients meeting the multi-component endpoint has therefore been provided for the below subgroups in Appendix A.

- Baseline GFR<60 (mL/min/1.72m$^2$)
- Baseline GFR>=60 (mL/min/1.72m$^2$).
- Baseline HPES-Symptom Total Score <= 20
- Baseline HPES-Symptom Total Score > 20 - <= 40
- Baseline HPES-Symptom Total Score > 40 - <= 60
- Baseline HPES-Symptom Total Score > 60

It should be noted however that a minimum eGFR of ≥ 30 mL/min/1.73 m2 during screening was required for inclusion in the trial so there are no patients with an eGFR <30 in the trial.

With respect to disease severity, there is no clinically validated or routinely recorded severity classification for HypoPT. Therefore to undertake subgroup analysis based on severity, the HPES-Symptom total score has been used to represent severity level (see B2e for further information regarding this).

## *PaTHway Trial*

**A3. In PaTHway placebo patients had a large mandatory decrease in their active vitamin D dose at start of treatment. Please comment on:**

a. **The impact this had on maintaining calcium level and calcium dosage,**

b. **How this represents a fair comparison between palopeg and conventional therapy, given the change to conventional therapy**

**Response:** The decrease in active vitamin D was part of the protocol designed to assess the benefit: risk profile of palopegteriparatide following discussions with regulatory agencies.

Both arms of the trials used the same standardised titration algorithm method based on serum calcium levels to ensure therapy changes were driven by protocol and were not at the free will of the investigator.

Serum calcium levels in the placebo arm remained within the target range defined by international guidelines (above 7.8mg/dL)[4] through frequent monitoring and responsive dose adjustments**.** This proactive approach to monitoring was important to ensure patient safety and stability, mitigating of the risk of hypocalcaemia. The titration algorithm allowed for conventional therapy (CT) doses to be increased where there was persistent hypocalcaemia for less than 7 days since the last dose change of the injectable therapy; therefore, it is not the case that CT would always be decreased over time.

All participants were on CT at baseline, so the attempted down titration in both study arms was assessing their ability to become independent from CT (and the effectiveness of palopegteriparatide to replace the parathyroid function) required an attempt at discontinuation in both arms of the study. Otherwise, it would have been a foregone conclusion that every placebo participant would have failed the primary endpoint.

As a result of the titration protocol described above, in both treatment arms, patients maintained mean serum calcium levels within the reference range, in line with the

therapeutic guidelines for optimising treatment with CT. Furthermore, this standardised approach also supported the maintenance of blinding throughout the trial, supporting overall trial integrity.

**A4. Although a goal of palopeg may be to become independent of CT, that is not the goal of CT. Please comment on the value of "independence from CT":**

a. **As an outcome for evaluating palopeg improvements when compared to CT as it would be used in the NHS,**

b. **In terms of its applicability to the NHS setting.**

c. **Please provide a justification for its prominent use in this appraisal.**

**Response:** The goal of treatment with palopegteriparatide is to replace the parathyroid function and restore normal calcium homeostasis, removing the need of CT typically given for symptomatic relief. Achievement of independence from CT is used as surrogate for restoration of physiological PTH function, enabling evaluation of palopegteriparatide's effectiveness as a replacement hormone.

Achievement of independence from CT is also valuable in that it removes the risk of long-term complications, such as renal damage, associated with CT. This is of particular relevance to patients who are not adequately controlled on CT as they are more likely to develop complications, which have a significant and noticeable impact on HRQoL and healthcare resource.[5] Furthermore, independence from CT allows for a reduction in pill burden, improved physiological regulation and possibly fewer risks associated with high-dose calcium and vitamin D such as hypercalciuria.

In the NHS setting, independence from CT will allow for a simplified treatment regime that could provide substantial benefits to both the patient and NHS. It could help to improve treatment adherence, reduce patient inconvenience, improve quality of life especially in those who are not adequately controlled on CT. As mentioned above, this can reduce the long-term risks and costs associated with complications of CT in particular healthcare resource costs. Independence from CT has the

potential to align with broader NHS objectives around patient-centred care and optimised long-term management.

Independence from CT is prominently used within this appraisal because, as mentioned, it serves as a surrogate for restoration of physiological PTH function, which is central to the drug's benefit. It offers a measurable, objective and clinically relevant endpoint that distinguishes it from CT, allowing a clear assessment of its added value. While CT can be effective in maintaining calcium levels in some patients, it does not restore hormonal regulation, therefore, independence from CT is not only a relevant outcome but a necessary one to fully capture the therapeutic potential of palopegteriparatide and to justify its use and cost in NHS care pathway.

**A5. Please state the rationale for prohibiting thiazide diuretics in the PaTHway trial. Please also state how many patients discontinued taking a thiazide diuretic at least 4 weeks prior to the baseline Screening 24-hour urine collection scheduled during the week prior to Visit 1, and how many were not randomised because they were still taking a thiazide diuretic.**

**Response:** Thiazide diuretics were prohibited medications in the PaTHway trial due to their potential confounding effect on the assessment of endpoints, in particular, urinary calcium.

The use of thiazide diuretics in the context of the trial was not considered necessary as they are commonly prescribed to treat hypercalciuria (abnormally high levels of calcium in the urine) in patients with HypoPT. Since palopegteriparatide decreases hypercalciuria, the concomitant use of thiazide diuretics (for the purpose of decreasing hypercalciuria in patients with HypoPT) is less likely to be needed with palopegteriparatide treatment.

Within the PaTHway trial, 11 of the 82 patients (13.4%) had a record of prior thiazide use. However, it is not possible to determine from this data whether these medications were stopped in response to the trial exclusion criteria or reflect prior use unrelated to the trial participation. No specific variable captures this reason for

discontinuation or its timing relative to screening. No patients were not randomised due to still taking a thiazide diuretic.

**A6. Given that no results have been reported in the submission which are based on a conservative approach to imputing missing data, please provide analyses of all secondary outcomes (including for the EQ-5D results reported on p96 of the submission) using a baseline-observation-carried-forward approach to missing data.**

**Response:** Given this is not a priority question, it has not been possible to undertake this analysis within the time period. However, given there was very limited missing data in the blinded period of the PaTHway trial as outlined below therefore use of the baseline-observation-carried-forward approach is not expected to yield different results regarding the estimated treatment effect.

For key secondary efficacy endpoints with prespecified hierarchical testing strategy implemented for trial HPES Symptom - Physical Domain Score and Cognitive Domain Score and HPES Impact - Physical Functioning Domain Score and Daily Life Domain Score, all 61/61 patients in the palopegteriparatide arm and 21/21 patients in the placebo arm completed questionnaires at baseline; and 59 (97%) patients in the palopegteriparatide arm and 19 (90%) patients in the placebo arm completed questionnaires at Week 26. The percentage of patients who completed the Week 26 was 90% or higher. The % missing for EQ-5D is the same as described above for HPES. Please see Appendix B for analyses of the secondary outcomes.

**A7. Please comment on the viability of patient blinding being adequately maintained during the PaTHway trial, given the large difference between the trial arms in the level of independence from calcium and vitamin D (CS Figures 15 and 16).**

**Response:** Blinding was well managed through protocol design and standardised procedures through titration algorithm of CT driven by serum calcium values

although it is acknowledged there may have been a degree of functional unblinding as participants and investigators were aware of the CT doses and/or serum calcium levels.

Although no placebo CT was administered, both arms followed the same algorithm-based titration of treatment, and investigators followed strict rules and could not make subjective decisions, which helped to maintain investigator blinding. Patients in the treatment group were more likely to reduce or stop supplements, but all patients were blinded to their treatment assignment. Blinding in the comparator arm was maintained, and these steps were taken to reduce potential bias. This allowed maintenance of the trial's structure, which helped to protect the validity of key outcomes. Furthermore, any functional unblinding that did occur, was considered to have had minimal impact on the magnitude of differences in scores observed between the palopegteriparatide and placebo arms. Any initial inflation of responses on the PRO measures due to an immediate euphoria effect of suspecting randomisation to the palopegteriparatide arm would likely diminish over the 26-week blinded treatment period and be replaced by patient reporting of their actual experience relating to symptoms and broader life impacts. Secondly, evidence from recently published studies suggests that arguments to support bias associated with intended or unintended unblinding for reporting of PRO data in clinical trials are not supported by empirical evidence.

**A8. Figure 10 of the CS reports 22 screen failures. Please provide a breakdown of the reasons why these 22 patients were not randomised. Please also state why two patients randomised to palopeg were not treated.**

**Response:** Please see Table 2 below for a breakdown of the reasons for the initial 22 screen failures reported in the CS. Please note that subjects can screen failure due to one or more criteria. The two patients who did not receive drug after randomisation were due to early discontinuation from trial prior to first dose: one subject due to "withdrawal by subject" and one subject due to "other: recurrence of thyroid cancer."

**Table 2: Inclusion and exclusion criteria for reasoning of screen failure in PaTHway trial**

| Reason for screen failure | Total Number (N=22) N (%) |
|---|---|
| Thyroid-stimulating hormone (TSH) outside of normal laboratory limits within the 6 weeks prior to Visit 1; if on suppressive therapy for a history of thyroid cancer, TSH level must be >=0.2 mIU/mL | 13 (59.1) |
| Chronic/severe cardiac disease within 26 wks prior to Screening such as congestive heart failure, myocardial infarction, severe/uncontrolled arrhythmias, bradycardia, symptomatic hypotension, etc. | 3 (13.6) |
| BMI outside of range 17-40kg/m^2 at screening | 3 (13.6) |
| Other reasons that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule | 2 (9.1) |
| Elevated 24-hour uCa excretion of >=125 mg/24h (on a sample collected within 52 weeks prior to/during Screening). | 2 (9.1) |
| Any disease/condition that may make subject unlikely to fully complete the trial or any condition with undue risk from IP/procedures, incl. treated malignancies likely to recur within 3.5-year of trial | 1 (4.5) |
| Likely to be non-compliant with respect to trial conduct | 1 (4.5) |
| Unstable thyroid hormone replacement therapy | 1 (4.5) |
| Unable and/or unwilling to provide written and signed ICF in accordance with GCP | 1 (4.5) |

**Abbreviations**: ICF, informed consent form; GCP, good clinical practice; uCa, urinary calcium; TSH, thyroid stimulating hormone

## A9. Please provide all the data tables listed in Section 16 of the PaTHway trial clinical study report.

**Response:** Please see Appendix C for the data tables listed in Section 16 of the PaTHway trial clinical study report. Please note, this is a large appendix with over 7,000 pages.

## *Other trials*

**A10. Priority question: Please provide a summary of the PaTH Forward, PaTH Forward OLE and the PaTHway OLE trial results. In particular:**

a. **Please present results for all scope outcomes, including serum phosphate and renal function (eGFR)**

b. **Please supply all publications arising these trials, or indicate where they can be found**

c. **Please supply CSRs for these trials**

Results for all scope outcomes have been provided in Appendix D from publications. Please note, further data can be provided from CSRs however, this data is over a large volume of pages.

The CSR for PaTH Forward is provided as Appendix D along with the publications arising from the PaTH Forward, PaTH Forward OLE and the PaTHway OLE. Interim CSRs and some scope outcomes are not currently available for the OLEs as the trials are currently ongoing; the CSR for the PaTHway OLE is expected to be available late 2025 and early 2026 for the PaTHForward OLE.

**A11. Priority question: For the open label extension (OLE) trials please supply data on:**

a. **How many initial primary outcome responders maintained a response at each timepoint**

b. **How many patients withdrew or were lost to follow-up, and what were the reasons (for the patients who withdrew).**

c. **How missing data were handled.**

d. **Whether any stopping rules were applied.**

**Response:Error! Reference source not found.** Table 3 below shows the number and proportion of responders that maintained a response at each timepoint within PaTHway and PaTH Forward trials (based on the ITT population).

**Table 3: Response to primary endpoint at each timepoint for PaTHway and PaTH Forward**

| Trial | Visit | Normocalcaemia | No active vit D | Calcium ≤600 mg | Stable dose 4 wks* | All criteria |
|---|---|---|---|---|---|---|
| PaTHway | Week 26 | 49/61 (80.3%) | 60/61 (98.4%) | 57/61 (93.4%) | 57/61 (93.4%) | 48/61 (78.7%) |
| | Week 52 | 50/59 (84.7%) | 59/59 (100%) | 57/59 (96.6%) | N/A | 48/59 (81.4%) |
| | Week 104 | 62/76 (81.6%) | 76/76 (100%) | 74/76 (97.4%) | N/A | 61/76 (80.3%) |
| | Week 156 | 64/73 (87.7%) | 73/73 (100%) | 70/73 (95.9%) | N/A | 61/73 (83.6%) |
| | | | | | | |
| **Trial** | **Visit** | **Normocalcaemia** | **No active vit D** | **Calcium ≤1000 mg**** | **Stable dose 4 wks** | **All criteria** |
| PaTH Forward | Week 4 | 38/44 (86.4%) | 43/44 (97.7%) | 41/44 (93.2%) | N/A | 22/44 (50.0%) |
| | Week 84 | 32/42 (76.2%) | 42/42 (100%) | 54/58 (95.2%) | N/A | 28/42 (66.7%) |
| | Week 162 | 54/56 (96.4%) | 55/56 (98.2%) | 51/56 (91.1%) | N/A | 49/56 (87.5%) |
| | Week 214 | 55/56 (98.2%) | 53/56 (94.6%) | 53/56 (94.6%) | N/A | 51/56 (91.1%) |

* From Week 26 onwards, the "all criteria" composite endpoint no longer included the requirement for a stable palopegteriparatide dose in the 4 weeks prior to assessment. Therefore, values reported for "all criteria" beyond Week 26 reflect all other endpoint components only

**From week 162 and 214, this endpoint was updated to 600mg in line with PaTHway trial

Six patients withdrew from the PaTHway OLE with all except one, due to withdrawal by subject. Where reasons were provided these were: relocation to another country, wanting to conceive, family emergency, feeling overwhelmed by new clinical situation and wanting to join another clinical study. The other patient who discontinued trial early was due to pregnancy. No patients were lost to follow-up. Two patients withdrew from the PaTH Forward OLE. One withdrew due to withdrawal by subject and the other withdrew due to protocol violation. No patients were lost to follow up.

Missing and incomplete data was identified through the study data quality review plan. Subjects with missing data for key secondary endpoints had their post-baseline data imputed using two multiple imputation methods:

- Under the assumption of missing at random (MAR), the multiple imputation model was stratified by treatment group. "Missing at random" meant that the missing data mechanism was assumed not to depend on unobserved missing values but could depend on any other available information collected in the trial (Schafer 1997, Schafer 1999).

- Under the assumption of missing not at random (MNAR), a copy reference imputation method was used, whereby off-treatment missing data were imputed based on the model built from the placebo group.

If any of the HypoPT disease history–related dates were partially missing, they were imputed using the following rules:

- If only the day was missing, the 15th was imputed.
- If both the day and month were missing, June 15th was imputed.
- If the year was missing, no imputation was performed, and the date remained missing.
- If the resulting imputed date fell after the informed consent form (ICF) date, the ICF date was assigned as the imputed date.

To impute missing birth dates, the following rules were applied:

- If the day was missing, the 15th was imputed.
- If both the day and month were missing, June 15th was imputed.
- If the year was missing, no imputation was performed, and the date remained missing.

The following conventions were used to impute missing portions of dates for adverse events and concomitant medications.

**Missing Start Dates**

- If the day was unknown:
    - If the month and year matched the month and year of the first dose of blinded study drug in this study, the day of the first dose date was imputed.
    - Otherwise, the first day of the month was assigned.
- If both day and month were unknown:
    - If the year matched the year of the first dose of blinded study drug in this study, the day and month of the first dose date were imputed.
    - Otherwise, January 1st was assigned.
- If the year was unknown, the date was not imputed and was assigned as missing.
- If the imputed start date was later than the end date, the start date was set to be the same as the end date.

**Missing End Dates (Not Ongoing)**

- If the day was unknown, the last day of the month was assigned.
- If both day and month were unknown, December 31st was assigned.
- If the year was unknown, the date was not imputed, was assigned as missing, and the event was considered ongoing.
- If the resulting imputed end date was after the study completion, discontinuation, or data cutoff date, the imputed end date was set to the earliest of those three dates.

If the causal relationship to the study drug was missing for an adverse event (AE) that started on or after the date of the first dose of blinded study drug, a causality of 'R' was assigned. The imputed values for the causal relationship to the study drug were used in the incidence summary; however, the values were shown as missing in the data listings.

For lab data, if the raw data was “<xx”, then the imputed value was 0.9*xx. If the raw data was “>xx”, then the imputed value was 1.1*xx. For PK data, if the raw data was “<xx” or “<BLQ”, then the imputed value was 0. The imputed zero would then be used for summary statistics with geometric mean and geometric CV% reported as NC (Not Calculated).

Participant level stopping rules were applied in the event of the following:

- Evidence of a severe hypersensitivity to palopegteriparatide
- Confirmed neutralizing anti-PTH antibodies that correlate with reduced PD response
- Suspicion of osteosarcoma (e.g., persistent localized pain or occurrence of a new soft tissue mass tender to palpation that could be consistent with osteosarcoma, in association with an elevation of bone-specific alkaline phosphatase)
- Pregnancy

Ascendis medical monitors would immediately notify the Data Monitoring Committee (DMC) and Ascendis pharmacovigilance of any such events for evaluation of potential broader safety concerns. One PathForward participant and two PaTHway participants discontinued the trials due to pregnancy or desire to become pregnant.

## *Definition of NAC*

**A12. Priority question: Please provide data to confirm your claim that most of the population in PaTHway meet a NAC definition, such as:**

a. **Report numbers by calcium/ Vitamin D dose levels at recruitment (not just mean dose)**

b. **Report number of hospital visits prior to recruitment**

c. **Report SF36 data at recruitment**

d. **If possible, cross-tabulate these data**

**Response:** As shown in Table 4 below, 94% (77/82) of the population in PaTHway at baseline would be classified as NAC using the Guidelines from the Second International Workshop on the evaluation and management of HypoPT (Khan et al, (2022).[2]

**Table 4: Second international workshop criteria applied to PaTHway baseline ITT population**

| Criteria | Frequency |
|---|---|
| Symptomatic hypocalcaemia (per medical history) | 6 |
| Hyperphosphataemia (>1.45 mmol/L) | 27 |
| Renal insufficiency (<60 mL/min, renal stone, etc. as per criteria) | 36 |
| Hypercalciuria | 60 |
| *Poor quality of life* (SF-36 < 40) | 20 |
| High dose of calcium ≥2000 mg daily | 33 |
| Met any above | 77 |

Abbreviations: SF-36, Short Form-36 Health Survey; NAC, not adequately controlled; mmol/L, millimoles per litre; mL/min, millilitres per minute.

Table 4

**A13. The submission uses two definitions of "not adequately controlled" in which 82% patients or 94% of patients in PaTHway met the definition. Please clarify this by providing a table to demonstrate exactly how PaTHway patients met each specific criterion.**

**Response:** The 94% (77/82) figure reflects the proportion of the baseline PaTHway population classified as NAC using the Guidelines from the Second International

Workshop on the evaluation and management of HypoPT (Khan et al, (2022) criteria.[2] The 82% (67/82) figure results from applying the European expert consensus on practical management of specific aspects of parathyroid disorders (Bollerslev et al**,** (2022) criteria.[6]

The Second International Workshop criteria were considered the most appropriate to inform the submission, as they represent the most recent published guidance and do not rely on supplementary sources. In contrast, the application of the European expert consensus criteria required reference to quantitative thresholds from earlier publications, including Chen et al. (2019) and the Second International Workshop, to enable their use in the PaTHway population.

Table 4 above presents how many PaTHway patients met each criterion.

**A14. Please explain how the trial inclusion criterion: "Stable doses of CT … were required for at least 5 weeks before screening" (CS Table 9) is consistent with most patients being classed as not adequately controlled.**

**Response:** The inclusion criterion requiring "stable doses of CT for at least 5 weeks before screening" ensured that patients entered the trial on a consistent treatment regimen. This requirement was not intended to imply that patients were adequately controlled**,** but rather that their treatment had not changed recently – a standard approach in clinical trials to establish a reliable baseline.

Patients were required to maintain a minimum period of biochemical stability, which could be confirmed by a single serum calcium result above 7.8mg/dL, in line with international guideline thresholds. This was an important safety consideration, particularly for patients in the placebo arm. Ensuring some degree of baseline stability reduced the risk of significant hypocalcaemia during the early trial phases.

**A15. Priority question: Although we accept data will be limited, please provide subgroup analyses for the primary outcome and for all quality-of-life outcomes as follows:**

a. **According to whether patients were deemed to be NAC or AC at time of recruitment**

b. **By eGFR rate at time of recruitment (e.g. <30, 30-60, >60)**

c. **By calcium / Vitamin D dose levels at recruitment**

**Response:** Please see Table 5 below for the subgroup analyses for responders meeting each primary outcome as listed. It should be noted however that a minimum eGFR of ≥ 30 mL/min/1.73 m2 during screening was required for inclusion in the trial so there are no patients with an eGFR <30 in the trial. Additionally, in response to A15c, clinical practice is not standardised, as dosing of calcium and vitamin D is left to the discretion of individual investigators and local clinical preferences. Therefore, no uniform conclusions can be drawn based on these values alone.

**Table 5: Subgroup analyses for responders meeting primary outcomes from baseline to week 26 in the palopegteriparatide arm**

| | NAC* | eGFR 30-60 | eGFR >60 | High dose Calcium (>2000mg) | High dose vitamin D |
|---|---|---|---|---|---|
| All criteria | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Normocalcaemia | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| No active vit D | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Calcium ≤600 mg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Stable dose 4 wks* | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*The total number of NAC patients includes only those in the palopegteriparatide arm of the trial, resulting in 57 of the 77 NAC patients at baseline (presented in question A12).

# Section B: Clarification on cost-effectiveness data

## *Model Structure*

**B1. In section 3.2 of CS, states that the model is a partitioned survival model. However, it appears that no survival curves are modelled and that constant transition probabilities are applied. Please confirm whether the model is a PSM or a state-transition (Markov) model.**

**Response:** In line with the response to question B3, the model is best described as an on/off treatment model comprising three mutually exclusive health states: on-treatment (palopegteriparatide associated with patients achieving disease control - AC), off-treatment (CT associated with patients failing to achieve disease control - NAC), and death. While the model was initially described as a PSM due to its three-state structure, it does not use formal survival curves to estimate time in each state. Instead, it reflects a simplified structure in which a simple exponential distribution is applied to model treatment discontinuation, representing the transition from AC to NAC. Given that efficacy is captured through a fixed discontinuation rate rather than observed or fitted survival data, it is not entirely accurate to label the model as either a conventional PSM nor a formal state-transition (Markov) model. As recommended in question B3, to avoid further confusion, we will refer to it consistently as an on/off treatment model in all responses.

**B2. Priority question: The model classifies patients into AC and NAC health states based on "response to treatment," but the definition remains unclear. Please clarify the following:**

a. **What is the precise clinical definition of AC and NAC based on biochemical, symptomatic, and treatment-specific criteria used, as stated in Section 3.3 of the company submission (CS).**

**Response:** Although published European clinical guidelines (Bollerslev et al. 2022 and Khan et al. 2022) include the types of patients that PTH replacement therapy

should be considered in (those that cannot achieve calcium control/homeostasis, have poor HRQoL, exhibit renal complications, or poor gastrointestinal absorption) and could therefore be considered NAC, there is no existing clear clinical definition of AC or NAC disease, used in practice.[2,6] In part this is because to date there has been no real alternative treatment option for patients whose disease is NAC and what response in these patients would mean they are AC. Therefore, the clinical definition of AC response used in the model and as stated in section 3.3 is a composite of biochemical, symptomatic, and treatment-related criteria, based on the clinical response observed in PaTHway. A patient is classified as AC if they meet any of the following:

1. Albumin-adjusted serum calcium within the normal range (8.3–10.6 mg/dL)
2. Independence from active vitamin D, defined as:
    - A daily standing dose of zero on all days
    - Use of any PRN active vitamin D on no more than 7 days during the 4 weeks prior to the Week 26 visit
3. Independence from therapeutic doses of calcium, defined as:
    - ≤600 mg/day of elemental calcium

In addition to the primary endpoint, the following secondary and exploratory endpoints from the PaTHway trial further support the classification of patients as adequately controlled:

- 24-hour urine calcium within the normal range (≤250 mg/day for women, ≤300 mg/day for men)
- Improvement in health-related quality of life (HRQoL).
- Stabilisation of bone turnover markers (e.g. P1NP and CTx)
- Improved renal function (e.g. reduction in urinary calcium excretion)

From the PaTHway ITT population, most of the patients achieved multiple responses across all of these endpoints and hence the rationale for a response to palopeg.

**b. Those that do not or cannot achieve one of these responses to treatment, are considered NAC.Was “respond to palopeg” defined solely**

**based on meeting the primary endpoint in PaTHway (e.g. CT independence and serum calcium control)?**

**Response:** “Respond to palopeg” was not only defined as solely meeting the primary endpoint but each of the components of the primary endpoint and additional endpoints as described in B2a above. Patients on palopegteriparatide in the trial had other benefits, which can be observed by the normalisation of urinary calcium, a return to normal bone turnover and an improvement in symptoms that are showed by the change from baseline scores in EQ-5D, HPES and SF-36. (see EQ5D/HPES/SF36 outcomes in Appendix C_A6_Secondary Outcomes). Expert clinical input also confirmed that the results observed outside of the primary endpoint would mean a patient can be considered AC.

This assumption is further supported by the mechanism of action of palopegteriparatide. As a PTH replacement therapy, it addresses the underlying hormonal deficiency in HypoPT and restores physiological regulation of calcium and phosphate. This contrasts with CT, which provides passive supplementation without correcting the root cause. Through its action on PTH receptors, palopegteriparatide is expected to improve renal calcium handling, stabilise serum calcium levels, and normalise bone turnover—mechanisms consistent with a sustained and broad treatment benefit.

c. **The model assumes that all CT patients are classified as NAC. However, the clinical definition of NAC outlined in Section 1.3.6.5 and Section 3.3 includes multiple criteria beyond treatment type. Please justify this simplified approach and explain whether it could introduce bias in favour of the intervention.**

**Response:** Classifying all CT patients as NAC reflects the target population of the model and the proposed positioning of palopegteriparatide: patients with chronic HypoPT who are not adequately controlled on CT. It is not the use of CT that defines NAC status; rather, patients are classified as NAC because their disease remains inadequately controlled despite being on CT. As CT is currently the only widely available treatment, all patients are expected to be receiving it, but clinical feedback

indicates that some patients remain inadequately controlled despite ongoing CT, and there is no expectation that these patients would become adequately controlled without a change in therapy. This population aligns with those most likely to benefit from palopegteriparatide, is appropriately reflected in the model, and corresponds with the clinical definition of NAC—supported by the high proportion of patients in PaTHway who met NAC criteria (**Error! Reference source not found.**).

Therefore, assuming all CT patients as NAC is not considered to bias in favour of the intervention but reflects the clinical characteristics of the target population.

**d. Please provide evidence supporting the assumption that patients cannot transition from NAC to AC unless initiating palopeg. (e.g. 4.8% responders with CT in the trial)**

**Response:** This assumption was based on clinical expert input that a patient who is NAC on CT (as the current available treatment option) is extremely unlikely to achieve control once the disease has progressed to the chronic stage.

In rare cases, spontaneous recovery of hypoparathyroidism may occur, but this is typically limited to acute cases and not representative of the chronic population included in the model.

Published evidence indicates that long-term persistence of HypoPT is common once chronicity is established. For example, Gafni & Collins (2019) highlight that spontaneous resolution after 6 months is rare, stating that “most patients with postsurgical hypoparathyroidism recover parathyroid gland function within several weeks to months… chronic complete hypoparathyroidism [is] relatively rare.”[7] Similarly, Cusano et al. (2013) note that HypoPT persisting beyond 6 months is usually considered permanent, with only rare cases recovering after 1 year.[8] These findings support the clinical expectation that regaining parathyroid function in chronic HypoPT is unlikely.

e. **Please clarify whether any alternative health state structures (e.g. based severity) were considered and why they were rejected.**

**Response:** Two alternatives were considered to model the target population of treating those that are NAC on CT. The first approach included health states based on disease severity and models incorporating progression to CKD or CVD. These approaches were not implemented due to lack of a clinically validated or routinely recorded severity classification for HypoPT and limited long-term data on CKD/CVD progression in this population.

A model structure based on AC/NAC with or without CKD/CVD was considered. However, incorporating CKD and CVD directly into the primary health states raised concerns around face validity due to the heterogeneity of these complications and their variable clinical impact. It also introduced issues of competing risks between disease progression and complication onset. In light of these limitations, the final model retained an AC/NAC structure—reflecting on/off treatment benefit—and captured long-term complications through event-based modelling in a separate complication sub-model. This approach allowed clinically meaningful stratification while maintaining structural clarity and minimising bias.

The second was to use HPES to categorise disease severity as the higher the score the greater the disease burden. As defined severity thresholds have not been established for the HPES measure, we used a statistically significant correlation between PGIS and the HPES-Symptom total score as demonstrated in Brod et al. (2021). This relationship was used to identify patients with moderate and severe symptom burden based on the baseline HPES-Symptom total score. We next considered whether this population ‘could’ be considered more reflective of the NAC population based on having a greater disease severity and potentially align with a subgroup as defined within the NICE scope. We also considered whether this subgroup could provide data to indicate that palopegteriparatide would lead to a positive treatment benefit in a more severe population in case there were concerns that our positioning of treatment in the NAC population was considered a more ‘severe’ group of patients. The structure of the model would have remained the same, however, efficacy would have been informed only by [redacted]/82 patients from the

PaTHway trial. We did not present this case mainly for two reasons:

1. Although HPES scoring could be used to define severity if the correlation with HPES was accepted. However, we do not know whether this would be implementable in routine NHS clinical practice to identify the eligible population for palopegteriparatide and expert clinical feedback stated that symptoms are not the only consideration for those that are NAC.

2. We believed that we would have faced criticism for presenting this small population given it would have left only [redacted] from the ITT and may have made decision making uncertain. However, we have assessed the primary endpoint for this group and analysed the EQ-5D data and provided the data below.

**Table 6: Primary endpoint response at week 26 for moderate/severe HPES group**

| Treatment arm | Normocalcaemia | No active vit D | Calcium ≤600 mg | Stable dose 4 wks* | All criteria |
|---|---|---|---|---|---|
| Palopegteriparatide | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 7: Summary of the change from baseline to week 26 in EQ-5D-3L from ANCOVA analysis**

| | Treatment group | | Control group | | Comparison | |
|---|---|---|---|---|---|---|
| **Baseline subgroup** | **N** | **LS Mean (SE)** | **N** | **LS Mean (SE)** | **Difference in LS Means (SE)** | **P-value** |
| ITT population | 59 | [redacted] | 19 | [redacted] | [redacted] | 0.005 |
| HPES health state of Moderate/Severe at baseline | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 0.004 |

The data show that the response to treatment, based on the primary endpoint definition and each component of the primary endpoint, are consistent with the ITT population. We believe this data indicates that patients who may be considered more 'severe' would respond to treatment with palopegteriparatide and that the treatment benefit could be potentially greater. We have provided a cost-effectiveness estimate based on this data which we believe supports our claim that we are being

conservative in our base case (Table 8).

**Table 8: Scenario outcomes for HPES moderate/severe baseline utility**

| | Base case | HPES moderate/severe |
|---|---|---|
| **Baseline utility** | | |
| **AC** | [redacted] | [redacted] |
| **NAC** | [redacted] | [redacted] |
| **Outcomes** | | |
| **Incremental costs** | [redacted] | [redacted] |
| **Incremental QALYs** | [redacted] | [redacted] |
| **ICER (£/QALY)** | £19,895 | £ 12,452 |

**B3. Priority question: The model structure outlined in the CS appears to conflate two distinct structures: i) A response-based approach in which health states are defined with respect to the trial primary outcome, ii) An on-treatment, off-treatment approach in which health states are defined with respect to whether patients are receiving palopeg. The EAG specifically highlights that the current input values appear to align with the 2nd approach, while the description of the model structure aligns with the former.**

a. **Please confirm which model structure represents the company base case and justify your approach.**

**Response:** The company base-case model is an on–off-treatment structure: patients accrue outcomes according to whether they are receiving palopegteriparatide and can be considered AC, or CT and would be considered NAC (based on the target population of NAC on CT).

This approach was directly informed by PaTHway evidence showing that patients treated with palopegteriparatide attain clinically meaningful benefits:

- High and durable attainment of the composite primary endpoint (serum-calcium control + independence from CT ≤ 600 mg Ca / 0 µg active vit D + no recent dose increase) was observed in ≥79 % of palopegteriparatide patients at Week 26 and ≥81 % at Week 52, with maintenance through Week 104. The outcomes of the PaTHForward trial support these findings (**Error! Reference source not found.**).

Health-related quality of life improved across the entire treated cohort (Table 10). These findings are further supported by the physiological mechanism of action of palopegteriparatide. As a PTH replacement therapy, palopegteriparatide directly addresses the underlying hormonal deficiency in chronic HypoPT, restoring PTH signalling and enabling endogenous regulation of calcium and phosphate homeostasis. This mechanism contrasts with CT, which relies on passive supplementation and does not restore physiological control. By acting on PTH receptors, palopegteriparatide is likely to improve renal calcium handling, maintain more stable serum calcium, and normalise bone turnover – factors that support a sustained and clinically meaningful treatment effect.

Because benefit is delivered while the drug is taken – irrespective of whether a patient meets the single-timepoint composite definition – the on-off treatment framework accurately captures real-world treatment dynamics and aligns with clinical practice, whereas using the response-based model would underestimate the full value observed in trials.

The assumption that all CT patients are NAC is in line with the understanding that chronic HypoPT patients who are NAC are unlikely to achieve AC while remaining on CT as outlined in responses to B2c/d. This reflects clinical expert input and the model's target population, where CT has failed to provide adequate control.

As further outlined in B2d, while rare spontaneous recovery may occur, it is typically limited to acute cases and is not representative of the chronic NAC population.

**b. If the company's preferred base case is a response-based approach, the EAG recommends updating the following:**

- **Revise the proportion of responders to align with the evidence from the PaTHway trial, e.g. update the proportion of responders in the palopeg arm to 78.7% to align with the proportion achieving the primary outcome.**

- **Consider whether it is appropriate to model and assess period in which response to treatment is evaluated, and clarify whether non-responders would continue on palopeg after the initial**

**assessment period. Update transition probabilities to align with the company's preferred approach.**

- **Update utility values applied to the AC and NAC health states so that they represent the HRQoL of patients who achieved response; the current utility values are based on treatment received.**

**Response:** Question not relevant with on/off treatment base-case

c. **If the company's preferred base case is an on-treatment, off-treatment approach, the EAG suggests renaming the AC health state "on palopeg" and renaming the NAC health state "on CT". Input values do not need to be changed.**

**Response:** Model health state names have been updated accordingly.

## *Treatment Effect*

**B4. Priority question: An important modelled benefit of palopeg is the reduction in the rates of hypocalcaemia and hypercalcaemia. The EAG, however, notes that the rates used in the economic model are based on the frequency of grade 1 to 4 adverse events, whereas the costs associated with these events are based on grade 3 to 4 adverse events. Please justify your approach and explain this inconsistency.**

**Response:** The rates of hypocalcaemia and hypercalcaemia used in the model were based on grade 1–4 adverse events reported in PaTHway. These events were selected because they provide a comprehensive estimate of the frequency with which biochemical calcium abnormalities occur, even if not all reach the severity of grade 3–4. However, it is important to note that the clinical trial environment includes frequent monitoring (weekly to monthly), allowing early detection and proactive management of calcium deviations before they become symptomatic or severe.

In real-world clinical practice, such intensive monitoring is not routinely feasible. As a result, episodes of calcium imbalance are more likely to go unrecognised until symptoms become more serious. Therefore, the grade 1–4 event rates observed in the trial are expected to better reflect the incidence of clinically significant (i.e. cost-

generating) events in real-world settings, where delays in detection and intervention could lead to more frequent grade 3–4 outcomes.

This interpretation is further supported by the 14.3 serum hypocalcaemia events per patient-year observed during the randomised period of PaTHway, compared to [redacted] hypocalcaemia TEAEs per patient-year (based on the observed paraesthesia and hypocalcaemia TEAEs per patient-year in PaTHway). This indicates a higher frequency of biochemical instability than is captured by reported TEAEs and supports the plausibility that a subset of these events would require inpatient management outside of the trial context.

The cost applied to hypocalcaemia events in the base case reflects the economic burden associated with serious calcium-related complications requiring inpatient care. This is considered clinically appropriate given the expected severity of unmanaged hypocalcaemia events in real-world NAC patients.

**B5. The model applies a 100% response rate for the palopeg arm and 0% for the CT arm. These assumptions are unclear and appear inconsistent with trial data.**

a. **Please explain how this assumption was derived from the reported <u>91.9%</u> value (<u>57/61</u> patients)**

**Response:** Firstly, we would like to acknowledge that although the numbers were correct (57/61) the % reported in the CS should have been 93.4%. Furthermore, the 57/61 patients was reference to the number that were independent from therapeutic calcium not those meeting the multi-component endpoint.

We recognise that within the CS we have not clearly explained the rationale for the 100% response rate for all on-treatment (palopegteriparatide) patients in the model. Please refer to **Error! Reference source not found.** which provides the response data to achieving independence of vitamin D and therapeutic calcium at week 26 and during the OLE period. The data shows these two specific endpoints are above 95% during the OLE period. However, assessing only these endpoints or only focusing on the primary endpoint ignores the improvement observed in QoL. PaTHway, as direct evidence based on EQ-5D, demonstrates a clear QoL benefit in all patients who

receive palopegteriparatide. Therefore the 100% response also takes into account the improvement observed in symptoms, which would be used to assess treatment benefit in routine clinical practice. As outlined in the response to question B8, the response to EQ-5D is maintained over the OLE. In addition, no patients discontinued due to a lack of efficacy and no loss of treatment benefit was observed. Therefore, we believe this supports the assumption of 100% response and that the response is durable across the treated population and is reflective of the Pathway trial. This is supported by PaTHway trial evidence, which showed high rates of improvement across all components of the composite primary endpoint, consistent biochemical control, and meaningful gains in quality of life.

b. **Please clarify the discrepancy between the 91.9% and the 78.7% response rate (48/61 patients) reported in the PaTHway trial ITT population. Which population was used to calculate the 91.9%, and why was this preferred over the ITT-based outcome?**

**Response:** The 78.7% value (48/61 patients) represents the proportion of the ITT population meeting all four components of the composite primary endpoint at Week 26. This includes achieving serum calcium within the normal range, no active vitamin D, calcium ⩽600 mg/day, and no dose increase in the 4 weeks prior. This value was not used in isolation to define response but illustrates the extent of benefit seen across the population. The model does not define response based on a single timepoint or component but rather assumes that all patients experience clinically meaningful benefit while on treatment, in line with trial findings.

**B6. The model assumes that patients who initially respond to palopeg maintain this response indefinitely unless they discontinue treatment. Please provide supporting evidence (from PaTHway OLE or PaTHForward) and explain how this informs assumptions on the durability of the treatment effect.**

**Response:** The assumption that patients who respond to palopegteriparatide maintain response for the duration of treatment is directly informed by long-term data from PaTHway and PaTHForward as shown in **Error! Reference source not**

**found.**. Across both trials, durability of effect was demonstrated through consistent maintenance of primary endpoint components and overall treatment response over extended periods:

- In PaTHway, patients meeting the primary endpoint at Week 26 (78.7%) continued to maintain high response rates at Week 52 (81%) and Week 104 (80.3%), with no evidence of waning effect. Both trials showed high rates of independence from CT at all timepoints, with more than 90% of patients achieving this endpoint at each visit (**Error! Reference source not found.**).
- No patients discontinued palopegteriparatide due to loss of efficacy, with discontinuation due to breaks in protocol, supporting the stability of benefit with continued treatment.

This sustained biochemical control, independence from CT, and stable quality of life over two years or more supports the modelling assumption that treatment effect persists for as long as patients remain on therapy. As such, the model conservatively assumes durability of benefit is conditional on treatment continuation, with no benefits maintained following the discontinuation of treatment, in alignment with trial evidence.

**B7. Priority question: The economic analysis presents several projected benefits of palopoeg treatment, including reduced complication rates, increased life expectancy, and decreased resource utilisation. However, these outcomes are not directly supported by evidence from the PaTHway study. Please provide a further justification for this approach. This should include: (i) the biological rationale for the implied surrogate relationships, (ii) evidence supporting the validity and relevance of the implied surrogate-outcome relationships, and (iii) a clear explanation of how the current approach aligns with the requirements set out in Sections 4.6.5 to 4.6.8 of the Methods Manual.**

**Response:** The modelled long-term benefits of palopegteriparatide—reduced complications, increased life expectancy, and decreased healthcare resource use—are supported through mechanistic, clinical, and methodological justification, in line

with the expectations of the NICE Methods Manual (Sections 4.6.5–4.6.8) on surrogate outcomes.

(i) Biological rationale:

Palopegteriparatide is a replacement therapy that restores PTH signalling, targeting the underlying pathophysiology of HypoPT rather than compensating for its effects. Restoration of PTH leads to improved calcium–phosphate homeostasis, reduced urinary calcium excretion, improved renal handling of calcium and phosphate, and stabilisation of serum calcium. These biological effects directly address the mechanisms responsible for long-term complications such as renal impairment, calcifications, cardiovascular events, and neuromuscular instability. Therefore, reductions in complications, and in turn improved survival and reduced HCRU, are biologically plausible and expected.

(ii) Supporting evidence for surrogate-outcome relationships:

The composite primary endpoint in PaTHway—serum calcium control without active vitamin D or high-dose calcium—is a direct surrogate of stable mineral balance and reduced treatment burden. Achievement of this endpoint is strongly associated with reduced exposure to CT, which has been linked in observational literature to renal complications and other adverse outcomes. Observational studies (e.g. Chen 2019) show that inadequately controlled HypoPT is associated with increased HCRU, poorer QoL, and higher risks of CKD and hospitalisation.[5] The link between sustained biochemical control and reduced complication risk is further supported by expert consensus (Brandi 2016; Khan 2022) and forms the basis of current management goals.[2,9] While direct long-term data on hard outcomes are lacking due to the rarity of the disease and trial duration, these indirect associations are consistent and clinically supported.

(iii) Alignment with the NICE Methods Manual:

Sections 4.6.5–4.6.8 of the NICE Methods Manual permit the use of surrogate outcomes when there is a strong biological rationale, consistent evidence of a correlation between the surrogate and final outcomes, and when direct evidence is impractical due to feasibility constraints. HypoPT is a rare condition, and long-term

trials powered to detect differences in mortality or complications are not feasible. The surrogate–final outcome relationship used in the model is supported by biological mechanism, consistent clinical observation, and expert validation. The assumptions used in the model are transparently justified and explored in sensitivity analyses.

In summary, while the benefits are not directly observed in PaTHway due to study duration, they are grounded in a mechanistic understanding of disease and intervention, supported by clinical literature, and appropriately extrapolated in line with NICE's guidance on surrogate outcome use.

## *HRQOL*

**B8. For each time point that the EQ-5D questionnaire was administered in PaTHway, please provide a summary, stratified by treatment arm, of the total patients available and the number of completed questionnaires.**

**Response:** The sample size for the completed questionnaires is shown in Table 9**Error! Reference source not found.**. The scheduled data collection for EQ-5D was baseline, Week 10, Week 20, and Week 26.

**Table 9: EQ-5D observations by visit**

| Visit | Palopegteriparatide arm | | CT arm | | Total population | |
|---|---|---|---|---|---|---|
| | Patients in study | Completed EQ-5D | Patients in study | Completed EQ-5D | Patients in study | Completed EQ-5D |
| Baseline | 61 | 61 | 21 | 21 | 82 | 82 |
| Week 2 | 61 | 2 | 19 | 0 | 80 | 2 |
| Week 4 | 61 | 0 | 19 | 1 | 80 | 1 |
| Week 10 | 61 | 55 | 19 | 16 | 80 | 71 |
| Week 12 | 61 | 2 | 19 | 2 | 80 | 4 |
| Week 20 | 60 | 54 | 19 | 17 | 79 | 71 |
| Week 26 | 59 | 59 | 19 | 19 | 78 | 78 |

**B9. Please clarify whether EQ-5D was collected as part of the questionnaire PaTHway OLE study. For each time point that the EQ-5D questionnaire was administered in PaTHway OLE, please provide a summary of mean EQ-5D 5L**

**values (mapped 3L) and a summary of the total patients available and the number of completed questionnaires.**

**Response:** EQ-5D data was collected as part of the PaTHway OLE study. Table 10Error! Reference source not found. below shows the mean EQ-5D-3L and sample size stratified by analysis visit and randomised treatment arm. It is important to note that in the OLE patients crossover to palopegteriparatide, therefore the control therapy mean EQ-5D-3L beyond week 26 should be considered with caution and can't be considered solely reflective of control therapy.

**Table 10: EQ-5D observations by visit and randomised treatment arm**

| Visit | Palopegteriparatide arm | | | CT arm | | | Total population | | |
|---|---|---|---|---|---|---|---|---|---|
| | Patients in study | Completed EQ-5D | Mean EQ-5D | Patients in study | Completed EQ-5D | Mean EQ-5D | Patients in study | Completed EQ-5D | Mean EQ-5D |
| Baseline | 61 | 61 | [redacted] | 21 | 21 | [redacted] | 82 | 82 | [redacted] |
| Week 2 | 61 | 2 | [redacted] | 19 | 0 | [redacted] | 79 | 2 | [redacted] |
| Week 4 | 61 | 0 | [redacted] | 19 | 1 | [redacted] | 79 | 1 | [redacted] |
| Week 10 | 61 | 55 | [redacted] | 19 | 16 | [redacted] | 79 | 71 | [redacted] |
| Week 12 | 60 | 2 | [redacted] | 19 | 2 | [redacted] | 78 | 4 | [redacted] |
| Week 20 | 60 | 54 | [redacted] | 19 | 17 | [redacted] | 78 | 71 | [redacted] |
| Week 26 | 60 | 59 | [redacted] | 19 | 19 | [redacted] | 78 | 78 | [redacted] |
| Week 34 | 60 | 54 | [redacted] | 18 | 17 | [redacted] | 77 | 71 | [redacted] |
| Week 38 | 60 | 1 | [redacted] | 18 | 0 | [redacted] | 77 | 1 | [redacted] |
| Week 46 | 60 | 1 | [redacted] | 18 | 0 | [redacted] | 77 | 1 | [redacted] |
| Week 52 | 59 | 57 | [redacted] | 18 | 18 | [redacted] | 76 | 75 | [redacted] |
| Week 78 | 59 | 53 | [redacted] | 18 | 17 | [redacted] | 76 | 70 | [redacted] |
| Week 104 | 58 | 56 | [redacted] | 18 | 18 | [redacted] | 75 | 74 | [redacted] |
| Week 117 | 58 | 1 | [redacted] | 18 | 0 | [redacted] | 75 | 1 | [redacted] |
| Week 130 | 58 | 52 | [redacted] | 18 | 15 | [redacted] | 75 | 67 | [redacted] |
| Week 143 | 54 | 3 | [redacted] | 18 | 1 | [redacted] | 72 | 4 | [redacted] |
| Week 156 | 54 | 54 | [redacted] | 17 | 17 | [redacted] | 71 | 71 | [redacted] |

**B10. Priority question: The company's base case uses an ANCOVA model applied to data from the PaTHway trial to estimate the health state utility values.**

a. **Please justify this approach.**

**Response:** ANCOVA allows a simple analysis to capture the change from baseline aligned with the prespecified analysis for the change from baseline endpoints. The accuracy of the ANCOVA model and avoidance of potential bias, in our opinion justifies the exclusion of the potential bias interim study visits that would support a MMRM analysis.

If a MMRM was to include visits between baseline and week 26 this would include a mix of heterogeneous patients at different stages of benefiting from treatment. Therefore, including data representative of quality of life prior to treatment effect being established which would impact change from baseline estimates at week 26. While the additional visits may inform the change in utility, the additional visits would introduce bias as they are not fully reflective of the treatment effect at week 26.

Given the economic model uses the utility value for beyond week 26, the inclusion of visits between baseline and week 26 would misalign the analysis and economic model.

By only considering the change from baseline to week 26, this gives the fairest representation of change from baseline for the treatment arms and the associated benefit of treatment.

b. **Please provide details of any covariates included in the ANCOVA model and justify the selection.**

**Response:** The ANCOVA analysis covariates aligned with the prespecified trial analysis for consistency with the clinical study report and other subsequent analyses. The covariates included were:

- Etiology of hypoparathyroidism - categorised according to whether the cause was surgical complications or other.
- Baseline EQ-5D-3L.
- Randomised treatment arm.

c. **The EAG prefers to use Mixed Model for Repeated Measures (MMRM), where repeat measurements are made. Please reanalyse the PaTHway EQ-5D data using an MMRM model. Note that this analysis should not include HPES Physical Functioning or other HRQoL independent covariates.**

**Response:** An analysis of EQ-5D-3L predicted by aetiology and treatment arm is shown in Table 11**Error! Reference source not found.**. The goodness of fit statistics are shown in Table 12**Error! Reference source not found.**.

**Table 11: MMRM regression output (EQ-5D-3L ~ Treatment + Aetiology of hypoparathyroidism)**

| | Coefficient | Standard error | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | [redacted] |
| Treatment arm: TransCon PTH | [redacted] | [redacted] | [redacted] |
| Aetiology of hypoparathyroidism: Non-surgical | [redacted] | [redacted] | [redacted] |

*Abbreviations: EQ-5D-3L: European quality of life 5 dimensions 3 level version; MMRM, Mixed model-repeated measures.*

**Table 12: Goodness of fit statistics for MMRM (EQ-5D-3L ~ Treatment + Etiology of hypoparathyroidism)**

| | $R^2_m$ | $R^2_c$ | AIC | BIC |
|---|---|---|---|---|
| EQ-5D-3L ~ Treatment + Aetiology of hypoparathyroidism | [redacted] | [redacted] | [redacted] | [redacted] |

*Abbreviations: AIC, Akaike information criterion; BIC: Bayesian information criterion; EQ-5D-3L, European quality of life 5 dimensions 3 level version; $R^2_c$, R-squared conditional, $R^2_m$, R-squared marginal.*

**B11. Priority question: To aid the EAG in better understanding the drivers of HRQoL. Please reanalyse EQ-5D data from the PaTHway to evaluate the impact of :**

i. **Treatment arm.**
ii. **Response status, i.e. whether patients achieve the primary outcome.**
iii. **Treatment arm and response status.**

**The model should preferably run using an MMRM and include appropriate control covariates such as age, sex and baseline values. Do not include HPES**

**Physical Functioning or other QoL measures as covariates. For each model, please compare: Coefficient sizes, $R^2$/adjusted $R^2$, AIC/BIC fit statistics, and the statistical significance of treatment vs. response (model iii).**

**Response:** The MMRM was run with treatment arm and a selection of baseline covariates in Table 13**Error! Reference source not found.**. The model with response status included is shown in **Error! Reference source not found.**Table 14. For the analysis with treatment arm and response status, this is shown in **Error! Reference source not found.**Table 15 with the two aspects independently and **Error! Reference source not found.**Table 16 with the term capturing the interaction. The goodness of fit statistics are shown in **Error! Reference source not found.**Table 17.

The covariates included aligned with those suggested in the question. If the covariates aligned with the ANCOVA analysis were to be used, the analysis shown in Table 15**Error! Reference source not found.** would align with the analysis in Table 11**Error! Reference source not found.**, with Table 11**Error! Reference source not found.** focusing on change from baseline rather than absolute EQ-5D-3L. The implementation of response and aetiology are aligned with the analysis above.

**Table 13: MMRM regression output (EQ-5D-3L ~ Treatment arm + Age +BBMI + Sex + Aetiology of hypoparathyroidism**

| | Coefficient | Standard error | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | [redacted] |
| Treatment arm: TransCon PTH | [redacted] | [redacted] | [redacted] |
| Age | [redacted] | [redacted] | [redacted] |
| Sex: Male | [redacted] | [redacted] | [redacted] |
| BBMI | [redacted] | [redacted] | [redacted] |
| Aetiology of hypoparathyroidism: Non-surgical | [redacted] | [redacted] | [redacted] |

*Abbreviations: BBMI: Baseline body mass index; EQ-5D-3L: European quality of life 5 dimensions 3 level version; MMRM, Mixed model-repeated measures.*

**Table 14: MMRM regression output (EQ-5D-3L ~ Primary response + Age +BBMI + Sex + Aetiology of hypoparathyroidism)**

| | Coefficient | Standard error | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| Primary responder: Yes | [redacted] | [redacted] | [redacted] |
| Age | [redacted] | [redacted] | [redacted] |
| Sex: Male | [redacted] | [redacted] | [redacted] |
| BBMI | [redacted] | [redacted] | [redacted] |
| Aetiology of hypoparathyroidism: Non-surgical | [redacted] | [redacted] | [redacted] |

*Abbreviations: BBMI: Baseline body mass index; EQ-5D-3L: European quality of life 5 dimensions 3 level version; MMRM, Mixed model-repeated measures.*

**Table 15: MMRM regression output (EQ-5D-3L ~ Treatment arm + Primary response + Age +BBMI + Sex + Aetiology of hypoparathyroidism)**

| | Coefficient | Standard error | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | [redacted] |
| Treatment arm: TransCon PTH | [redacted] | [redacted] | [redacted] |
| Primary response: Yes | [redacted] | [redacted] | [redacted] |
| Age | [redacted] | [redacted] | [redacted] |
| Sex: Male | [redacted] | [redacted] | [redacted] |
| BBMI | [redacted] | [redacted] | [redacted] |
| Aetiology of hypoparathyroidism: Non-surgical | [redacted] | [redacted] | [redacted] |

*Abbreviations: BBMI: Baseline body mass index; EQ-5D-3L: European quality of life 5 dimensions 3 level version; MMRM, Mixed model-repeated measures.*

**Table 16: MMRM regression output (EQ-5D-3L ~ Treatment arm * Primary response + Age +BBMI + Sex + Aetiology of hypoparathyroidism)**

| | Coefficient | Standard error | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | [redacted] |
| Treatment arm: TransCon PTH | [redacted] | [redacted] | [redacted] |
| Primary response: Yes | [redacted] | [redacted] | [redacted] |
| Age | [redacted] | [redacted] | [redacted] |
| Sex: Male | [redacted] | [redacted] | [redacted] |
| BBMI | [redacted] | [redacted] | [redacted] |
| Aetiology of hypoparathyroidism: Non-surgical | [redacted] | [redacted] | [redacted] |
| Treatment arm: TransCon PTH \| Primary response: Yes | [redacted] | [redacted] | [redacted] |

*Abbreviations: BBMI: Baseline body mass index; EQ-5D-3L: European quality of life 5 dimensions 3 level version; MMRM, Mixed model-repeated measures.*

**Table 17: MMRM Goodness of fit statistics by model**

| | $R^2_m$ | $R^2_c$ | AIC | BIC |
|---|---|---|---|---|
| EQ-5D-3L ~ Treatment arm + Age +BBMI + Sex + Aetiology of hypoparathyroidism | [redacted] | [redacted] | [redacted] | [redacted] |
| EQ-5D-3L ~ Primary response + Age +BBMI + Sex + Aetiology of hypoparathyroidism) | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| EQ-5D-3L ~ Treatment arm + Primary response + Age +BBMI + Sex + Aetiology of hypoparathyroidism | [redacted] | [redacted] | [redacted] | [redacted] |
| EQ-5D-3L ~ Treatment arm * Primary response + Age +BBMI + Sex + Aetiology of hypoparathyroidism | [redacted] | [redacted] | [redacted] | [redacted] |

*Abbreviations: BBMI: Baseline body mass index; EQ-5D-3L: European quality of life 5 dimensions 3 level version; MMRM, Mixed model-repeated measures; $R^2_C$, R-squared conditional; $R^2_m$, R-squared marginal.*

**B12. Priority question: Please comment on the plausibility of the modelled difference in HRQoL between the palopeg and CT arm, given the limitations with the PaTHway trial outlined in question A3 and A7.**

**Response:** From the patient HRQoL, the change from baseline shown in the control arm shows a minimal difference at week 26 (and earlier visits). The observed change from baseline for control group non-responders was -0.0184 with a standard error of 0.0368.

This minimal and statistical insignificant change from baseline aligns with our expectation of CT having limited clinical benefit and a small change of response and supports the idea that patient quality of life wasn't impacted by a decrease in vitamin D dose.

Regarding potential challenges in maintaining treatment blinding, as outlined in the response to A7, all treatment received by patients was protocol-defined and not influenced by clinician judgement. As a result, the treatment environment was consistent across arms and would not be expected to introduce bias into quality-of-life responses.

## *Resource use*

**B13. Priority question: Resource use is a key driver of cost-effectiveness in the model. We note that the aetiology of chronic hypoPTH differs between the PaTHway trial and the CPRD dataset.**

a. **Please comment on the potential implications of this mismatch and the generalisability of the CPRD data to the modelled population.**

**Response:** The CPRD dataset does include a higher proportion of non-surgical patients than typically observed in clinical practice, where approximately 75–80% of chronic HypoPT cases are post-surgical. This distribution in CPRD is a result of the underlying study design, which aimed to identify incident cases using a clear diagnostic start point. Post-surgical HypoPT could be reliably captured as an incident population due to the presence of a defined surgical event and clear onset timing. In contrast, non-surgical cases – often linked to autoimmune, genetic, or idiopathic causes – may begin at any point after birth and are less amenable to incidence-based identification, especially given that CPRD data does not extend to birth and includes only adults. As a result, non-surgical patients were captured using a prevalent cohort approach, leading to a relative overrepresentation in the final dataset.

While this aetiological distribution does not reflect that of the PaTHway trial, which is more reflective of that seen in clinical practice, we do not expect the differences to materially affect model outcomes. Clinical input suggests that treatment patterns and healthcare utilisation are primarily driven by disease duration and control status, rather than aetiology, when duration on disease is controlled for. Since all patients included in the model had chronic HypoPT and were receiving CT, resource use estimates were therefore considered generalisable to the modelled population, regardless of underlying cause. This is supported by the reanalysis of the CPRD data presented below which shows limited differences in costs between the non-surgical and post-surgical total per-patient-per-year costs for the controlled (AC) and uncontrolled (NAC) total cohorts.

b. **Please reanalyse the CPRD data and provide separate results for HCRU cost, mortality and complications by surgical and non-surgical subgroups.**

**Response:** CPRD data were stratified by post-surgical (PS) and non-surgical (NS) cohorts for mortality and health state maintenance costs. As discussed during the clarification call, comorbidity data has been deprioritised, however, scenarios have been included to test the model with and without complications. While these results have been provided to support transparency, we do not consider it appropriate to separate model inputs by aetiology in the base case for the following reasons:

- **Insufficient PS sample size:** The number of post-surgical patients in the CPRD cohort was limited, resulting in greater uncertainty around estimates for this group.
- **Differences in study design:** PS and NS cohorts were derived using different methodologies (incident vs. prevalent populations), limiting comparability and introducing potential bias.
- **No expected difference in treatment once chronic:** Clinical input indicates that once disease is established, resource use and mortality are more strongly influenced by disease duration and control status than by aetiology.
- **The Chen publication**, which has demonstrated that there are differences in outcomes for patients who are considered AC vs NAC, and states that: *'results in the sub-groups defined by aetiology were generally consistent with those of the overall study population, although there were several differences. Specifically, patients with congenital and idiopathic hypoparathyroidism'*. The results are not reported due to small sample size.

To illustrate the potential impact, six alternative model scenarios were conducted using the CPRD aetiology-specific data:

- **NS scenario with/without complications:** Inputs reflect CPRD-derived costs and mortality for non-surgical patients.

- **PS scenario with/without complications:** Inputs reflect CPRD-derived values for post-surgical patients.
- **Weighted scenario with/without complications:** Applies a 75% PS / 25% NS weighting to approximate the real-world aetiological distribution of chronic HypoPT.

In each scenario, health state maintenance costs and mortality hazard ratios were updated accordingly. Costs were inflated from 2021 to 2025 values using Table 15a CPI All Items: 1998 to 2025 from the Office of National Statistics Consumer Price Inflation (indexed from 111.6 average in 2021 to 136.9 average in 2025 (up to May)) and were adjusted to match the cycle length of the model. Model outcomes including total costs, QALYs, ICERs, and NMB are reported in Table 18**Error! Reference source not found.**.

**Table 18: NS/PS scenario inputs and outcomes**

| | Base case | PS w complications | PS wo complications | NS w complications | NS wo complications | Weighted w complications | Weighted wo complications |
|---|---|---|---|---|---|---|---|
| **Maintenance cost** | | | | | | | |
| **AC** | [redacted] | [redacted] | | [redacted] | | [redacted] | |
| **NAC** | | | | | | | |
| **Mortality Hazard Ratio versus Gen pop** | | | | | | | |
| **AC** | [redacted] | [redacted] | | [redacted] | | [redacted] | |
| **NAC** | | | | | | | |
| **Outcomes** | | | | | | | |
| **Incremental costs** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Incremental QALYs** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ICER (£/QALY)** | £19,895 | £37,209 | £38,998 | £16,915 | £17,746 | £32,788 | £34,389 |

**B14. Priority question: The following thresholds were applied to classify patients in the CPRD dataset: i) AC: ≤5 outpatient visits and <1 inpatient admission per patient per year, ii) NAC: >5 outpatient visits and ≥1 inpatient admission per patient per year. The EAG is concerned that this classification approach is based on circular and tautological reasoning, as it assumes that patients with the highest expenditure have the most severe disease. This assumption is not substantiated in the submission, and a conceptual link between expenditure and disease severity is not necessarily evident, particularly given the co-morbidities associated with HypoPT. Please provide further justification for this approach.**

**Response:** The classification of patients in the CPRD dataset into AC and NAC groups was guided by clinical expert input, with the goal of applying a practical method to distinguish levels of disease control in the absence of laboratory or symptom data. Clinicians initially suggested that healthcare resource use could serve as a suitable proxy, as patients with NAC HypoPT generally require more frequent medical intervention due to calcium instability, complications, and treatment burden.

Following further engagement, experts advised that using a combination of outpatient and inpatient activity – specifically, >5 outpatient visits and ≥1 inpatient admission per year – would more accurately reflect inadequate disease control than either measure alone. This combined threshold was considered clinically meaningful and consistent with the pattern of care observed in NAC patients.

As a rare disease it is recognised that the published evidence is limited however this approach is supported by Chen et al. (2019) that showed that NAC HypoPT patients had significantly greater healthcare use with a higher number of outpatient visits (3.6 vs 2.6), and more hospitalisations and emergency room visits (all $p < 0.05$) than AC patients. As CPRD includes all-cause healthcare utilisation, which captures comorbidities and unrelated health events, whereas Chen reports HypoPT-specific events it was necessary to apply different absolute thresholds. Higher cut-offs were applied in CPRD to ensure that identified NAC patients reflect a comparable disease burden, not confounded by non-HypoPT-related usage.

## *Model Validation*

**B15. Priority question: Age adjustment is incorrectly implemented in the economic model. Please update the economic model using the values reported in the linked Excel spreadsheet: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d**)). **Please also ensure that age adjustment accounts for the current age of the cohort.**

**Response:** The model has been updated to use the direct general population estimates through the addition of column C in the Trace sheets (using an XLOOKUP to refer to the utility inputs from Range C227:F311 in the "Inputs" sheet).

**B16. Priority question: The model miscalculates the dose of calcium received by patients in the palopeg arm who have discontinued treatment; we believe that once patients come off palopeg, their dosage of calcium carbonate will go up resulting in higher costs. Please revise the model accordingly.**

**Response:** The model was updated in the previous fixed version of the model shared on the 6th of June to have discontinued Palopeg patients use the costs of the CT arm for the CT costs and therefore equating treatment costs between discontinued Palopeg patients and CT patients.

**B17. Priority question: The reference to column G in the calculations included in cells N38:O1103 of sheet 'Yorvipath Markov Trace' appears to be one row out. For example, cell N38 reads:**

=IF(M38=0,0,1)*(MIN($F$9,OFFSET(**G37**,-MIN($G$12,D37),0))*SUM(N37:O37)-(1+IFERROR(SUMPRODUCT($Q$9:$Q$22,TRANSPOSE(S37:AF37/SUM(N37:O37))),0))*(N37*Mortality_AC*XLOOKUP(ROUNDDOWN(F37,0),Inputs!$C$121:$C$221,Inputs!$G$121:$G$221,1,-1,1)))

**and should read:**

=IF(M38=0,0,1)*(MIN($F$9,OFFSET(**G38**,-MIN($G$12,D37),0))*SUM(N37:O37)-(1+IFERROR(SUMPRODUCT($Q$9:$Q$22,TRANSPOSE(S37:AF37/SUM(N37:O37

)))),0))*(N37*Mortality_AC*XLOOKUP(ROUNDDOWN(F37,0),Inputs!$C$121:$C$221,Inputs!$G$121:$G$221,1,-1,1)))

**Please confirm this error and update the economic model accordingly.**

**Response:** The error has been fixed, however, with a slight adjustment. The updated formula reads:

=IF(M38=0,0,1)*(MIN($F$9,OFFSET(**G38**,-MIN($G$12,**D38**),0))*SUM(N37:O37)-(1+IFERROR(SUMPRODUCT($Q$9:$Q$22,TRANSPOSE(S37:AF37/SUM(N37:O37))),0))*(N37*Mortality_AC*XLOOKUP(ROUNDDOWN(F37,0),Inputs!$C$121:$C$221,Inputs!$G$121:$G$221,1,-1,1)))

# Section C: Textual clarification and additional points

## *Search strategies*

**C1. The reporting of the database search strategies in Appendix B, E and F seem to indicate that all databases were searched together via one platform/interface. Please provide the name of the platform/interface used for the strategies presented in:**

a. **Appendix B, Table 3, p 11-15**
b. **Appendix E, Table 10, p 41-44**
c. **Appendix F, Table 16, p 57-60**

**If this is not the case and databases were searched separately please provide all individual database search strategies used for Appendix B, E and F.**

**Response:** All databases were searched together using one platform – Ovid. This platform was used for the strategies below;

a. Appendix B, Table 3, p 11-15
b. Appendix E, Table 10, p 41-44
c. Appendix F, Table 16, p 57-60

**C2. Please also provide the subject headings used to search the following databases, or confirm that no subject headings were used to search the following databases:**

a. **EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 26, 2025>**
b. **EBM Reviews - ACP Journal Club <1991 to March 2025>**
c. **EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>**
d. **EBM Reviews - Cochrane Clinical Answers <March 2025>**
e. **EBM Reviews - Cochrane Central Register of Controlled Trials <February 2025>**
f. **EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>**
g. **EBM Reviews - Health Technology Assessment <4th Quarter 2016>**
h. **EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>**
i. **Econlit <1886 to March 20, 2025>**

**Response:** Subject headings were used to identify the population in MEDLINE and Cochrane Central Register of Controlled Trials (Hypoparathyroidism/) and Embase (hypoparathyroidism/). Subject headings were not available for the other searched databases.

**C3. Please provide a description of the searches or search terms/strategy for the conference proceedings searches reported in:**

a. **Appendix B, Table 2, p 10**
b. **Appendix E, Table 9, p 40-41**
c. **Appendix F, Table 15, p 56-57**

**Response:** Searched terms used for each conference across three topics (clinical evidence, cost-effectiveness, and quality of life studies) were the same:

“hypoparathyroidism”, “parathyroid hormone deficiency”, and “PTHD”.

**C4. Please provide a description of the searches or search terms/strategy used for the grey literature searches reported in:**

a. **Appendix B, p 11**
b. **Appendix E, p 41 (include which HTA websites were searched)**
c. **Appendix F, p 57 (include which HTA websites were searched)**

**Response:** Searched terms used in ClinicalTrials.gov were “hypoparathyroidism” OR “parathyroid hormone deficiency” OR “PTHD”.

HTA websites searched were: National Institute for Health and Care Excellence; Scottish Medicines Consortium; Institut national d’excellence en sante et an services sociaux; Haute Authorite de Sante; Agenzia Italiana del Farmaco; International HTA Database; Institute for quality and efficiency in health care (iQWiG); the website of Ministry of Health, Directorate of Pharmaceutical and Health Products (Spain); Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV in Sweden); Danish Medicines Agency (DKMA in Denmark); Norwegian Medical Products Agency (NOMA in Norway); Pharmaceuticals and Medical Devices Agency (PDMA in Japan); Canadian Agency for Drugs and Technologies in Health; and Pharmaceutical Benefits Advisory Committee.

The terms searched in each HTA website were: “Hypoparathyroidism”, “Natpar”, “Natpara”, “PTHD”, and “parathyroid hormone”. Additionally, “hypoparathyroïdie” and “hypoparathyroidisme” were searched in the website of Institut national d’excellence en sante et an services sociaux; “hypoparathyroïdie, hypoparathyroidisme” were searched in the website of Haute Authorite de Sante.

**C5. Were any search filters used within the search strategies reported in:**

a. **Appendix E, Table 10, p 41-44**

b. **Appendix F, Table 16, p 57-60**

**If yes, please provide a reference for any search filters used.**

**Response:** Recommended filters were applied where appropriate. In cases where standard filters were not suitable, additional search terms were developed based on relevant published literature.

For Table 10 in Appendix E, the references of search terms used are as follows:

| Eligibility criteria | Database | | Term | Reference |
|---|---|---|---|---|
| **Disease: Hypoparathyroidism (HP)** | Medline | 1 | exp Hypoparathyroidism/ | Cytel internal search strings |
| | Embase | 2 | exp hypoparathyroidism/ | Cytel internal search strings |
| | All | 3 | (hypoparathyroidism or hypoparathyreosis or hypoparathyroidy or hypoparathyroid).ti,ab. | Cytel internal search strings |
| | | 4 | (parathyroid adj5 (hypofunction or insufficiency or deficiency or lack or low or little or decrease$ or reduce$)).ti,ab. | Cytel internal search strings |
| **Patients with HP** | | 5 | **1 or 2 or 3 or 4** | NA |
| **ECON Outcomes** | CEA | 6 | exp "economic evaluation"/ | Cytel internal search strings |
| | | 7 | economics/ or economic aspect/ | Cytel internal search strings |
| | | 8 | Economics, Pharmaceutical/ or health economics/ or pharmacoeconomics/ | Cytel internal search strings |
| | | 9 | cost-benefit analysis/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost benefit analysis"/ or "cost utility analysis"/ | CADTH: https://searchfilters.cadth.ca/link/15 |
| | | 10 | ((economic or human$) adj3 consequence$).ti,ab. | Cytel internal search strings |
| | | 11 | (economic$ or pharmaco?economic$ or pharmaco economic$).ti,ab. | CADTH: https://searchfilters.cadth.ca/link/15 |
| | | 12 | (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).ti,ab. | CADTH: https://searchfilters.cadth.ca/link/15 |
| | | 13 | (CEA or CMA or CBA or CUA).ti,ab. | Cytel internal search strings |
| | Model | 14 | models, economic/ or economic model/ | CADTH: https://searchfilters.cadth.ca/link/15; |

| Eligibility criteria | Database | | Term | Reference |
|---|---|---|---|---|
| | | | | https://searchfilters.cadth.ca/link/16 |
| | | 15 | decision theory/ or decision trees/ or "decision tree"/ | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 |
| | | 16 | monte carlo method/ | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 |
| | | 17 | econom$ model$.ti,ab. | CADTH: https://searchfilters.cadth.ca/link/16 |
| | | 18 | markov$.ti,ab. | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 |
| | | 19 | (discrete-event simulation$ or discrete event simulation$ or microsimulation$).ti,ab. | Cytel internal search strings |
| | | 20 | monte carlo.ti,ab. | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 |
| | | 21 | (decision$ adj2 (tree$ or anal$ or model$)).ti,ab. | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 |
| | | 22 | ("de novo" adj1 model$).ti,ab. | Cytel internal search strings |
| | BIM | 23 | budgets/ or budget/ | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 |
| | | 24 | budget$.ti,ab. | CADTH: https://searchfilters.cadth.ca/link/15; https://searchfilters.cadth.ca/link/16 Cytel removed “kf.” in order to search in multiple databases. |
| | Cost | 25 | Costs and Cost Analysis/ or cost/ | SIGN: https://www.sign.ac.uk/assets/search-filters-economic-studies.docx |
| | | 26 | cost of illness/ | SIGN: https://www.sign.ac.uk/assets/search-filters-economic-studies.docx |
| | | 27 | health care costs/ or "health care cost"/ or health expenditures/ | SIGN: https://www.sign.ac.uk/assets/s |

| Eligibility criteria | Database | | Term | Reference |
|---|---|---|---|---|
| | | | | earch-filters-economic-studies.docx |
| | | 28 | cost$.ti,ab. | Cytel internal search strings |
| | HCRU | 29 | Drug Utilization/ or "drug use"/ | Cytel internal search strings |
| | | 30 | Health Resources/ or health care utilization/ | |
| | | 31 | ((resource$ or health care or healthcare or health service$ or drug$ or medication$) adj4 (use$ or usage$ or utilit$ or utili#ation$)).ti,ab. | |
| | | 32 | Hospitalization/ or "Length of Stay"/ or Patient Admission/ or hospital patient/ or hospital admission/ | |
| | | 33 | (hospitali$ or length of stay).mp,af,tw. | |
| | BOI | 34 | disease burden/ | |
| | | 35 | burden$.ti,ab. | |
| | Productivity | 36 | (productivit$ or employ$).ti,ab. | |
| | | 37 | ((work or working) adj1 (absen$ or loss$ or disabilit$ or abilit$ or impairment$ or limitation$ or incapacit$ or capacit$)).ti,ab. | |
| | ITC | 38 | (indirect?treatment?comparison$ or indirect?comparison$ or indirect treatment comparison$ or indirect comparison$).ti,ab. | |
| | HTA | 39 | (health technology assessment$ or health technolog$ or HTA).ti,ab. | |
| | | 40 | or/6-39 | NA |
| **ECON Outcomes in Patients with HPT** | | **41** | **5 and 40** | NA |
| **Irrelevant Study Design** | | 42 | (addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or monograph or news or "newspaper article" or practice guideline or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt. | Cytel internal search strings |
| | | 43 | (animals/ not (humans/ and animals/)) or (animal/ not (human/ and animal/)) | BMJ: https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/ |
| | | 44 | case report/ or case reports/ | Cytel internal search strings |
| | | 45 | or/42-44 | Cytel internal search strings |
| | | 46 | 41 not 45 | NA |
| **Limits** | | **47** | **limit 46 to human** | NA |

| Eligibility criteria | Database | | Term | Reference |
|---|---|---|---|---|
| | | | EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 26, 2025> | NA |
| | | | EBM Reviews - ACP Journal Club <1991 to March 2025> | NA |
| | | | EBM Reviews - ACP Journal Club <1991 to March 2025> | |
| | | | EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> | NA |
| | | | EBM Reviews - Cochrane Central Register of Controlled Trials <February 2025> | NA |
| | | | EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> | NA |
| | | | EBM Reviews - Health Technology Assessment <4th Quarter 2016> | NA |
| | | | EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> | NA |
| | | | Econlit <1886 to March 20, 2025> | NA |
| | | | Embase <1974 to 2025 March 26> | NA |
| **FINAL SELECTED: Econ Outcomes in Patients with HPT** **FINAL SELECTED: Econ Outcomes in Patients with HPT** | | **48** | Ovid MEDLINE(R) ALL <1946 to March 26, 2025> | NA |
| | | **48** | **Remove duplicates from 47** | NA |
| | | | EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 26, 2025> | NA |
| | | | EBM Reviews - ACP Journal Club <1991 to March 2025> | NA |
| | | | EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> | NA |
| | | | EBM Reviews - Cochrane Central Register of Controlled Trials <February 2025> | NA |
| | | | EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> | NA |
| | | | EBM Reviews - Health Technology Assessment <4th Quarter 2016> | NA |
| | | | EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> | NA |
| | | | Econlit <1886 to March 20, 2025> | NA |
| | | | Embase <1974 to 2025 March 26> | NA |

Abbreviation: NA, not applicable.

For Table 16 in Appendix F, the references of search terms used are as follows:

| Eligibility criteria | Database | | Term | References |
|---|---|---|---|---|
| **Disease: Hypoparathyroidism (HPT)** | Medline | 1 | exp Hypoparathyroidism/ | Cytel internal search strings |
| | Embase | 2 | exp hypoparathyroidism/ | Cytel internal search strings |
| | All | 3 | (hypoparathyroidism or hypoparathyreosis or hypoparathyroidy or hypoparathyroid).ti,ab. | Cytel internal search strings |
| | | 4 | (parathyroid adj5 (hypofunction or insufficiency or deficiency or lack or low or little or decrease$ or reduce$)).ti,ab. | Cytel internal search strings |
| **Patients with HPT** | | **5** | **or/1-4** | NA |
| **QOL Outcomes** | QOL | 6 | quality of life/ | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | | 7 | (QOL$ or HQL$ or HQOL$ or H QOL$ or HRQL$ or HRQOL$ or HR QOL$).ti,ab. | Cytel internal search strings |
| | | 8 | (quality adj4 life).ti,ab. | Cytel internal search strings |
| | | 9 | (quality adj2 well?being).ti,ab. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | QALY or DALY | 10 | Quality-Adjusted Life Years/ or quality adjusted life year/ | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | | 11 | (quality adjusted life$ or quality-adjusted life$ or disability adjusted life$ or disability-adjusted life$).ti,ab. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | | 12 | (QALY or qal$ or qwb$ or qald$ or qale$ or qtime$ or daly$).ti,ab. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | PRO | 13 | Patient Reported Outcome Measures/ or patient-reported outcome/ | Cytel internal search strings |
| | | 14 | (patient adj2 reported adj2 outcome$).ti,ab. | Cytel internal search strings |
| | | 15 | PRO.ti,ab. | Cytel internal search strings |
| | Utility | 16 | european quality of life 5 dimensions 3 level questionnaire/ or "european quality of life 5 dimensions 5 level questionnaire"/ or "european quality of life 5 dimensions questionnaire"/ or "european quality of life 5 dimensions visual analogue scale"/ | Cytel internal search strings |
| | | 17 | (euroqol$ or euro qol$ or euro-qol$ or euroqual$ or euro qual$ or euro-qual$ or eq5d$ or eq 5d$ or eq-5d$ or eqoL-5d$ or eqoL5D$ or eqoL 5d$).mp,af,tw. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities. Cytel added variations: euroqual$, euro qual$, eqoL5D$, eqoL 5d$ and “mp,af,” to broaden the search |
| | | 18 | (utilit$ or disutilit$).mp,af,tw. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities Cytel added “mp,af,” to broaden the search. |
| | | 19 | (standard gamble$ or time-trade-off or time trade-off or time trade off or time tradeoff).ti,ab. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |

| Eligibility criteria | Database | | Term | References |
|---|---|---|---|---|
| | | 20 | (willingness adj4 pay).ti,ab. | CADTH: https://searchfilters.cadth.ca/link/18<br>Cytel replaced “to” with “adj4” to broaden the search, and removed “kf.” to search in multiple databases |
| | | 21 | (SG or TTO or WTP).ti,ab. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | | 22 | ((valu$ or measur$) adj4 (health or outcome$ or effect$ or change$ or state$)).ti,ab. | Cytel internal search strings |
| | | 23 | (VAS or visual analogue scale$ or visual-analogue scale$).mp,af,tw. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities.<br>Cytel added VAS and “mp,af,” to broaden the search. |
| | QOL scales | 24 | short form 36/ or short form 12/ | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities |
| | | 25 | (sf-36$ or sf36$ or sf 36$ or sf-12$ or sf12$ or sf 12$ or sf-6$ or sf6$ or sf 6$ or short form$ or shortform$ or RAND$).mp,af,tw. | NICE TSD 9: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities<br>Cytel added “mp,af,” to broaden the search. |
| | | 26 | (WHO-5 or Well-Being Index or Well Being Index or WellBeing Index or Caregiver Strain Index or MCSI or Beck depression Index or Middlesex Hospital Questionnaire or Pittsburgh Sleep Quality Index or PSQI or HPT-SD or HPT SD or Functional Assessment of Chronic Illness Therapy or FACIT or FACIT-F or FACIT-Fatigue or HADS or "Hospital Anxiety and Depression Scale" or Activities of daily living or ADL or ADLQ or IADL or Instrumental Activities of Daily Living or WPAI).tw. | Cytel internal search strings |
| | | 27 | or/6-26 | NA |
| **QOL Outcomes in Patients with HPT** | | **28** | **5 and 27** | NA |
| **Irrelevant Study Design** | | 29 | (addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or monograph or news or "newspaper article" or practice guideline or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt. | Cytel internal search strings |
| | | 30 | (animals/ not (humans/ and animals/)) or (animal/ not (human/ and animal/)) | BMJ: https://bestpractice.bmj.com/inf |

| Eligibility criteria | Database | | Term | References |
|---|---|---|---|---|
| | | | | o/toolkit/learn-ebm/study-design-search-filters/ |
| | | 31 | case report/ or case reports/ | Cytel internal search strings |
| | | 32 | or/29-31 | NA |
| | | 33 | 28 not 32 | NA |
| **Limits** | | **34** | **limit 33 to human** | NA |
| | | | EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 26 , 2025> | NA |
| | | | EBM Reviews - ACP Journal Club <199 1 to March 2025> | NA |
| | | | EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> | NA |
| | | | EBM Reviews - Cochrane Clinical Answers <March 2025> | NA |
| | | | EBM Reviews - Cochrane Central Regi ster of Controlled Trials <February 202 5> | NA |
| | | | EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> | NA |
| | | | EBM Reviews - Health Technology Assessment <4th Quarter 2016> | NA |
| | | | EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> | NA |
| | | | Econlit <1886 to March 20, 2025> | NA |
| | | | Embase <1974 to 2025 March 26> | NA |
| | | | Ovid MEDLINE(R) ALL <1946 to March 26, 2025> | NA |
| **FINAL SELECTED: QOL Outcomes in Patients with HPT** | | **35** | **remove duplicates from 34** | NA |
| | | | EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 26 , 2025> | NA |
| | | | EBM Reviews - ACP Journal Club <199 1 to March 2025> | NA |
| | | | EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> | NA |
| | | | EBM Reviews - Cochrane Clinical Answers <March 2025> | NA |
| | | | EBM Reviews - Cochrane Central Regi ster of Controlled Trials <February 202 5> | NA |
| | | | EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> | NA |
| | | | EBM Reviews - Health Technology Assessment <4th Quarter 2016> | NA |
| | | | EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> | NA |
| | | | Econlit <1886 to March 20, 2025> | NA |
| | | | Embase <1974 to 2025 March 26> | NA |

| Eligibility criteria | Database | | Term | References |
|---|---|---|---|---|
| | | | Ovid MEDLINE(R) ALL <1946 to March 26, 2025> | NA |

# References


1. Ascendis P. Ascendis Pharma.Briefing Book for Patient Reported Outcome Instruments Included in the Phase 3 Clinical Trial of Palopegteriparatide in Adults with Hypoparathyroidism.
2. Khan AA, Rubin MR, Schwarz P, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. 2023.
3. Rejnmark L, Gosmanova EO, Khan AA, et al. Palopegteriparatide Treatment Improves Renal Function in Adults with Chronic Hypoparathyroidism: 1-Year Results from the Phase 3 PaTHway Trial. 2024.
4. Jens Bollerslev LR, Claudio Marcocci , Dolores M Shoback , Antonio Sitges-Serra , Wim van Biesen , Olaf M Dekkers European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. *European Journal of Endocrinology.* Aug 2015;173(2):G1–G20.
5. Chen K, Krasner A, Li N, Xiang CQ, Totev T, Xie J. Clinical burden and healthcare resource utilization among patients with chronic hypoparathyroidism, overall and by adequately vs not adequately controlled disease: a multi-country chart review. 2019.
6. Jens Bollerslev LRCMDMSAS-SWvBOMD. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. *European Journal of Endocrinology.* 2015;173(2):G1–G20.
7. Gafni RI, Collins MT. Hypoparathyroidism. *N Engl J Med.* 2019;380(18):1738–1747.
8. Cusano NE, Anderson L, Rubin MR, et al. Recovery of parathyroid hormone secretion and function in postoperative hypoparathyroidism: a case series. *J Clin Endocrinol Metab.* 2013;98(11):4285–4290.
9. Brandi ML, Bilezikian JP, Shoback D, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab.* 2016;101(6):2273–2283.

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

# NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | NHS England |
| **3. Job title or position** | [redacted], [redacted] |

| | |
|---|---|
| **4. Are you (please select Yes or No):** | Commissioning services for an ICB or NHS England in general? Yes<br>Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes<br>Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No<br>An expert in treating the condition for which NICE is considering this technology? Yes<br>An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | NHS England Specialised Commissioning |
| **5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## Current treatment of the condition in the NHS

| | |
|---|---|
| **6. Are any clinical guidelines used in the treatment of the condition, and if so, which?** | Yes<br>ESE – currently being revised (launch May 2025) and I sit on that group.<br>Current: https://academic.oup.com/ejendo/article/173/2/G1/6668000?login=false<br><br>Older international - https://academic.oup.com/jcem/article/101/6/2273/2804718?login=false |
| **7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | No – pathway of care not well defined and significant inter-individual variation in care, from treatment approach and in particular monitoring.<br>Have awareness of England/UK/Europe and global |
| **8. What impact would the technology have on the current pathway of care?** | Likely would become a standard of care over a protracted period. Specialised centres with expertise in managing hypoparathyroidism are more likely to receive referrals from elsewhere and potentially patients who have been followed up only in primary care would need to come into a secondary care environment. Initiation of this treatment will involve quite intensive monitoring initially to stabilisation. In the long term, this type of treatment may well reduce complications of hypoparathyroidism, particularly around renal function. Improvement in symptoms, quality of life, and ability to remain engaged within the workforce may well improve. |

## The use of the technology

| | |
|---|---|
| **9. To what extent and in which population(s) is the technology being** | Currently not being used. |

| | |
|---|---|
| **used in your local health economy?** | |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | Not currently being used in this formulation in England. Is likely to take the place of the current sub optimal standard of care with active vitamin D with or without calcium supplementations.<br>Some PTH preparations are being used, largely off label, in England. Those patients receiving such would likely transition to a licenced product early if approved. |
| **10a. How does healthcare resource use differ between the technology and current care?** | Drug cost of new treatment would be substantially more than current drug costs.<br>During potential switch from current care to new technology, intensive monitoring would be required (blood tests) over a number of weeks to provide stabilisation. One stabilisation has occurred, frequency of monitoring will reduce and drift towards current care.<br>More patients are likely to achieve good biochemical and symptom control with new technology meaning that there will be less difficult to manage cases who in perhaps 10 to 15% of cases have frequent emergency admissions with disturbances of calcium balance.<br>As above, renal outcome data in the long term may be better with the new technology, meaning that risk of kidney stones and potentially chronic renal impairment may reduce. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Secondary care although a strong case could be made for narrowing access through designated specialised services for rare forms of bone and calcium disorder. |
| **10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)** | Standard awareness and training but no other significant investment. |
| **10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does** | There will be initiation and monitoring protocols. As above, more frequent blood tests around initiation to stabilisation. Longer term monitoring will be very similar to current care. |

| | |
|---|---|
| **this include any additional testing?** | |
| **11. What is the outcome of any evaluations or audits of the use of the technology?** | Not available in England.<br>Outside study settings, I am not aware of audits yet in other countries. |

## Equality

| | |
|---|---|
| **12a. Are there any potential equality issues that should be taken into account when considering this treatment?** | As things stand, GIRFT reviews in endocrinology suggest that management of hypoparathyroidism varies across the country and is often delivered poorly. The main issue around equality is ensuring that all patients with hypoparathyroidism are seen by a specialist with insight to emerging treatments and longer term monitoring. |
| **12b. Consider whether these issues are different from issues with current care and why.** | Current care is accepted as being sub optimal for managing a hormone deficiency state, hypoparathyroidism. If there is a new technology to replace the hormone, it is important that all patients have equal opportunity and access to treatment that is likely to improve long term outcomes. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

**Please select YES** if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

# Patient Organisation Submission

## About you

| | |
|---|---|
| **1.Your name** | [redacted] |
| **2. Name of organisation** | Parathyroid UK |
| **3. Job title or position** | [redacted] |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | Parathyroid UK is a national patient organisation set up in 2005 to provide support and information to patients with all types of parathyroid conditions via our website, online support groups, telephone helpline and patient information leaflets and newsletters. It is affiliated to the Society for Endocrinology (SfE), the European Society of Endocrinology (ESE) and soon the British Association of Endocrine and Thyroid Surgeons (BAETS) and works closely with these and its team of specialist advisors to educate healthcare professionals, raise awareness and engage in research. It has a growing membership of around 6,000 patients and is funded primarily by volunteer support and occasional grants from the Society for Endocrinology and donations from industry partners. |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?** | We received a fee of £5,000 from Ascendis Pharma via Decisive Consulting for involvement in a patient survey in 2024.<br><br>We also received two donations of £4,000 each from Amolyt Pharma in 2022 and 2023 for awareness projects. |

| | |
|---|---|
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | None |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | We conducted two patient surveys with our hypoparathyroidism members which had excellent responses and which we hope will soon be published. The first was an in-house study about symptom management (219 responses) and the second, with Ascendis (402 responses), on the burden of treatment. As well as these, we have nearly 20 years of continuously gathered qualitative information from our online support groups and helpline calls. This has given us a very specific and detailed knowledge of how hypoparathyroidism impacts patients and carers on a daily basis. |
| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | **Living with hypoparathyroidism** is a lifelong challenge due to the constant need to maintain calcium homeostasis and prevent a life- threatening crisis. The profound and life changing impact of the dual lack of parathyroid hormone and vitamin D is compounded by the lack of access to testing, appropriate treatment and adequate care. This amplifies the climate of anxiety in which patients already live due to the effect of low calcium levels. Symptoms of tetany increase in severity without immediate treatment and can occur without warning. Both long and short term symptoms affect patients physically, cognitively and emotionally so the impact on quality of life (QoL) and mental health can be significant. With the exception of a small group of very stable patients who lead normal lives we find this to be the experience of most patients living with hypoparathyroidism.<br><br>• '*It's like being on a rollercoaster and unable to get off'. (Jenny)*<br>• *It's a battle each day, some not so bad, other days a complete write off, feeling exhausted, useless and scared.' (Jo)*<br>• *I miss being me. The old me was active, bubbly and energetic, always up for adventure. The new me has to factor in how being active, bubbly and energetic will affect my calcium. Life is less these days and I'm not the same person.' (Tania)*<br><br>**Patient reported outcomes** show an adverse impact on QoL due to symptom severity; physical functioning, psychological well-being, social life and work may all be affected[1]. Symptoms are unpredictable and can range from mild to severe without warning. Significant long-term complications including renal impairment, renal stones, nephrocalcinosis as well as cataracts and calcification of the brain can occur[2] and the condition is a challenge for doctors and patients to manage on a daily basis. Studies show greater rates of mortality, infection, renal and cardiovascular complications in hypoparathyroidism patients than the general population, which is reflected in our groups[3,4]. Patients are often mismanaged and experience a high frequency of hospitalisation as a result. In a recent in-house study, 25% of study participants required hospitalisation over the past 12 months[5]. |

- *'My condition is unbearable, debilitating on every level of physical and mental well-being, unable to work, unable to socialise or function on a day to day basis causing ongoing health issues - kidney failure, high potassium, low vitamin D levels, visual impairment, tetany, heart problems, digestive problems. The list is endless.' (Jackie)*

**The burden on carers is heavy** as managing calcium levels is individual, unpredictable and dependant on many factors including infection, diet, stress, medication etc. Decision making in a crisis is very difficult; a 'hypo' may be successfully self- managed at home or the patient may need urgent hospital treatment. Symptoms such as pain, fatigue and weakness may occur after a busy day, leading to days off to recover or be so ongoing and debilitating as to need to give up work entirely. Care can be needed at any time of day and night, in and out of the house, so the carer is on constant call and must also tread a difficult line between supporting the patient and allowing independence where possible. The lifelong emotional and physical strain on the carer should not be underestimated[6]. In severe cases, where the patient may be receiving PIP the carer will need to assist full time with care (washing and dressing), meals (shopping, cooking, feeding) and mobility. In more mild cases care often falls to the partner or family who have to step in at a moment's notice to take over until the patient feels better. Whether occasional or permanent this often requires a significant change in family roles and expectations.

- '*It's soul destroying for my family as everything revolves around how I feel daily.' (Yvonne)*

**Groups living with mild, moderate and severe hypoparathyroidism**

At Parathyroid UK we have around 3,000 members with different types of hypoparathyroidism; approximately 75% of these cases were iatrogenically induced. While a small percentage of members manage relatively well on conventional therapy (calcium and/or activated vitamin D), are able to work full time, exercise and require only occasional adjustments to their medication, others have a more difficult time. The majority of our members have unstable calcium levels to some degree and frequency, some just occasionally, others constantly. In the smaller group of more severe and brittle cases calcium levels are rarely stable and extremely difficult to manage for both doctors and patients.

- *'For me, 95% or more of the time, I'm stable. But it has meant I have to think about the exercise I may want to do and guess the amount of calcium I need to take in my diet and what my current level may be. I'm pretty good at it, but don't always get it right.' (Stephen)*
- *'In general my quality of life has been hugely depleted. I don't suffer huge swings in calcium, i am fairly stable, however, I am constantly fatigued, and my brain doesn't function. Its like living in a much older body with early stage dementia. It's really impacted my ability to be the head of the household and breadwinner that everyone could rely on. It has knocked my confidence and self image.' (Ruth)*
- *'Living with brittle hypoparathyroidism is a lifelong endurance test. The long term kidney issues are bad enough but you are constantly having to guess what your calcium level is, to decide what to do about it and how it will impact what you need to do that day. Will you get it right or will you end up in hospital? My calcium can drop very suddenly so my life is one of anxiety and constantly changing plans.' (Lizzy)*

**Patient experiences**

Hypoparathyroidism is an illness with a high symptom burden. Despite treatment with conventional therapy, most patients continue to experience frequent symptoms, poor symptom control and a subsequent compromised QoL. The side effects from the long-term use of conventional therapy also contribute to this burden.

| | |
|---|---|
| | A recent study, conducted on 219 hypoparathyroid members of Parathyroid UK, aimed to investigate the patient experience of symptom management[5]. Participants were asked to rate the frequency and severity of their symptoms from a list of 18 options, identified as those most commonly occurring from the literature and disease specific tools[7,8]. The perceived impact on QoL was also assessed by rating participants ability to exercise, work, sleep, participate in hobbies and leisure activities, and interact with family and friends; the factors identified as those most likely to be impaired in persons with hypoparathyroidism[6,7,8].<br><br>From the study, the symptoms of fatigue/tiredness (74%), changes in body temperature (50%), confused thinking (47%), tingling/numbness (43%), bone pain (40%), anxiety (40%), muscle spasm (35%) and muscle cramp (32%) were those experienced most frequently or all the time by participants. These same symptoms were also those reported as occurring most severely; fatigue/tiredness (70%), confused thinking (48%), anxiety (44%), tingling/numbness (40%), changes in body temperature (40%), bone pain (35%), muscle cramp (35%) and muscle spasm (34%) respectively.<br><br>These findings highlight the multi-system aspect of hypoparathyroidism; an illness which affects patients physically, mentally and emotionally and unsurprisingly, also significantly diminishes their QoL. The percentage of participants reporting a 'frequent or always' impact on QoL factors was: Ability to exercise (47%), work (37%), sleep (37%), participate in leisure/hobbies (32%) and socialise (23%). These findings are consistent with previous research on QoL in hypoparathyroidism[6,9].<br><br>Fatigue is a major factor in hypoparathyroidism and has an over-arching impact on all aspects of life. It can make exercise and work exceptionally difficult or impossible but also limits patients' ability to socialise and generally enjoy life. Impaired brain function, often too simply referred to as 'brain fog', causes confused thinking and is a major limiting symptom for many.<br><br>Cognitive effects such as brain fog, memory loss, attention or poor recall also interfere with the activities of daily living and learning and hinder patients' ability to work[9]. A hidden condition is not always recognised by employers and patients have had to reduce hours or give up work altogether due to their inability to function as required or by becoming unfit/unsafe in the work environment.<br><br>The physical symptoms experienced by most patients also serve as limiting factors. The muscle spasms, cramps, bone pain and tingling and numbness which are common to sufferers can make movement very difficult. All muscle contractions require calcium, the more intense the activity, the more calcium required. For many people with hypoparathyroidism, intense physical activity is simply prohibitive. For others, even simple activities like going on a long walk, are out of reach. Many are unable to meet NHS guidelines on physical exercise which increases the risk of stroke and/or cardiovascular disease[4].<br><br>Loss of PTH also affects mood, energy and hormonal balance and hypoparathyroid patients often report mental health impairments such as anxiety and depression. Claustrophobia and agoraphobia have also been reported. Anxiety is a common symptom and appears to persist even when serum calcium levels are restored[10]. This may be due to the unpredictable nature of symptom onset which again makes it so hard for patients to travel, make plans or hold down work. In addition to its role in calcium homeostasis, it has also been suggested that parathyroid hormone may serve other important roles and its absence in hypoparathyroidism may have a direct effect on well-being[11].<br><br>An often-overlooked aspect of the impact of hypoparathyroidism is its effect on diet. Calcium supplements are frequently prescribed in large doses, and these are well known to cause gastrointestinal upset, with diarrhoea, constipation and stomach pain as common side-effects[12]. Long-term use of calcium supplements is also documented as contributing to renal complications[13]. To reduce the likelihood of these complications, many patients opt to obtain their calcium predominately from |

| | |
|---|---|
| | dietary sources, however, this too can prove complicated. Due to the lack of PTH at the kidney level, calcium is excreted while phosphate is retained. This leaves patients in the often-difficult situation of trying to balance their calcium needs while simultaneously reducing their phosphate intake.<br>**Managing calcium levels**<br>The need to manage calcium levels to stay safe is, of necessity, a large part of many patients lives. The aim of treatment is to keep levels low enough to protect the kidneys but high enough to prevent symptoms. In reality this is not easy and is a juggling game that leads many patients to feel they live on a rollercoaster, dictated by constantly swinging calcium levels. To manage this without a blood tester is extremely difficult. To have to self- manage because your doctor does not know what to do is extremely frightening. PTH, however, is known to improve calcium stability.<br>• *'Vulnerable. Often when you reach out for help, it's because you're feeling symptomatic. It's difficult to be your own advocate when you're feeling vulnerable due to symptoms. Especially so against a backdrop of much misinformation.' (Emma)*<br>• *'Exhausting and unpredictable - you have to consider calcium every day and in absolutely everything you do.' (Emma Kate)*<br>• *'I feel like I have to beg for basic blood tests when I am trying to figure out if I am high or low. GP needs more education on hypopara and to realise we need tests and results quickly.' (Sally)*<br>1. Hypopara UK (2017). Living with Chronic Hypoparathyroidism.<br>2. Khan (2019). Standards of care for hypoparathyroidism in adults: a Canadian and International Consensus.<br>3. Vadiveloo et al. (2019). Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study.<br>4. Gosmanova et al. (2021). Risk of cardiovascular conditions in patients with chronic hypoparathyroidism: A retrospective cohort study.<br>5. Gelmetti (2023). Managing hypoparathyroidism: A comparison of symptom management experiences in persons with hypoparathyroidism taking calcium supplements versus those using dietary calcium sources. [Unpublished manuscript]<br>6. Siggelkow et al. (2020). Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-county patient and caregiver survey.<br>7. Brod, et al. (2021). Living with hypoparathyroidism: development of the Hypoparathyroidism Patient Experience Scale-Impact (HPES-Impact).<br>8. Wilde et al. (2020). The HPQ-Development and First Administration of a Questionnaire for Hypoparathyroid Patients.<br>9. Sikjaer et al. (2024). Hypoparathyroidism: changes in brain structure, cognitive impairment, and reduced quality of life.<br>10. Hadker et al. (2014). Understanding the burden of illness associated with hypoparathyroidism reported among patients in the paradox study.<br>11. Arlt et al. (2002). Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D.<br>12. Al-Sharefi et al. (2019). Is calcium supplementation always needed in patients with hypoparathyroidism?<br>13. Underbjerg et al. (2013). Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. |
| **7. What do patients or carers think of current treatments and care available on the NHS?** | In our second patient survey[1], designed with Ascendis to assess the burden of managing hypoparathyroidism in the UK with a medication regimen of conventional therapy, we found that adults with hypoparathyroidism have evident treatment dissatisfaction. Fewer than half of the 402 respondents reported satisfaction with their treatment regimen (44.1%). Treatment dissatisfaction was driven by poor communication with healthcare professionals (82.6%), concerns about long-term complications eg heart and kidney (69.3%), and the burden of managing their medication regimen (55.1%). These results suggest that programmes to improve physician communication on hypoparathyroidism should be considered and highlight the need for an effective and safe treatment with reduced risk of long-term complications. Except for those lucky enough to be treated by the few existing calcium specialists, patients across the UK continually report to us that they experience very poor care. We are constantly asked for recommendations |

| | |
|---|---|
| | to specialists and people will travel long distances to see an expert in calcium metabolism. Among endocrinologists and GPs there is poor communication and considerable lack of knowledge about the condition or how to diagnose or manage it. There are frequent hospital admissions due to mismanagement by doctors. Provision is patchy and needs to be standardised across the UK particularly post operative care and follow up, as reported in our UK audit of endocrine departments[2]. Patients strongly feel that current treatment is not effective, is not fit for purpose, wasn't designed to treat hypoparathyroidism, doesn't meet their needs and causes poor long term outcomes. The impact of this on patient QoL remains significant. Patient views on treatment and care:<br><br>• *'In no other hormone deficient condition are patients expected to guess whether they need to self medicate ( and how much to take) in order to avoid a crisis'.(Helen)*<br>• *'It's a postcode lottery – some of us have the very best care and some of us don't. Many of us have endocrinologists or GPs with a limited understanding. (Jenny)*<br>• *'It's frightening to recall the number of times I've been given completely negligent and potentially harmful advice! We need more people trained to understand the condition or at least trained to listen to us when we explain it!' (Kathy)*<br>• *'Hit and miss, my endo is dismissive. Doesn't seem to grasp that just like insulin levels, calcium levels can rapidly fluctuate the assumption is if your blood calcium measurement was good yesterday it will be good for the next 6 months.'(Tania)*<br>• *'It's dreadful. The information is out there but most GP's and Endos don't bother to read it. Even if you give them a copy!' (Maxine)*<br>• *'It's inadequate, the drugs damage our kidneys and are just a patch to keep us going, care is brief and blood tests impossible to get most of the time. You are left self managing and by the time the results are through days later everything has changed again. It's laughable really. It's a guessing game. (Lynn)*<br>• *'There is no care at the moment at my local hospital. My Endo retired due to ill health and they haven't replaced him. Called last week and they don't know when my next appointment will be!' (Jaqueline)*<br>• *'Remind me what that is' was a comment from a Dr when I hadn't long been diagnosed and it just really depressed me that I was seeking for help for something that he had no idea about. That's not good enough. I think too many of us are only offered calcium and vitamin D when there are better treatments that should be available to us..' (Emma)*<br>1. **Glenister & Ascendis (2024). Burden of managing hypoparathyroidism medication regimens: a patient survey (Abstract to be presented at BES2025).**<br>2. **Kiam (2022). UK national chronic hypoparathyroidism audit.** |
| **8. Is there an unmet need for patients with this condition?** | There are many significant unmet needs for patients with hypoparathyroidism.<br>• Diagnosis: routine calcium blood tests are needed.<br>• Surgery: only high volume surgeons should operate; there needs to be standardised post surgical guidelines and follow up<br>• Training & guidelines: many endocrinologists do not know how to manage hypoparathyroidism and ignore clinical guidelines. GP training needed.<br>• Treatment: current treatment causing fluctuating levels and long term conditions. Conventional therapy involves replacing calcium and activated vitamin D, but it does not address hyperphosphatemia. Treatment decisions need to be customised to meet each patient's unique needs, but guesswork is common. Management is generally poor and hospitalisation occurs unnecessarily. |

| | |
|---|---|
| | • Testing: testing needs to be accessible *when needed* with immediate results, as in diabetes. Urgent care needed. Emergency response in hospitals is very poor.<br>• Long term outcomes: calcifications, cataracts, significant nephrocalcinosis, nephrolithiasis and CKD.<br>• Quality of life: significant impact on QoL affecting family and social life, work, travel, self image and mental health issues. Also, carer burden. |

| | |
|---|---|
| **9. What do patients or carers think are the advantages of the technology?** | Patients feel very strongly that parathyroid hormone treatment will make a significant difference to their lives and their physical and mental wellbeing. Indeed, those who have trialled previous PTH therapies have reported calcium stability, renewed energy and strength and improved or even reversed kidney function.<br>• '*It was if a lightbulb had been switched on in my brain.' (Ray)*<br>Patients have been campaigning for PTH replacement therapy since 2010 and closely follow the progress of fellow patients around the world who are in or have been in clinical trials. They see the positive feedback and they want it badly for themselves. They know that replacement hormone therapy is standard practice in the UK and are aware that it exists for every other endocrine condition where there is a decrease in hormone production.<br>• *'I hope that it willl give me a better QoL, protect my kidneys and reduce my chances of developing bone & teeth problems. I would like to 'feel normal'. Ive coped with fatigue and poor health for a long time. I would love to be given the opportunity to find out for myself if this can make a meaningful and lasting difference to my life and that of my family.' (Jenny)*<br>• *'As someone who has been receiving PTH I can categorically say that it allows me to continue to work and contribute to society. Life is worth living again. Without it I am scared of the place I could go back to!' (Teresa)*<br>• *'I am now receiving PTH and within 3 weeks I stopped all other meds, regained my QoL, it's like a miracle, I feel NORMAL again, although we have found that my arteries are calcified sadly. If we were not taking chalk (as my doctor calls it) perhaps this would not have happened. There's a saying - cheap is expensive in the long run.' (Jacquie)*<br>• *'I would love to have the chance of a better quality of life, being able to face each day with confidence I wasn't going to drop or go high would be amazing.' (Jo)*<br>• *'Advantages would be a huge improvement in QoL, not taking a medicine that is damaging your kidneys, treating the issue and not just the side effects.' (Kathy)*<br>• *'Hopefully a better quality of life for patients to be able to work, study. This would lead to a quality of life for the whole family.' (Christine)*<br>• '*According to USA trial patients, Yorvipath enables us to regain QoL, virtually eliminate calcifications, regain normal kidney function, regain normal heart function, regain normal brain function, regain normal response, regain being able to function normally, regain normal bloods, the list is endless. There is no question Yorvipath can enable us to regain our health and prevent hospital visits/admissions thus saving the NHS huge amounts of money/time.' (Jackie)* |

| | |
|---|---|
| **10. What do patients or carers think are the disadvantages of the technology?** | In our questionnaire three people out of 177 asked about potential negative effects and one about costs. Most people had read up about Palopegteriparatide and had followed clinical trial results closely. The most common worry among patients appears to be that they may not be eligible to get PTH.<br>• *None that I can see except the chances of us not getting it are high if we are fairly stable. I suppose we may have bruises from injections, but in comparison to symptoms we deal with daily I'd take the bruises.' (Lynn)*<br>• *Possible negative impact on bones - do they know long term effects?.' (Jaqueline)*<br>• *'Unknown long term complications' (Jay)*<br>• *'Eligibility for people who are more stable than others, even if not well.' (Kathy)*<br>• *'Cost and getting funding.' (Deborah)*<br>• *I'm worried that it will be a battle to get a shot at trying the new drugs. I'm not hopeful at all because I am quite stable levels wise so trying to convince anyone I feel the effects of this condition every day of my life falls on deaf ears and is soul destroying. (Jayne)*<br>• *'I worry a disadvantage may be that I've had this condition too long, but I would like the opportunity to find out if it would work for me.' (Jo)*<br>• *The disadvantage for me would be any side effects from the drug / fillers because I am sensitive to current medications for hypopara or if I could inject myself every day.' (Sally)* |
| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | The aforementioned 3 groups (mild, moderate and severe) would all benefit from receiving the technology because they all have individual unmet needs due to the lack of PTH. While there is a small group experiencing severe difficulties, there is a large population perceived as stable with 'normal' calcium yet have persistent symptoms and a further small group who may be asymptomatic but all may have secondary conditions eg hypercalcuria, kidney disease, eye problems and organ calcifications. It must be recognised that *all* patients would benefit from replacement of their essential hormone, as is standard practice in other endocrine conditions. Patients strongly feel that replacing their missing hormone will have untold, and as yet unknown, benefits regardless of their current situation |

| | |
|---|---|
| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | • Patients whose doctors do not recognise their hypoparathyroidism or the full extent of their symptoms may have difficulty accessing the treatment, so a true and accurate picture of this rare condition needs to be recognised.<br>• Not all doctors are aware of PTH opportunities for hypoparathyroid patients so greater awareness needed.<br>• Patients unable to work and/or are on disability benefits or PIP because of hypoparathyroidism should not be left out as their conditions could be greatly improved.<br>• Ethnic minority patients are under represented in our membership so we would be concerned about access for this group. Greater publicity needed.<br>• There can be regional disparities; we are concerned that there will be a postcode lottery depending on local commissioning- ICS's with some prioritising new medicines more quickly than others.<br>• The variations in healthcare policies between England, Scotland, Wales and Northern Ireland can lead to unequal access.<br>• Funding constraints appertaining to rare conditions may affect delivery of the treatment. |
| **Other issues**<br><br>**13. Are there any other issues that you would like the committee to consider?** | As a rare condition hypoparathyroidism is not well understood and lacks the recognition and support of other endocrine conditions, such as diabetes, although it shares similar needs in terms of regulation of an important blood circulating molecule and is no less challenging to manage. A diabetic patient has a replacement hormone, a home tester, regular clinics, access to emergency support and a good structure of care provision. Without appropriate medication patients with hypoparathyroidism are prone to fluctuating levels and dangerous decreases in calcium which have to be managed without a home tester or a replacement hormone. Specialist centres do not exist, there is a high level of unmet need, standards of care across the UK are variable and it is a challenging condition for clinicians and patients alike to manage. As a result, patients are vulnerable and angry and feel they deserve equality of access to replacement hormone alongside other endocrine conditions and hypoparathyroid patients already on PTH in other countries. Few patients in the UK have had the chance to try PTH but those that have inspired others and the demand for that opportunity is great.<br>• '*I have been on PTH for almost 10 years now. It undoubtably gives me far more stable calcium levels and a much better QoL. I would not want to go back to life before PTH. Disadvantages – there aren't any!' (Jane, former nurse)* |
| **14. How is disease severity defined in this condition?** | There is a high burden of disease in hypoparathyroidism with increased mortality and additional morbidities[1] and a significant impact on patient and carer quality of life[3]. However, disease severity in hypoparathyroidism is generally underestimated leading to inadequate care, poor clinical decisions and high risk for the patient. The condition is chronic and progressive and both hypo- and hypercalcaemia are life threatening conditions. Symptoms may be frequent, severe, and highly distressing and patients largely perceive symptom treatment as inadequate. The difficulties of managing the condition can cause a worsening of both acute and irreversible long term complications. Describing the disease severity of hypoparathyroidism, Dr Shoback[2] wrote "This is a rare, chronic disease. Day-to-day symptoms can be significant and interfere with quality of life for patients. They have the propensity to develop kidney stones and chronic kidney disease. Their bones can be abnormally dense. They need frequent blood tests, checks of kidney function and calcium levels, and ophthalmology evaluations for cataracts. A lot of these patients have a high burden of disease because they may have other conditions, like heart disease or high blood pressure. Hypoparathyroidism can affect how those other conditions behave and are treated." |

| | |
|---|---|
| | 1. Vadiveloo et al. (2019). Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study.<br>2. Shoback (2023). Second International Workshop on the Evaluation and Management of Hypoparathyroidism.<br>3. Siggelkow et al. (2020). Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey.<br>4 Hypopara UK (2019). Living with Chronic Hypoparathyrodism. |

**Key messages**

| | |
|---|---|
| **15. In up to 5 bullet points, please summarise the key messages of your submission.** | • Hypoparathyroidism is a rare, chronic condition with a high burden of disease severity which is not widely recognised or properly treated.<br>• Patients are vulnerable to a high level of risk and uncertainty in daily life (unstable calcium levels, lack of testing, mismanagement, poor emergency provision and irreversible complications) creating a climate of anxiety and fear. The impact on QoL is significant and it is seen by patients as a scandal that this is not being properly addressed.<br>• Current treatment is inadequate and causes long and short term complications. Patients are dissatisfied with their treatment regime.<br>• The Pathway trial showed that Palopegteriparatide improved and maintained patients' serum calcium levels. It is also known that it improves QoL, reinstates physiological functions and minimises renal damage.<br>• We believe that Palopegteriparatide can help all patients not just those with poorly controlled levels. Now that it is available in Europe, patients in the UK feel very strongly that they should also be offered the opportunity to lead a better life. |

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

**Your privacy** The information that you provide on this form will be used to contact you about the topic above.

**Please select YES** if you would like to receive information about other NICE topics - **YES** or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]**

**Clinical expert statement**

# Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

NICE National Institute for Health and Care Excellence

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **10/09/2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

Clinical expert statement

Palopegteriparatide for treating chronic hypoparathyroidism ID6380

NICE National Institute for Health and Care Excellence

# Part 1: Treating Hypoparathyroidism and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Gowri Malka Ratnayake, Ratnayake Mudiyanselage |
| **2. Name of organisation** | East Kent Hospital University NHS Foundation Trust |
| **3. Job title or position** | Consultant in Endocrinology in Diabetes |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with Hypoparathyroidism?<br>☐ A specialist in the clinical evidence base for Hypoparathyroidism or technology? Yes<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |

| | |
|---|---|
| **8. What is the main aim of treatment for Palopegteriparatide**<br>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | To maintain the serum calcium levels in the lower part or slight lower limit of normal reference range to ensure patients are free or symptoms or signs have a good quality of life |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | 1. Maintain serum calcium levels to be in the lower half of the normal reference range or just below the normal reference range<br>2. Alleviate symptoms of hypoparathyroidsm<br>3. Maintain 24-hour urine calcium excretion <6.25 mmol/24 hours<br>4. Maintain serum phosphate concentrations in the normal reference range |
| **10. In your view, is there an unmet need for patients and healthcare professionals in Hypoparathyroidism?** | Parathyroid hormone plays a key role in maintaining the calcium haemostasis in the body and hypoparathyroidism is characterised by insufficient amounts of parathyroid hormone levels in the body resulting in hypocalcaemia. Hypocalcaemia could lead to dysfunctions in the neurological, cognitive, muscular and cardiac systems.<br>Currently, the disorder is treated with the calcium and active vitamin d replacement rather than treating with parathyroid hormone replacement. Despite maximum optimisation of this conventional treatment strategy does to normalise the biochemistry, symptomatology and/ or quality of life of some patients warranting treatment with parathyroid hormone replace therapy.<br>Hence, lack of availability of parathyroid hormone replacement therapy for treatment of hypoparathyroidism had been an unmet need for patients with hypoparathyroidism and the healthcare professionals. |
| **11. How is Hypoparathyroidism currently treated in the NHS?** | |

| | |
|---|---|
| • Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | • Yes<br>1. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults 2015<br>2. Management of Hypoparathyroidism: Summary Statement and Guidelines , JCEM 2016<br>3. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2021)<br>4. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop, JBMR 2022<br>• The technology would allow the patients with hypoparathyroidism who don't have their symptoms or biochemical parameters or quality of life not adequately controlled by the conventional therapy to receive parathyroid hormone replacement and to improve clinical and biochemical parameters, |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | • Currently Palopegteriparatide is not available for the NHS patients with hypoparathyroidism who have inadequate response to conventional therapy.<br>• The technology should be used in specialist clinics<br>• Training for health care providers, training patients on injection technique/ administration, equipment necessary for proper storage and dispense of technology. Eg: Palopegteriparatide should be stored in a refrigerator (2- |

| | |
|---|---|
| | 8℃) and protected from light. It may be stored at room temperature (below 30℃) after opening and should be discarded within 14 days. |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | • The technology has shown clinically meaningful benefits compared to the currently available conventional treatement by normalising the calcium, 24 hour urinary excretion of calcium, imporving the renal functions, improving quality of life of these patient. It may improve the length of the life but more data is necessary to conclude this point.<br>• Yes, the technology has shown to improve the health-related quality of life on double blind placebo controlled clinical trials |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | N/A |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient | Patients would need measuring of serum calcium 7 days after starting treatment and within 7 to 14 days after each dose adjustment during treatment.<br>In addition, would need assessment for signs and symptoms of hypo- and hypercalcaemia, and adjust active vitamin D and calcium supplement as necessary |

| | |
|---|---|
| acceptability or ease of use or additional tests or monitoring needed) | Abrupt interruption or discontinuation can result in hypocalcaemia and the patient would need to be monitored for signs and symptoms if 3 or more consecutive doses are affected. If this is the case measuring serum calcium and reintroduction of conventional therapy (calcium supplement and active vitamin D treatment) may be needed as required.<br><br>Some patients might not accept the treatment as the technology is an injectable preparation. |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | Before starting treatment following tests may be indicated:<br>• If the patient is < 25 years a Xray of the non-dominant wrist confirming epiphyseal closure<br>• Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m<br>When stopping treatment:<br>• Patient would need to be restarted on conventional treatment (calcium and active vitamin D) and will need monitoring of serum calcium levels. |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | The technology is a subcutaneous injection in comparison to the conventional treatment which are oral tablet. However, people with Hypoparathyroidism often has to take several frequent tablets/day. Hence, the technology will improve the pill burden in the patients and the technology could be self-administered by the patient/carer. |

| | |
|---|---|
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | Currently, parathyroid hormone replacement is not offered to patients with hypoparathyroidism and is the only common hormone deficiency where hormone replacement therapy is currently not offered in NHS.<br>Hence for those patients who are unable to achieve the therapeutic targets mentioned above, offering this technology would be a step change and will be addressing an unmet need of this patient population. |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Patient would need frequent monitoring biochemistry during the initial period of starting and during dose adjustments of the technology as hypocalcaemia and hypercalcaemia are both know side effects of the treatment. Despite the side effect PaTHway Trial showed improvement of quality of life. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | • The clinical trials have recruited the patients who had been receiving the conventional therapy for hypoparathyroidism similar to the UK patients<br>• Most important outcomes include normalisation of serum calcium levels, 24 hour urine calcium excretion, independence from conventional treatment (calcium and active vitamin d supplements), sustained improvement of quality of life, physical functioning and wellbeing.<br>• A subgroup analysis performed on PatTHway trial showed significant improvement of eGFR at 52 weeks |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| 22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology | No |

| | |
|---|---|
| appraisal guidance [TA Palopegteriparatide for treating chronic hypoparathyroidism]**?** | |
| **23. How do data on real-world experience compare with the trial data?** | Early US Real-World Treatment Patterns and Outcomes in Palopegteriparatide Treatment for Patients with Hypoparathyroidism published in August 2025 revealed that treatment with Palopegteriparatide for hypoparathyroidism outside of a clinical trial setting reaffirms its efficacy and safety profile. |
| **24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population | • Clinical trials on Palopegteriparatide had not included pregnant and lactating patients. Hence, more data would be necessary before approving medication for pregnant and lactating women.<br>• Also,the current evidence for this medication come from an adult population. Therefore, there is insufficient evidence to approve it for be used in children and young people (< 18 years of age) |

| | |
|---|---|
| • lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Current evidence suggest that that Palopegteriparatide once a day subcutaneous injections normalises the serum calcium levels, 24 hour urinary calcium excretion, improvement of renal functions and improve the quality of life of the patients with hypoparathyroidism with independency from the conventional treatment
2. Palopegteriparatide could be used in patients with hypoparathyroidism who don't have their symptoms or biochemical parameters or quality of life not adequately controlled by the conventional therapy
3. There is inadequate data to recommend it in pregnant women, children and young people and also during lactation
4. There is evidence on the efficacy and safety of palopegteriparatide treatment outside the clinical trial in the real world patients.
5. Palopegteriparatide treatment for hypoparathyroidism address the long-term unmet need of patients with hypoparathyroidism by offering the parathyroid hormone replacement and therefore normali

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

## Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

## Clinical expert key questions and response

| | |
|---|---|
| **Name:** | Dr Gowri Ratnayake Mudiyanselage |
| **Job title or position:** | Consultant in Diabetes and Endocrinology,<br><br>East Kent Hospitals University NHS Foundation Trust |
| **Organisation:** | Society for Endocrinology, UK |
| **Question** | **Response** |
| **1. Definition of 'not adequately controlled' (NAC) with conventional therapy** | |
| For adults with chronic hypoparathyroidism, how would NAC be defined? | - Inability to maintain serum calcium levels to be in the lower half of the normal reference range or just below the normal reference range<br>- Presence of symptoms of hypoparathyroidsm/ poor quality of life<br>- 24-hour urine calcium excretion >6.25 mmol/24 hours<br>- Serum phosphate concentration above the normal range. |
| What proportion of patients with hypoparathyroidism in the NHS are | 43.5% have poor qulity of life related to symptoms (Ref: Joint survey conducted by |

| | |
|---|---|
| NAC with conventional therapy using this/these definition(s)? | Ascendis Pharma and Parathyroid UK, 2025) |
| The company's definition of NAC is listed below. Is this an appropriate definition of NAC?<br><br>**ANY of:**<br>• Symptomatic hypocalcaemia (per medical history)<br>• Hyperphosphataemia (>1.45 mmol/L)<br>• Renal insufficiency (<60 mL/min, renal stone, etc. as per criteria)<br>• Hypercalciuria<br>• Poor quality of life (SF-36 < 40)<br>High dose of calcium ≥2000 mg daily | |
| Would this population be suitable for treatment with palopegteriparatide? | While above criteria could be suitable for palopegteriparatide, cases should be selected on individual basis considering the other co-morbidities etc. |
| **2. Conventional therapy in the PaTHway trial** | |
| The PaTHway trial mandated a reduction in active vitamin D at the start of the treatment period. Also, the use of thiazide was not permitted. Given this, the EAG is concerned that conventional therapy may have been suboptimal in PaTHway.<br><br>Could you comment on whether conventional therapy in PaTHway represents conventional therapy that would be used in the NHS? | UK national chronic hypoparathyroidism audit published in 2022 revealed that combination of active vitamin D analogue therapy and calcium supplements in divided doses as the primary therapy was only seen among 62.5% of the patients and thiazide diuretics were received only by 6.3%. However, total percentage of patients who |

| | |
|---|---|
| | were on activated vitamin D analogues were 98.8%.<br><br>An individual case-based analysis would be needed to comment whether the conventional therapy was suboptimal. |
| **3. Appropriateness of primary outcome in PaTHway trial** | |
| The primary outcome of PaTHway was a composite outcome in which patients had to achieve all of the following:<br>• Albumin adjusted serum calcium levels in the normal range (2.07 to 2.64 mmol/L [8.3 to 10.6 mg/dL])<br>• Independence from conventional therapy – defined as requiring no active vitamin D and ≤ 600 mg/day of calcium supplementation, and<br>• No increase in prescribed study treatment within 4 weeks prior to week 26<br><br>The EAG is concerned that the component on achieving independence from conventional therapy is an unrealistic expectation for people on conventional therapy and so this outcome does not permit a fair comparison of the two treatment arms.<br><br>Can you comment on the appropriateness of the primary outcome for evaluating palopegteriparatide and conventional therapy, and its applicability to NHS practice? | Agree that it may be an unrealistic expectation for people on conventional therapy to achieve independence of conventional therapy. However, rest of the outcome measures should be comparable. In the NHS should this medication is given, patients would need reduction of doses of active vitamin D and calcium while introducing the palopegteriparatide. Moreover,1 year results of Phase 3 Pathway Trial with open labelled extension revealed consistency with the mentioned primary outcomes. |
| **4. Drug wastage assumptions** | |

| | |
|---|---|
| The company model does not include drug wastage for palopegteriparatide. The EAG consider this to be unrealistic, and that wastage is likely to occur when patients transition between pack sizes.<br><br>Can you comment on:<br>a) whether it is appropriate to assume drug wastage for palopegteriparatide?<br><br>b) the need for long-term dose adjustments of palopegteriparatide? | Drug wastage could occur during the initial period where the dosage of the injection is titrated. |
| **5. Self-administration of palopegteriparatide** | |
| The company model assumes that all patients will be able to self-administer palopegteriparatide. The EAG is concerned that some people (such as older adults or those with disabilities) may not be able to and may require support.<br><br>Can you comment on:<br>a) what proportion of patients, if any, are likely to require nursing support to administer palopegteriparatide?<br><br>b) how feasible it would be for the NHS to provide this on a daily basis? | For those cannot administer the injections by them self or with a help of a trained carer, professional help would be needed (eg: district nurse referral etc). |

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Palopegteriparatide for treating chronic hypoparathyroidism (ID6380)**

**Patient expert statement**

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

## Information on completing this form

In part 1 we are asking you about living with hypoparathyroidism or caring for a patient with hyppoparathyroidism. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

### Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **28th August.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

Patient expert statement

**Palopegteriparatide for treating chronic hypoparathyroidism ( ID6380)**

NICE National Institute for Health and Care Excellence

# Part 1: Living with this condition or caring for a patient with hypoparathyroidism

**Table 1 About you, hypoparathyroidism, current treatments and equality**

| | |
|---|---|
| **1. Your name** | Elizabeth Glenister |
| **2. Are you (please tick all that apply)** | ☒ A patient with hypoparathyroidism?<br>☐ A patient with experience of the treatment being evaluated?<br>☐ A carer of a patient with hypoparathyroidism?<br>☒ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | Parathyroid UK |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☒ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☒ I am drawing from personal experience<br>☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: CEO of Parathyroid UK for 20 years; running support groups and helpline; PPI in research studies. |

Patient expert statement

**Palopegteriparatide for treating chronic hypoparathyroidism ( ID6380)**

| | |
|---|---|
| | ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **6. What is your experience of living with hypoparathyroidism?**<br>**If you are a carer (for someone with hypoparathyroidism) please share your experience of caring for them** | I have lived with post surgical hypoparathyroidism for 33 years following a total thyroidectomy for thyroid cancer at age 37. Despite surgery the condition was not properly recognised or diagnosed for many years during which time I was badly mismanaged and undertreated. Every aspect of my life was dramatically affected. In 2005 I founded Parathyroid UK to find others like me, raise awareness and improve care and treatment. Today, although on sufficient doses of current treatment my condition remains brittle and my calcium levels remain unstable, swinging from high to low and back without warning and with frequent precipitous hypo and hypercalcaemic events. My husband is now my carer, I am unable to go far alone and lose many days to recovering and rebalancing my levels. Despite always trying to keep fit and healthy, lack of PTH and current treatment has left me with a very poor quality of life, constant fatigue, debilitating anxiety, stage 3 kidney disease, kidney stones and deteriorating bone. |
| **7a. What do you think of the current treatments and care available for hypoparathyroidism on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | Current treatment was not designed to treat hypoparathyroidism; at best it acts, to some degree, as a temporary holding mechanism while causing additional long term issues and failing to address those caused by our missing hormone**.** Because it's a rare condition, hypoparathyroidism doesn't receive the recognition or provision it deserves, unlike diabetes to which it is very similar in many ways. As our UK audit showed, care across the UK is patchy, does not follow guidelines and badly needs standardising. Few endocrinologists properly understand how to manage the current treatment and patients are regularly admitted to hospital unnecessarily as a result. |

| | |
|---|---|
| | Having run Parathyroid UK groups and helpline for 20 years I have had daily contact with patients in crisis, desperate for help and support, so I can say that the majority of patients feel the same about current treatment and care. They feel like second class citizens, left to manage life threatening crises alone with a treatment that is causing them harm and prescribed with little more than guesswork. As ordinary endocrinologists often don't fully understand the condition we have not only had to refer many people to our medical advisors who are specialists in calcium and bone but have also had to step in with emergency support which we shouldn't have to do. |
| **8. If there are disadvantages for patients of current NHS treatments for hypoparathyroidism (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | The disadvantages of current treatment are challenging and it does not always provide relief from symptoms or improve quality of life. The aim of treatment is to alleviate symptomatic hypocalcaemia while avoiding hypercalciuria but achieving this with current therapy can be very difficult. Doses must be carefully titrated and patients often feel they are on a rollercoaster as levels swing up and down; monitoring is insufficient and difficult to access when needed; understanding of how dose adjustments affect patients is limited; prescribed calcium supplementation is often excessive with not enough active vitamin D while vitamin D and magnesium levels are ignored; and the pill burden is great. Calcium supplements are frequently over prescribed, are abrasive and unpleasant to take and can cause gastric issues and long term renal problems such as hypercalciuria and kidney stones. Inadvertent overdosing can cause distressing symptoms of hypercalcaemia. Active vitamin D is a potent steroid- like analogue that needs careful use but is frequently under prescribed. Multiple dosing across the day is needed and (as calcium levels are affected by exercise, stress, infection, diet etc) self management is necessary to maintain levels. Regular monitoring is essential ( as in diabetes) yet this is not readily available. Many difficulties arise from poor management and understanding of the condition. |
| **9a. If there are advantages of Palopegteriparatide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your** | a)We know from clinical trial results that Palopegteriparatide can achieve normal calcium levels and independence from conventional therapies. Additionally, it has been shown to improve kidney function, indeed one of our members has recently |

| | |
|---|---|
| **ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does Palopegteriparatide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | avoided dialysis thanks to this treatment. It also improves quality of life, giving the patient back a social life, the ability to plan ahead, hold down work and feel like a valued member of society again with renewed self confidence and better mental and physical health.<br><br>b)I consider restoring parathyroid hormone levels to be the most important advantage as we still do not know the extent to which this lack affects the body, and because all the other benefits lead on from this. Patients on Palopegteriparatide have spoken of feeling as if a 'lightbulb has been being switched back on'. We need to regain our lost selves, our joie de vivre and ability to function. To have a better quality of life and to have kidney function improved would be miraculous.<br>c)Yes, if we can reduce or remove current therapy then the above mentioned disadvantages may be addressed, in particular the long term problems it causes and the difficulties in day to day management as well as the unpredictability of symptoms which lead to a poor quality of life, stress and anxiety, and the impact on family/social life and work. |
| **10. If there are disadvantages of Palopegteriparatide over current treatments on the NHS please describe these.**<br>For example, are there any risks with Palopegteriparatide? If you are concerned about any potential side effects you have heard about, please describe them and explain why | The most common side effect seems to be a reaction at the injection site. Otherwise there are initial symptoms of high or low calcium as doses are adjusted but which appear to settle down once the correct dose is achieved. The biggest concern among patients is that they may not be eligible to get Palopegteriparatide. |
| **11. Are there any groups of patients who might benefit more from Palopegteriparatide or any who may** | All groups would benefit from replacement of parathyroid hormone as they all have individual unmet needs caused by it's lack. |

| | |
|---|---|
| **benefit less? If so, please describe them and explain why**<br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | |
| **12. Are there any potential equality issues that should be taken into account when considering hypoparathyroidism and Palopegteriparatide? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | Unequal access, regionally or by individual doctors who are unaware of patientneeds or the availability of Palopegteriparatide; and funding.<br>Ethnic minority patients are under represented in our organisation so I would be concerned they may miss out. |
| **13. Are there any other issues that you would like the committee to consider?** | The parathyroid gland is the sole endocrine gland lacking a replacement hormone and we have waited and advocated for PTH for many years in order to attain parity with our fellow endocrine patients.The needs of individuals suffering from hypoparathyroidism require immediate attention and feeling among patients here runs high especially as Palopegteriparatide is now available in other countries. |

NICE National Institute for Health and Care Excellence

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I agree with the patient group submission on all these messages.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Report
# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]


| | |
|---|---|
| **Produced by** | York Technology Assessment Group, University of York, Heslington, York, YO10 5DD |
| **Authors** | Sumayya Anwer, Research Fellow, CRD, University of York<br>Joy Chen, Research Fellow, CRD, University of York<br>Mark Corbett, Research Fellow, CRD, University of York<br>Diarmuid Coughlan, Research Fellow, CRD, University of York<br>Melissa Harden, Senior Information Specialist, CRD, University of York<br>Mark Simmonds, Senior Research Fellow, CRD, University of York<br>Robert Hodgson, Senior Research Fellow, CRD, University of York |
| **Correspondence to** | Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD |
| **Date completed** | 23/07/2025 |



**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR170273

**Declared competing interests of the authors**

None

**Acknowledgements**

The EAG would like to thank Prof S Balasubramanian (University of Sheffield) and Prof S Pearce (Newcastle University) for their clinical advice on hypoparathyroidism and this report in general.


**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows**:
S Anwer, J Chen, M Corbett, D Coughlan, M Harden, M Simmonds, R Hodgson. Palopegteriparatide for treating chronic hypoparathyroidism: A Single Technology Appraisal. York Technology Assessment Group. 2025

**Contributions of authors**
S Anwer wrote the critique of the decision problem (Section 2) and contributed to Sections 1 and 3.
J Chen performed the critical review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 1, 4, 5, 6 and 7 of the report.
M Corbett wrote the critique of the clinical effectiveness and safety data (Section 3) and contributed to Sections 1 and 2.
D Coughlan performed the critical review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 1, 4, 5, 6 and 7 of the report.
M Harden reviewed the systematic review searches, wrote sections of the report pertaining to the searches and provided editorial support.
M Simmonds took overall responsibility for the clinical sections of the report and the report as a whole.
R Hodgson oversaw the review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 1, 4, 5, 6 and 7 of the report, commented on drafts of the report and takes joint responsibility for the report as a whole.

**Note on the text**
All commercial-in-confidence (CON) data have been redacted, all depersonalised data (DPD) are redacted.

**Copyright statement**

# Table of Contents


Table of Contents 3

List of abbreviations 7

1 Executive summary 9

1.1 Overview of the EAG's key issues 10

1.2 Overview of key model outcomes 11

1.3 The decision problem: summary of the EAG's key issues 12

1.4 26-week clinical effectiveness evidence: summary of the EAG's key issues 13

1.5 The cost-effectiveness evidence: summary of the EAG's key issues 15

1.6 Summary of EAG's preferred assumptions and resulting ICER 20

2 INTRODUCTION AND BACKGROUND 22

2.1 Introduction 22

2.2 Background 22

2.2.1 Hypoparathyroidism 22

2.2.2 Burden of disease 23

2.2.3 Palopegteriparatide 24

2.2.4 Clinical pathway of care 25

2.2.4.1 Diagnosis and classification 25

2.2.4.2 Current standard of care treatment 25

2.2.4.3 Intended positioning of palopeg 26

2.2.5 Equality considerations 27

2.2.6 Other relevant appraisals in progress 27

2.3 Critique of company's definition of decision problem 28

2.3.1 Population 28

2.3.2 Comparators 29

2.3.3 Outcomes 30

2.3.4 Subgroups 30

3 CLINICAL EFFECTIVENESS 34

3.1 Critique of the methods of review(s) 34

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these) 35

3.2.1 Critical appraisal of the PaTHway trial 35

3.2.1.1 Risk of bias 35

3.2.1.2 Applicability of the PaTHway results to the NHS setting 36

3.2.2 Clinical efficacy results of the PaTHway trial 39

3.2.3 PaTH Forward trial 41

3.2.4 Open-label extension studies 42

3.2.5 Adverse events and safety data 42
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 43
3.4 Critique of the indirect comparison and/or multiple treatment comparison 43
3.5 Additional work on clinical effectiveness undertaken by the EAG 43
3.6 Conclusions of the clinical effectiveness section 43
4 COST EFFECTIVENESS 46
4.1 EAG comment on company's review of cost-effectiveness evidence 46
4.1.1 Search strategy 46
4.1.2 Inclusion/exclusion criteria 46
4.1.3 Identified studies 46
4.1.4 Interpretation of the review. 47
4.2 Summary and critique of the company's submitted economic evaluation by the EAG 48
4.2.1 NICE reference case checklist 48
4.2.2 Model structure 49
4.2.2.1 Points for critique 50
4.2.3 Population 53
4.2.3.1 Points for critique 53
4.2.4 Interventions and comparators 54
4.2.4.1 Points for critique 56
4.2.5 Perspective, time horizon and discounting 56
4.2.6 Treatment effectiveness and extrapolation 56
4.2.6.1 Efficacy of palopegteriparatide 56
4.2.6.2 Discontinuation rates 57
4.2.6.3 Complication rates 58
4.2.6.4 Mortality 59
4.2.6.5 Adverse event rates 60
4.2.7 Health related quality of life 61
4.2.7.1 Health-related quality-of-life studies 61
4.2.7.2 Health-related quality of life from clinical trials 62
4.2.7.3 Complication related disutilities 64
4.2.7.4 Adverse events 65
4.2.8 Resources and costs 66
4.2.8.1 Drug acquisition and administration costs 66
4.2.8.2 Health state unit costs and resource use 70
4.2.8.3 Adverse event costs 72
4.2.8.4 Confidential pricing arrangements 73
5 COST EFFECTIVENESS RESULTS 74

5.1 Company's cost effectiveness results 74
5.1.1 Deterministic Results 74
5.1.2 Probabilistic Results 75
5.2 Company's deterministic sensitivity analyses 76
5.3 Company's additional scenario analyses 77
5.4 Model validation and face validity check 78
5.4.1.1 Validation undertake by the EAG 78
6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES 80
6.1 Exploratory and sensitivity analyses undertaken by the EAG 80
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG 83
6.3 EAG's preferred assumptions 85
6.4 Conclusions of the cost effectiveness section 86
7 Severity Modifier 89
8 References 90
9 APPENDIX 94

## Table of Tables

Table 1 Summary of EAG's key issues ..... 10
Table 2 EAG Exploratory fully incremental scenario analyses (deterministic) ..... 20
Table 3 EAG's base case (Deterministic) ..... 21
Table 4. Available doses for pre-filled Palopegteriparatide pens[15] ..... 25
Table 5 Definitions of NAC used in the CS ..... 29
Table 6 Summary of decision problem ..... 31
Table 7 'Not adequately controlled' criteria applied to PaTHway baseline ITT population ..... 37
Table 8 Subgroup analyses for responders meeting primary outcomes from baseline to week 26 in the palopeg arm ..... 39
Table 9 EQ-5D utility scores at Baseline and Week 26 in PaTHway* ..... 41
Table 10 NICE reference case checklist ..... 48
Table 11: Adverse event incident rate per cycle ..... 60
Table 12: EQ-5D-3L utility score at baseline vs week 26 ITT (based on Table 28 of the CS) ..... 62
Table 13: Health state utilities ..... 63
Table 14: Complication disutility ..... 64
Table 15: Adverse event disutility ..... 65
Table 16 Percentage of double pen patients ..... 67
Table 17 Drug unit costs, doses, and dose intensity ..... 68
Table 18 Summary administration costs for palopegteriparatide and CT ..... 68
Table 19 Revised company base case results: deterministic ..... 74
Table 20 Outcomes as per revised company base case results ..... 74
Table 21 Health state costs as per revised company base case results ..... 75
Table 22 Company base case results: probabilistic pairwise analysis ..... 75
Table 23 Company's additional scenario analysis (deterministic): CT vs palopeg (inclusive of palopeg PAS) ..... 77
Table 24 Summary of health state utility values ..... 80
Table 25 EAG Exploratory scenario analyses (deterministic) ..... 84
Table 26 EAG's base case (Deterministic) ..... 85
Table 27 EAG's base case (Probabilistic) ..... 86
Table 28 Summary of QALY shortfall analysis ..... 89

## Table of Figures

Figure 1. Company's proposed positioning of Palopegteriparatide in the treatment pathway ..... 26
Figure 2: Palopegteriparatide model structure ..... 49
Figure 3 Titration algorithm ..... 55

Figure 4 Cost-effectiveness plane (generated from company model)..... 76
Figure 5 Multi-way cost-effectiveness acceptability curve (generated from company model)..... 76
Figure 6 Tornado diagram: palopeg versus CT (generated from company model)..... 76

## List of abbreviations

| | |
|---|---|
| A&E | Accident & Emergency |
| AC | Adequately controlled |
| AE | Adverse event |
| BMI | Body mass index |
| BNF | British national formulary |
| CDSR | Cochrane Database of Systematic Reviews |
| CKD | Chronic kidney disease |
| CPI | Consumer Price Index |
| CPRD | Clinical Practice Research Datalink |
| CS | Company submission |
| CSR | Clinical study report |
| CT | Conventional therapy |
| CVD | Cardiovascular disease |
| DSA | Deterministic sensitivity analysis |
| DSU | Decision support unit |
| EAG | External assessment group |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| eMIT | Electronic market information tool |
| EPAR | European public assessment report |
| EQ-5D | EuroQol 5 Dimensions |
| EQ-5D-5L | EuroQol 5 Dimensions 5 Levels |
| EQ-5D-3L | EuroQol 5 Dimensions 3 Levels |
| EQ5D-VAS | EuroQol 5 Dimensions Visual Analogue Scale |
| ESE | European Society of Endocrinology |
| HPES | Hypoparathyroidism Patient Experience Scale |
| HRG | Healthcare Resource Group |
| HRQL | Health-related quality of life |
| HSE | Health survey from England |
| HTA | Health Technology Appraisal |
| HypoPT | Hypoparathyroidism |
| HTA | Health Technology Assessment |
| ICER | Incremental cost-effectiveness ratio |
| IFR | Individual funding request |
| ITT | Intent-to-treat |
| LS | Least squares |
| LYG | Life years gained |
| m | Metre |
| mcg | Microgram |

| | |
|---|---|
| mg | Milligram |
| MHRA | Medicines & Healthcare Products Regulatory Agency |
| min | Minute |
| mL | Millilitre |
| mmol/L | Millimoles per litre |
| MMRM | Mixed-model for repeated measures |
| NAC | Not adequately controlled |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NS | Non-surgical |
| OLE | Open-label extension |
| ONS | Office for National Statistics |
| PAS | Patient access scheme |
| PARAT | Parathyroid Disorders Educational Program |
| PfC | Points for clarification |
| PS | Post-surgical |
| PSA | Probabilistic sensitivity analysis |
| PSM | Partitioned survival model |
| PSS | Personal Social Services |
| PTH | Parathyroid hormone |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RDI | Relative dose intensity |
| rhPTH | Recombinant human parathyroid hormone |
| SC | Subcutaneous |
| SF-36 | 36-Item Short Form Survey |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| SR | Systematic review |
| T2DM | Type 2 diabetes mellitus |
| TEAE(s) | Treatment-emergent adverse events |
| TTO | Timed trade-off |
| UK | United Kingdom |
| US | United States |
| UTI | Urinary tract infection |
| VAS | Visual analogue scale |
| WTP | Willingness-to-pay |

# 1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues is in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

## *1.1 Overview of the EAG's key issues*

Table 1 Summary of EAG's key issues

| ID | Summary of issue | Report sections |
|---|---|---|
| 1. | Uncertain definition of the "Not Adequately Controlled" population: Submission proposes limiting population to patients not adequately controlled by conventional therapy (CT). This population is not consistently defined and may be a small minority of patients with hypoparathyroidism (HypoPT). | 2.3.1<br>3.2.1.2 |
| 2. | Uncertainty in the patient-reported quality of life outcomes in PaTHway trial: Participants may have experienced "functional unblinding" due to their awareness of calcium and vitamin D doses received. This could bias results of quality-of-life outcomes in favour of palopegteriparatide (palopeg). The company also used an Analysis of Covariance (ANCOVA) model to analyse EQ-5D data rather than a Mixed Model Repeated Measures analysis (MMRM). This approach is less efficient and more vulnerable to bias. | 3.2.1.1<br>3.2.2<br>4.2.7.2 |
| 3. | Use of sub-optimal conventional therapy in the PaTHway trial: The PaTHway trial mandated a large reduction in active vitamin D dose and prohibited the use of thiazide diuretics, so the CT arm may not reflect treatment use in practice. | 2.3.2<br>3.2.1.2 |
| 4 | Primary outcome in PaTHway trial does not permit a fair comparison with conventional therapy: The trial used independence from CT as a key component of its primary outcome, which is innately not achievable with CT, and does not measure actual clinical benefits. | 3.2.1.2<br>3.2.2 |
| 5. | Model structure: The model structure uses an on/off treatment approach and does not use the primary outcome report in the PaTHway trial. | 4.2.2 |
| 6. | Lack of direct evidence for complication and mortality benefits: The PaTHway trial does not provide direct evidence supporting the modelled reductions in complications and mortality. Instead, the model relies on surrogate relationships between disease control and clinical outcomes, which are inadequately justified. | 4.2.2<br>4.2.6.3<br>4.2.6.4 |
| 7. | Modelling of adverse event rates and costs: Adverse event (AE) rates are modelled based on all grades of severity, while associated costs are derived from cases requiring emergency hospital care. AE costs for hypercalcaemia and hypocalcaemia are based on hospitalisation costs for heart failure. | 4.2.6.5<br>4.2.8.3 |
| 8. | Drug wastage assumptions: The model assumes no drug wastage and presumes that dose reductions and skipped doses directly translate into reduced drug acquisition costs | 4.2.8.1 |
| 9 | Self-administration of palopeg: The company model assumes all patients will be able to self-administer palopeg. It is unclear if this is appropriate with implications for both costs and equity of access. | 4.2.8.1 |
| 10. | Non–reference case approach to healthcare resource use: The model adopts a non–reference case approach by including background care costs that are not attributable to HypoPT. | 4.2.8.2 |
| 11. | Modelling of healthcare resource use: Reductions in resource use are not directly supported by data from the PaTHway trial and instead rely on a poorly justified surrogate relationship between disease control and resource utilisation. Clinical Practice Research Datalink (CPRD) data used to inform resource use does not reflect the mix of surgical and non-surgical patients in the modelled population. | 4.2.8.2 |

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers to use an MMRM analysis to generate health state utilities rather than the ANCOVA model preferred by the company.
- The EAG prefers to use hypercalcaemia or hypocalcaemia AE rates leading to hospital care rather than any grade of event.
- The EAG prefers to remove complication related disutilities.
- The EAG prefers to use a published values to inform excess mortality associated with HypoPT and to assume that no survival benefit is associated with HypoPT treatment.
- The EAG prefers to set relative dose intensity (RDI) for palopeg to 100%
- The EAG prefers to include drug wastage for palopeg to account for dosing changes that require a different pack size
- The EAG prefers to revise CT acquisition costs in the CT arm of the model, so they use the baseline dosing of CT from the PaTHway trial.
- The EAG prefers to revise the costs of alfacalcidol to use electronic market information tool (eMIT) costs.
- The EAG prefers to set health state costs to zero.
- The EAG prefers to include an administration cost for patients who are unable to self-administer the injection.

### *1.2 Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Improved health-related quality of life (HRQL)
- Reduced complication rates
- Improved survival

Overall, the technology is modelled to affect costs by:

- Increasing drug acquisition costs
- Reducing AE rates and associated costs

- Reducing healthcare resource use

The modelling assumptions that have the greatest effect on the ICER are:

- The AE rates modelled
- The source of AE costs
- The inclusion of health state costs
- How health states costs are estimated and the mix of surgical and non-surgical patients

### *1.3 The decision problem: summary of the EAG's key issues*

Issue 1 Uncertain definition of the "Not Adequately Controlled" population

| | |
|---|---|
| **Report section** | 2.3.1 and 3.2.1.2 |
| **Description of issue and why the EAG has identified it as important** | The population in the NICE scope is all adults with HypoPT. The company submission proposes limiting the population to patients not adequately controlled by conventional therapy. While the EAG agrees with this in principle, this population is not consistently defined, with several differing definitions used across the submission. There is also uncertainty as to the size of the population, but it may be a small minority of patients with HypoPT. |
| **What alternative approach has the EAG suggested?** | The EAG would prefer that a more precise and consistent definition of who is eligible for palopeg, that is consistent with clinical opinion, be used throughout the assessment. |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown |
| **What additional evidence or analyses might help to resolve this key issue?** | Evidence on what would reasonably be considered inadequate control, and proportions of patients with hypoparathyroidism in the NHS who are not adequately controlled (NAC) with CT, according to various definitions, is needed. |

### *1.4 26-week clinical effectiveness evidence: summary of the EAG's key issues*

Issue 2 Uncertainty in the patient-reported quality of life outcomes in PaTHway trial

| | |
|---|---|
| **Report section** | 3.2.1.1, 3.2.2 and 4.2.7.2 |
| **Description of issue and why the EAG has identified it as important** | Although the PaTHway trial was placebo-controlled the EAG has concerns about the adequacy of participant blinding. Given the large differences between the trial arms in the amount of calcium and vitamin D taken, participants may have been "functionally unblinded" as they were likely to know which trial treatment they had been allocated. This may have biased any patient reported outcomes (such as quality-of-life measures).<br><br>The company also used an ANCOVA model to analyse EQ-5D data from the PaTHway trial. This approach does not use data collected at interim time points, accounting only for baseline and 26-week scores. |
| **What alternative approach has the EAG suggested?** | No suggested alternative for functional unblinding concerns, but the magnitudes of patient-reported outcomes should be viewed with caution.<br>The EAG prefers to use a MMRM analysis, as it can incorporate data from interim time points and serves as a more efficient estimator. |
| **What is the expected effect on the cost-effectiveness estimates?** | This increases uncertainty in the estimated HRQL differences between patients treated with palopeg and those receiving CT, likely biasing the results in favour of palopeg. Any reduction in the assumed HRQL benefit associated with palopeg would lead to an increase in the ICER.<br><br>Generating utility values using a MMRM analysis increases the ICER from £52,602 (company corrected base case) per QALY to £59,925 per QALY gained. |
| **What additional evidence or analyses might help to resolve this key issue?** | None, as functional unblinding would be difficult to avoid in this assessment. |

Issue 3 Use of sub-optimal conventional therapy in the PaTHway trial

| | |
|---|---|
| **Report section** | 2.3.2 and 3.2.1.2 |
| **Description of issue and why the EAG has identified it as important** | The large mandatory reduction in active vitamin D and the prohibition of thiazide use in the PaTHway trial means that the CT used in PaTHway will not have been as comprehensive and effective as the CT available in the NHS setting. This may result in a bias favouring palopeg in many trial outcomes. |
| **What alternative approach has the EAG suggested?** | No alternative approach that is based on the PaTHway trial data is feasible, but results from the PaTHway trial should be viewed with caution. |
| **What is the expected effect on the cost-effectiveness estimates?** | This increases uncertainty in the estimated HRQL differences between patients treated with palopeg and those receiving CT, likely biasing the results in favour of palopeg. Any reduction in the assumed HRQL benefit associated with palopeg would lead to an increase in the ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | Ideally, a new randomised controlled trial (RCT) comparing palopeg to CT as used in practice without restrictions would be required. |

Issue 4 Primary outcome in PaTHway trial does not permit a fair comparison with conventional therapy

| | |
|---|---|
| **Report section** | 3.2.1.2 and 3.2.2 |
| **Description of issue and why the EAG has identified it as important** | The multi-component primary outcome used in PaTHway is a surrogate outcome, which does not directly measure clinical benefit. The EAG does not believe that the primary outcome allows for a fair comparison of CT with palopeg because achieving independence from CT (in the trial time frame of 26 weeks) does not seem to be a plausible goal for patients taking CT. |
| **What alternative approach has the EAG suggested?** | The EAG prefers to focus on outcomes of genuine clinical relevance, such as physical and renal function |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown. |

| | |
|---|---|
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG would like to have seen healthcare resource use analysis using relevant clinical measures from the PaTHway trial. |

### *1.5 The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 5 Model structure

| | |
|---|---|
| **Report section** | 4.2.2 |
| **Description of issue and why the EAG has identified it as important** | The model structure adopts an approach in which health states are defined by treatment received rather than by a clinical endpoint. While this approach is valid, it represents a conceptually weak foundation. This is because it decouples the model structure from the underlying pathophysiology of the condition and obscures the mechanisms by which health benefits are generated. |
| **What alternative approach has the EAG suggested?** | The EAG considers the model structure valid for decision making, but also considers that an alternative approach based on a response-based approach may represent a valid alternative. |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown |
| **What additional evidence or analyses might help to resolve this key issue?** | Additional evidence supporting the validity of the primary outcome and its suitability for use in clinical practice may help justify the adoption of a response-based approach. |

Issue 6 Lack of direct evidence for complication and mortality benefits

| | |
|---|---|
| **Report section** | 4.2.2, 4.2.6.3 and 4.2.6.4 |
| **Description of issue and why the EAG has identified it as important** | The PaTHway trial and open-label extension (OLE) provide no clinical evidence to support the modelled reductions in complications and improved survival. The model relies on data from CPRD to estimate reductions in both complication rates and mortality, which assumes that resource use is a suitable proxy for both these outcomes. This is not justified by the available evidence. |

| | |
|---|---|
| **What alternative approach has the EAG suggested?** | Given the lack of supporting evidence, the EAG suggests equalising the complication and mortality rates applied in the model. |
| **What is the expected effect on the cost-effectiveness estimates?** | Removing complications for the model increases the ICER from £52,602 (company corrected base case) per QALY to £54,185 per QALY gained. Removing mortality benefits from the model increases the ICER from £52,602 per QALY to £56,396 per QALY gained. |
| **What additional evidence or analyses might help to resolve this key issue?** | Additional evidence on the relationship between disease control and complication or mortality rates would be valuable. Evidence on complication rates and mortality for another recombinant human parathyroid hormone may also be informative in justifying the modelled benefits |

Issue 7 Modelling of adverse event rates and costs

| | |
|---|---|
| **Report section** | 4.2.6.5 and 4.2.8.3 |
| **Description of issue and why the EAG has identified it as important** | Avoidance of AE-related costs due to hypercalcemia and hypocalcemia is a key driver of cost-effectiveness in the model. In the company's base case, AE rates are based on the incidence of treatment-emergent events of any grade reported in the PaTHway trial. However, this is inconsistent with the modelled AE disutilities and costs, which assume emergency hospital care. By definition, Grade 1 and 2 AEs do not require hospitalisation. Furthermore, the costs applied are based on emergency admissions for heart failure, which likely overestimate the true costs associated with these AEs. |
| **What alternative approach has the EAG suggested?** | The EAG prefers to use AE rates leading to hospital care from the PaTHway trial to inform the model. It also prefers to use the HRG code KC05 (Fluid or Electrolyte Disorders), assuming a non-elective short stay admission, to model AE costs. |
| **What is the expected effect on the cost-effectiveness estimates?** | Revising the AE rates used in the model increases the ICER from £52,602 (company corrected base case) per QALY to £66,553 per QALY gained. Revising the AE costs increases the ICER from £52,602 per QALY to £64.404 per QALY gained. |

| | |
|---|---|
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG considers the scenario analysis to resolve this issue. |

Issue 8 Drug wastage assumptions

| | |
|---|---|
| **Report section** | 4.2.8.1 |
| **Description of issue and why the EAG has identified it as important** | The company's base-case analysis assumes no drug wastage. The EAG considers this assumption unrealistic, as wastage is likely to occur when patients transition between pack sizes (a requirement when dosing crosses certain thresholds). Such transitions were frequently observed in both the PaTHway and OLE studies. Furthermore, the EAG remains uncertain about the potential for additional dose adjustments and associated wastage over the duration of treatment.<br><br>The company adjusts drug acquisition costs according to the RDI observed in the PaTHway trial. However, the EAG considers it unlikely that dose reductions or missed doses will lead to proportional cost savings, as each injectable pen has a fixed maximum usage period of 14 days, irrespective of the number of doses administered. |
| **What alternative approach has the EAG suggested?** | The EAG prefers to include drug wastage, accounting for movements between pack sizes. It also prefers to remove the RDI adjustment. |
| **What is the expected effect on the cost-effectiveness estimates?** | Adding drug wastage increases the ICER from £52,602 (company corrected base case) per QALY to £52,917 per QALY gained. Setting RDI to 100% i.e. assuming no cost savings increase the ICER from £52,602 per QALY to £57,920 per QALY gained. |
| **What additional evidence or analyses might help to resolve this key issue?** | Additional data or clinical insight regarding the need for long-term dose adjustments would be beneficial. |

Issue 9 Self-administration of palopeg

| | |
|---|---|
| **Report section** | 4.2.8.1 |
| **Description of issue and why the EAG has identified it as important** | The company's model assumes that all patients will be able to self-administer palopeg. However, the EAG is concerned that some patients (such as older adults or those with disabilities) may not be able to do so and may require support to access treatment. Providing such support would likely necessitate daily visits to patients, and the EAG is uncertain whether NHS services could feasibly accommodate the administration of daily subcutaneous injections. If this level of provision cannot be supported, it may raise important equity concerns, as it could exclude more vulnerable patients who would otherwise be eligible for treatment. |
| **What alternative approach has the EAG suggested?** | The EAG considers that it may be appropriate to add administrative costs equivalent to daily nurse visit in 10% of patients aligning with appraisals of monoclonal antibodies for migraine which similarly considered the issue of self-administration of subcutaneous injections. |
| **What is the expected effect on the cost-effectiveness estimates?** | Adding in administration costs for 10% of patients increases the ICER from £52,602 (company corrected base case) per QALY to £61,127 per QALY gained. |
| **What additional evidence or analyses might help to resolve this key issue?** | Additional evidence on the feasibility of providing nursing support on a daily or twice-daily basis would be valuable, as would further information on the proportion of patients likely to require such support. |

Issue 10 Non–reference case approach to healthcare resource use

| | |
|---|---|
| **Report section** | 4.2.8.2 |
| **Description of issue and why the EAG has identified it as important** | The company uses CPRD data to model healthcare resource use and associated costs. However, these data do not differentiate between resource use directly attributable to HypoPT and background healthcare costs related to comorbidities or other care needs, which are likely to be prevalent in this patient population. The EAG considers that this approach is inconsistent with the NICE reference case, which stipulates that only costs directly related to the condition of interest should be included in |

| | |
|---|---|
| | the economic evaluation, and that unrelated costs should be excluded.<br><br>The EAG is concerned that the company's approach is likely to result in a substantial overestimation of costs attributable specifically to HypoPT. |
| **What alternative approach has the EAG suggested?** | The EAG prefers to include only resource use directly attributable to HypoPT in line with the reference case. |
| **What is the expected effect on the cost-effectiveness estimates?** | Removing the health state costs increases the ICER from £52,602 (company corrected base case) per QALY to £126,697 per QALY gained. |
| **What additional evidence or analyses might help to resolve this key issue?** | The analysis of CPRD data should either be revised to include only those elements of care directly attributable HypoPT, or alternatively, health state costs should be informed by a comprehensive and methodologically robust clinical elicitation exercise specifically designed to identify resource use associated with the care and management of HypoPT. |

Issue 11 Modelling of healthcare resource use

| | |
|---|---|
| **Report section** | 4.2.8.2 |
| **Description of issue and why the EAG has identified it as important** | The company's analysis of CPRD data categorises patients without reference to any clinical criteria and instead relies on a circular rationale: patients are stratified based on healthcare resource utilisation, and this stratification is subsequently used to infer a causal relationship between resource use and disease severity. No empirical evidence is provided to demonstrate a direct association between disease severity and resource use.<br><br>Moreover, the HypoPT population in the CPRD dataset predominantly consists of non-surgical patients, whereas in the PaTHway trial and clinical practice, the vast majority of patients are of surgical aetiology. This distinction is important when determining the appropriate health state costs to apply. |
| **What alternative approach has the EAG suggested?** | As noted in Issue 9, the EAG considers the company's approach to modelling health state costs to be fundamentally inconsistent with the reference case. If CPRD data are to be used, they should |

| | |
|---|---|
| | be reweighted to reflect the aetiological mix observed in the PaTHway trial, as this is more representative of clinical practice. |
| **What is the expected effect on the cost-effectiveness estimates?** | Reweighting the health state costs to align with the proportion of surgical patients in the PaTHway trial increases the ICER from £52,602 (company corrected base case) per QALY to £67,145 per QALY gained. |
| **What additional evidence or analyses might help to resolve this key issue?** | Substantial additional evidence is needed to support the cost savings predicted by the model. Given the magnitude of the claimed savings, the EAG considers that this should ideally be substantiated by evidence from a RCT. In the absence of such evidence, a robust analysis of observational data comparing healthcare resource use in patients receiving CT versus those treated with palopeg or another recombinant human parathyroid hormone is required. |

### *1.6 Summary of EAG's preferred assumptions and resulting ICER*

Table 2 summarises the scenario analyses undertaken by the EAG. Table 3 summarises the EAG's preferred assumptions. These results include the PAS discount for palopeg only. For further details of the exploratory and scenario analyses done by the EAG, see Section 6. All ICERs are deterministic and are exclusive of severity weighting.

Table 2 EAG Exploratory fully incremental scenario analyses (deterministic)

| Scenario | | Technology | Total | | Incremental | | ICER |
|---|---|---|---|---|---|---|---|
| | | | Costs | QALYs | Costs | QALYs | |
| **Company base case** | | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £19,895 |
| **Company base case, inclusive of EAG suggested calculation corrections** | | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £52,602 |
| **1** | **Utility values (MMRM)** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £59,925 |
| **2** | **Exclude complication rates** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £54,815 |
| **3a** | **No survival benefit** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £56,396 |
| **3b** | **Use survival HR from literature** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £56,802 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **4** | **Use AE rate that results in hospitalisation** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £66,553 |
| **5** | **Alternative AE costs** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £64,404 |
| **6a** | **Set RDI to 100%** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £57,920 |
| **6b** | **Include wastage based on trial dose band changes** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £52,917 |
| **6c** | **Extrapolate wastage from last period over the model time horizon** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £53,161 |
| **7** | **CT dosing** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £50,381 |
| **8** | **eMIT costs** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £53,214 |
| **9a** | **Remove health state maintenance costs** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £126,697 |
| **9b** | **Reweigh PS/NS health state maintenance costs to PaTHway trial** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £67,145 |
| **9c** | **Use alternative company weighting of PS/NS health state maintenance costs** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £65,455 |
| **10** | **Nurse visit for 10% of chronic HypoPT patients** | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £61,127 |

**Abbreviations**: AE, adverse event; CT, conventional therapy; CPRD, Clinical Practice Research Datalink; EAG, evidence assessment group; eMIT, electronic market information tool; HR, hazard ratio; HypoPT, hypoparathyroidism; ICER, incremental cost effectiveness ratio; MMRM, mixed models for repeated measures; NHS, National Health Service; NS, non-surgical; PAS, patient access scheme; PS, post -surgical; QALY, quality-adjusted life-year; RDI, relative dose intensity.

Table 3 EAG's base case (Deterministic)

| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER** |
|---|---|---|---|---|---|---|---|
| **Palopeg vs CT** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £225,502 |

**Abbreviations**: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years

# 2 INTRODUCTION AND BACKGROUND

## *2.1 Introduction*

This report presents a critique of the company's submission to NICE on the clinical and cost-effectiveness of palopegteriparatide (Yorvipath®, referred to as "palopeg" throughout this report for convenience) for treating chronic hypoparathyroidism (HypoPT).

Palopeg was authorised by the European Medicines Agency (EMA) on 17th November 2023 and licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) on 24th April 2024 for the treatment of adults with chronic HypoPT.

## *2.2 Background*

### 2.2.1 Hypoparathyroidism

The company describes chronic HypoPT in the company submission (CS) section B.1.3, a brief summary of which is included here.

Chronic HypoPT is a rare endocrine disease caused by insufficient parathyroid hormone (PTH). PTH and vitamin D are key regulators of calcium and phosphate homeostasis. PTH is secreted in response to low serum calcium levels and binds to PTH1 receptors in the bones and kidneys. PTH stimulates bone reabsorption, enhances renal calcium reabsorption, promotes phosphate excretion, and activates vitamin D (calcitriol), which increases calcium reabsorption.[1] In chronic HypoPT, the absence of PTH contributes to impaired bone reabsorption, increased renal calcium loss, and reduced vitamin D synthesis (which limits intestinal calcium absorption) and can result in persistent hypocalcaemia. Hypocalcaemia can result in neuromuscular irritability, tetany (muscle spasms), seizures and cardiac arrhythmias. Patients with chronic HypoPT are also at an increased risk of bone fractures, cataracts, urinary tract infections (UTIs), renal complications (such as kidney stones, renal failure and chronic kidney disease), and cardiovascular complications (such as arrythmias, myocardial infarction and heart failure) due to chronic hypercalciuria (excessive calcium in the urine).

Patients with HypoPT can experience physical, cognitive, and emotional symptoms with paraesthesia (or 'pins and needles'), muscle cramps, fatigue, brain fog, irritability, and depression being the most commonly observed.

The company states that approximately 75% of chronic HypoPT cases are post-surgical, most often following head or neck procedures where the parathyroid glands are inadvertently damaged or removed. The remaining 25% are non-surgical cases attributed to autoimmune, genetic, or idiopathic conditions.[2, 3] The company state that the prevalence of chronic HypoPT in the UK was reported to be

20.7 per 100,000 in 2024.[4] While the prevalence of non-surgical HypoPT is similar in both males and females, post-surgical HypoPT is more common in females due to an increased risk of thyroid disease and the likelihood of having thyroidectomy. The EAG's clinical advisor noted that the incidence of post-surgical HypoPT may be declining as surgical techniques improve, reducing the risk of damage to the parathyroid glands.

According to the EAG's clinical advisor, in the NHS the percentage of chronic HypoPT cases that are post-surgical may be higher than stated in the company submission: approximately 90-95% of HypoPT cases may be post-surgical. In this submission, the company does not explore the differences between the post-surgical and non-surgical populations. The EAG's clinical advisor and the company's clinical experts all stated that there are differences between the post-surgical and non-surgical populations; non-surgical patients are younger and may have had HypoPT for many years. One of the company's clinical experts stated that non-surgical patients may have a higher burden of comorbidities and kidney disease. The EAG's clinical advisor suggested that it may be possible to wean post-surgical patients off conventional therapy (CT). The company's clinical advisors stated that any differences between surgical and non-surgical patients would be minimal, as the most important differentiator, time from diagnosis, was similar in both groups. The EAG has concerns that there may be differences between the two groups based on the differences in patient profiles.

### 2.2.2 Burden of disease

The company provides an account of the burden of disease in section B.1.3.5 of the CS. A summary is provided below.

The company states that the symptomatic and treatment-related burden of chronic HypoPT has a profound impact on patients' health related quality of life (HRQL). The company cited evidence that patients with HypoPT had reduced QoL,[5, 6] had to adjust treatments multiple times since diagnosis,[7] and experienced measurable cognitive impairment and smaller hippocampal volumes. [8] Reduced HRQL in patients with HypoPT has a negative effect on the ability to work and perform daily activities. [5, 6, 9, 10] Caregivers of patients with chronic HypoPT are also impacted negatively in terms of their daily activities and ability to work, with caregiver burden increasing with symptom severity.[6]

A company-sponsored survey[11] with 402 respondents indicated that dissatisfaction and poor HRQL were driven by continued symptom burden (69.2%), lack of peer and clinical support (55.1%), and the need for more effective treatments (43.5%).

The company undertook an analysis of the burden of chronic HypoPT in the UK.[12] This study found that patients with chronic HypoPT whose disease could be considered not adequately controlled (NAC) were associated with significantly higher resource use. The total direct costs (all-cause costs of

primary and secondary care) were 5-7 times higher in patients with HypoPT compared to the general population.[12] These patients experienced higher risk of serious renal complications, which would also be associated with higher healthcare resources.[12]

In the study, the company used having had more than 5 outpatient appointments and at least one inpatient appointment per year as a proxy for defining patients with NAC (Table 5 in the CS). The EAG questions the use of the frequency of inpatient and outpatient appointments as a reasonable proxy to define HypoPT control as it was not explicit whether these appointments were exclusively for HypoPT-related complications. According to the EAG's clinical advisor the frequency of outpatient visits and inpatient admissions can depend on physician judgement and are therefore subjective. The company's clinical advisors also pointed out that while it could be reasonable to assume that patients with uncontrolled HypoPT may need increased resources (such as more hospital visits and longer stays) this could be due to comorbidities unrelated to chronic HypoPT; and while they were reasonable indicators of disease control they needed to be interpreted in the context of a patient's clinical picture.[13]

### 2.2.3 Palopegteriparatide

Palopeg is a prodrug of parathyroid hormone (PTH), composed of PTH 1-34. When exposed to physiological pH and temperature, autocleavage occurs that separates the PTH from the linker and carrier. This provides a sustained release of active PTH which binds to target receptors including on the kidney and bone. The linker and carrier are excreted via the kidneys.[14] This mechanism is depicted in Figure 1 in Section 1.2 of the CS.

Palopeg is licensed as a once-daily subcutaneous (SC) injection, delivered using a pre-filled pen. The recommended starting dose is 18 micrograms (mcg) per day with dose adjustments in 3 mcg increments. The daily dose range is between 6 mcg and 60 mcg. The dosage of palopeg may be increased by 3 mcg after a minimum of seven days since the last dose adjustment. Palopeg can be decreased by 3 mcg no more than every 3 days in response to hypocalcaemia. The maintenance dose maintains serum calcium within the normal range without needing active vitamin D or therapeutic doses of calcium.

The pre-filled pens are available in three sizes that can each deliver three different doses (Table 4). Pens must be discarded 14 days after first use, irrespective of whether the pen is empty or not. This means that there will always be drug wastage unless a patient is on the maximum dose of their pen. Additionally, with the possibility of dose changes every 3 (for dose decreases) or 7 (for dose increases) days, there is potential for further wastage every time a patient moves onto a different pen.

Table 4. Available doses for pre-filled Palopegteriparatide pens[15]

| Pen | Doses Available |
|---|---|
| Yorvipath 168 mcg/0.56 mL solution | 6 mcg, 9 mcg, and 12 mcg |
| Yorvipath 294 mcg/0.98 mL solution | 15 mcg, 18 mcg, and 21 mcg |
| Yorvipath 420 mcg/1.4 mL solution | 24 mcg, 27 mcg, and 30 mcg |

While the mode of administration (i.e. subcutaneous injection) is generally well-received, there may be problems with adherence due to needle phobias and injection site reactions

### 2.2.4 Clinical pathway of care

#### *2.2.4.1 Diagnosis and classification*

HypoPT is diagnosed when serum PTH levels are absent or insufficient in the presence of hypocalcaemia (low ionised or total serum calcium adjusted for albumin), confirmed on two separate occasions at least two weeks apart.[16, 17] HypoPT is considered chronic if it persists for more than 6 months[16, 17] and permanent if it persists for more than 12 months post-surgery. [16]

#### *2.2.4.2 Current standard of care treatment*

There are no UK-specific guidelines for the management of HypoPT. UK clinical experts follow European guidelines: the guidelines from the second International Workshop (2022)[16] and the European Society of Endocrinology (ESE) 2022.[18] Both these guidelines recommend CT, defined as the oral administration of calcium and active vitamin D, as first-line treatment for chronic HypoPT. The goal of CT is to control the symptoms of hypocalcaemia. Some guidelines also recommend adjunctive use of thiazide diuretics in patients with hypercalciuria. [18] These guidelines recommend the consideration of PTH replacement therapy for patients who cannot achieve calcium control/homeostasis, have poor HRQL, exhibit renal complication, or poor gastrointestinal absorption.[5, 16, 19, 20]

Two PTH analogues are available in the UK as potential treatments, however, teriparatide is not licensed for HypoPT so its use is off-label and under individual funding request (IFR), and Natpar® is not routinely commissioned and is being discontinued globally by the manufacturer.[21]

The updated ESE guidelines, orally presented at the Joint Congress ESPE and ESE in May 2025, and scheduled for publication in October 2025, recommend considering palopeg as a second-line treatment for patients with chronic HypoPT who are on optimised CT and meet at least one of the following criteria:

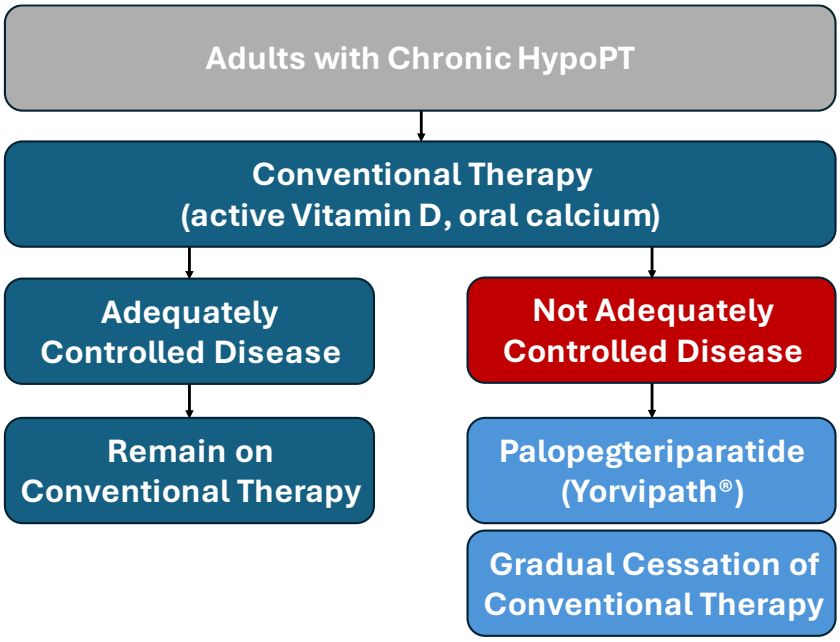
- frequent fluctuations in serum calcium or symptomatic hypocalcaemia

- impaired quality of life (QoL) attributable to chronic HypoPT
- reduced kidney function (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$)
- hypercalciuria (high levels of calcium in the urine)
- hyperphosphatemia (high levels of phosphate in the blood)

### *2.2.4.3 Intended positioning of palopeg*

The company describe the intended positioning of palopeg in CS Section B.1.3.6.4. The company suggest that palopeg is positioned as a second-line treatment for adults with chronic HypoPT whose disease is NAC with CT (Figure 1). The company's proposed positioning of palopeg was validated by their clinical experts, although one clinician suggested that the population could potentially be narrowed even further, requiring a defined number of comorbidities in addition to NAC disease.[13]

Figure 1. Company's proposed positioning of Palopegteriparatide in the treatment pathway




**Abbreviation:** HypoPT, hypoparathyroidism
Source: Adapted from SmPC[15]

According to the company, patients need to meet ANY of the following criteria to be classified as having NAC disease:

- High-dose conventional therapy
  - Calcitriol (active vitamin D) ≥ 1.0 mcg/day
  - Alfacalcidol (active vitamin D) ≥ 2.0 mcg/day
  - Calcium ≥ 2000 mg/day
- Severe symptoms and/or healthcare use

    - Emergency room or urgent care visits related to HypoPT (within 6 months)
    - Hospitalisations related to HypoPT (within 6 months)
    - Poor quality of life (defined as SF-36 Physical Functioning score < 40)
- Renal impairment and/or history of renal complications
    - Documented renal insufficiency
    - History of kidney stones (nephrolithiasis)
    - eGFR < 60 mL/min/1.73 $m^2$

and criteria for NAC were validated by their panel of clinicians.[13]

The EAG have concerns about some aspects of the company's criteria for NAC disease. According to the EAG's clinical advisor, renal impairment and/or a history of renal complications are relatively common and not specific to HypoPT, therefore they are likely not the best measures to determine NAC status. This was consistent with the opinion of the company's clinical experts who stated that while renal disease was a relevant marker of poor control, renal complications are irreversible and may reflect past periods of poor control rather than a patient's current status.[13] The EAG's clinical advisor suggested that 'worsening renal impairment' may be a better measure of determining NAC status. One of the company's clinical experts also suggested that high dose CT by itself does not necessarily indicate NAC as some patients on high dose CT may be stable. The EAG's clinical advisor also thought that SF-36 may not be the best measure to assess quality of life and Hypoparathyroidism Patient Experience Scale (HPES) may have been a better measure.

### 2.2.5 Equality considerations

The CS describes equality concerns in section B.1.4. The company states that post-surgical HypoPT is more common in women than men as women are more likely to have thyroid disease and undergo thyroidectomy.

The EAG did not identify any further equality considerations.

### 2.2.6 Other relevant appraisals in progress

There are currently no relevant appraisals in progress.

A NICE appraisal (TA625) for recombinant PTH for treating HypoPT was terminated in March 2020 as the company (Shire Pharmaceuticals which was acquired by Takeda) did not submit an evidence submission.

## *2.3 Critique of company's definition of decision problem*

A summary and critique of the decision problem addressed in the CS is provided in Table 6. The following sections provide a more detailed critique of the aspects of the decision problem that differed from the scope.

### 2.3.1 Population

The decision problem population is narrower than the NICE scope. The company restricts the decision population to people with chronic HypoPT who are NAC on CT, whereas the NICE scope includes all people with chronic HypoPT. The company focused their decision problem population on the NAC subpopulation as they claim this population will show the biggest clinical benefit as well as drive the cost-effectiveness.

The EAG considers the company's decision problem population to be appropriate, as a majority of HypoPT patients are well controlled on CT, so the restriction of palopeg to the subpopulation that would most need it is a suitable choice. However, the EAG have concerns about the company's definition of NAC disease, and whether this population is suitable for palopeg. A particular concern is that there is no single definition of NAC either in clinical practice or in the company submission. The company discussed three criteria to identify NAC patients, which are summarised in Table 5. Inconsistencies were also observed in how criteria were reported by the company. For instance, the guidelines from the Second International Workshop[16] in the company's clarification response were different from those included in the company submission; neither of which were explicitly stated in the publication referenced.

The definitions broadly agree that high-dose CT, inadequate calcaemic control, renal complications and high resource use define NAC (see Section 2.2.4.3). However, none of these criteria independently determine whether patients have NAC. The criteria have some notable differences, such as what constitutes high-dose CT, or do not specify precise levels of any outcome, such as for renal complications. Patients may have well-controlled/stable HypoPT while meeting any these criteria, as was suggested by both the EAG's clinical advisors and the company's clinical experts. [13] It is important, therefore, for HypoPT-related symptoms and/or biochemical parameters are considered when defining the eligibility criteria for palopeg, which is reflected in the updated ESE guidelines.

A further concern is that the size of the population who will be NAC with CT is not clear. Clinical advice to the EAG suggested that only a small proportion of post-surgical HypoPT patients are NAC. However, the CS claims that over 90% of patients in the PaTHway trial were NAC (see Section 3.2.1.2). The proportion of patients judged to be NAC will also vary according to which definition criteria are used.

Table 5 Definitions of NAC used in the CS

| **"UK expert" definition[13] and Chen (2019)** | **"Second International Workshop"† [16]** | **European expert consensus (PARAT 2022)[18]** |
|---|---|---|
| ANY of:<br><br>High-dose conventional therapy:<br>Active vitamin D:<br>Calcitriol ≥ 1.0 mcg/day<br>Alfacalcidol ≥ 2.0 mcg/day<br>Calcium ≥ 2000 mg/day<br><br>Emergency room or urgent care visits related to HypoPT (within 6 months)<br>Hospitalisations related to HypoPT (within 6 months)<br>Poor quality of life (SF-36 Physical Functioning score < 40)<br><br>Documented renal insufficiency<br>History of kidney stones (nephrolithiasis)<br>eGFR < 60 mL/min/1.73m² | ANY of:<br><br>Symptomatic hypocalcaemia (per medical history)<br><br>Hyperphosphataemia (>1.45 mmol/L)<br><br>Renal insufficiency (<60 mL/min, renal stone, etc. as per criteria)<br><br>Hypercalciuria<br><br>Poor quality of life (SF-36 < 40)<br><br>High dose of calcium ≥2000 mg daily | ANY of:<br><br>Inadequate control of serum calcium levels;<br><br>Dose of elemental calcium exceeds 2.5 g per day or large amounts of active vitamin D analogues are needed<br><br>Hypercalciuria, kidney stones, nephrocalcinosis or impaired renal function;<br><br>Hyperphosphatemia and/or increased phosphocalcic product;<br><br>Disorders of the gastrointestinal tract associated with malabsorption;<br><br>Significantly reduced quality of life |

† These are the criteria used by the company to categorise patients in the PaTHway trial and cited in the company's response to clarifications.

**Abbreviations:** eGFR, estimated glomerular filtration rate; mL/min, millilitre per min; mmol/L, millimoles per litre; PARAT, parathyroid disorders educational program; SF-36, short-form 36

### 2.3.2 Comparators

In the NICE scope, the comparator was established clinical management which could include teriparatide, recombinant parathyroid hormone, vitamin D analogues (e.g. alfacalcidol or calcitriol), calcium supplements, magnesium supplements, and thiazide diuretics. However, in the decision problem, the company only considered clinical management with active vitamin D analogues and calcium (that is, CT) as the only viable comparator.

The company excluded teriparatide from the decision problem as it is not licensed for use in HypoPT; and recombinant parathyroid hormone was excluded because the only licensed therapy, Natpar®, has been discontinued. The EAG finds this to be reasonable.

The company also excluded magnesium supplements and thiazide diuretics from the decision problem, as they were considered adjunct to CT rather than part of it. The EAG agrees that magnesium supplements can be excluded as a comparator as they are plausibly an infrequently used adjunct to CT, rather than a replacement for it. The EAG notes that, based on clinical advice and the

existing guidelines, thiazide diuretics may be given to some patients who would meet the criteria for being NAC on CT. So strictly thiazide diuretics could be a valid comparator. The EAG accepts that it is reasonable to not consider them as a direct comparator in terms of cost-effectiveness modelling as they are an adjunct to CT rather than a replacement. However, the EAG thinks that the evidence base should ideally include patients receiving thiazide diuretics, and these should be considered as part of CT. Alternatively, palopeg should be considered as possibly a "third-line" treatment, for use where patients are NAC both with CT alone and when using CT with thiazide diuretics.

### 2.3.3 Outcomes

The company did not incorporate all outcomes from the NICE scope in their decision problem, excluding change in physical symptoms (e.g. fatigue), change in cognitive symptoms and renal function. The company stated that change in physical and cognitive symptoms were excluded to avoid potential double counting of quality-of-life burden, as they are incorporated through utility values derived from the HPES and the EQ-5D instrument in the economic model.[22] The EAG found that the company focused on outcomes related to the maintenance of calcium levels, and reduction of calcium treatments (which don't necessarily indicate an improvement in disease control) rather than change in physical and cognitive outcomes.

### 2.3.4 Subgroups

The NICE scope specified two subgroups, based on eGFR and disease severity, provided the evidence allowed it. The company did not consider these two subgroups as neither was pre-specified in their trials. The EAG requested data on these subgroups at clarification, but accepts that, because of small numbers of patients in these subgroups in the evidence base, the value of subgroup analysis is limited.

Table 6 Summary of decision problem

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope† | EAG comment |
|---|---|---|---|---|
| **Population** | Adults with chronic hypoparathyroidism | Adults with chronic hypoparathyroidism who are not adequately controlled using conventional therapy | This submission targets the subpopulation of adults with chronic hypoparathyroidism who are not adequately controlled using CT for the following reasons;<br>• This subpopulation shows the biggest clinical benefit and drives the cost-effectiveness<br>• This subpopulation has been confirmed and validated by UK clinical experts[13] | The EAG agree with the company's choice to restrict the population to patients with HypoPT who are NAC on conventional therapy.<br><br>However, the EAG has concerns about how patients are classified as being NAC, as all of the criteria used by the company aren't necessarily indicators of poor disease control. |
| **Intervention** | Palopegteriparatide | Palopegteriparatide | As per final scope. | No comments. |
| **Comparator(s)** | Established clinical management without palopegteriparatide, which may include:<br>• Teriparatide<br>• Recombinant parathyroid hormone<br>• Vitamin D analogues such as alfacalcidol or calcitriol<br>• Calcium supplements<br>• Magnesium supplements<br>• Thiazide diuretics | Established clinical management without palopegteriparatide, which may include:<br>• Active Vitamin D analogues such as alfacalcidol or calcitriol<br>• Calcium | This submission focuses on established clinical management with active vitamin D and calcium as the comparator of interest as the standard of care for the threatment of chronic HypoPT.<br>The following have not been included as comparators due to the reasons provided below:<br>• Teriparatide: it has been minimally used off-label for HypoPT via individual funding requests.<br>• Recombinant parathyroid hormone: the manufacturing of all strengths of rhPTH 1-84 will be discontinued from the end of 2024.[21, 23] | The EAG finds the exclusion of teriparatide and recombinant parathyroid hormone appropriate per the reasons provided by the company.<br><br>The EAG also agrees with the exclusion of magnesium supplements as they are not commonly used as an adjunct to CT.<br><br>The EAG finds it reasonable to exclude thiazide diuretics as they are also an adjunct treatment. However, according to advice from the EAG's clinical advisor, thiazide diuretics may be given to patients |

| | | | | |
|---|---|---|---|---|
| | | | • Magnesium treatments: magnesium is considered an adjunct to CT if needed.<br>• Thiazide diuretics are considered an adjunct to CT if needed. | with NAC HypoPT, which could make it viable as a second-line treatment with palopeg being used as third-line. |
| **Outcomes** | The outcome measures to be considered include:<br>• change in physical symptoms such as fatigue<br>• change in cognitive symptoms<br>• hospital admissions<br>• reduction in calcium treatments and vitamin D analogues<br>• calcium levels<br>• serum phosphate levels<br>• renal function (eGFR)<br>• cardiovascular outcomes<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life | The below outcome measures are included in the submission:<br>• hospital admissions<br>• reduction in calcium treatments and vitamin D analogues<br>• Calcium levels<br>• Serum phosphate levels<br>• cardiovascular outcomes<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life | The outcome related to reduction in physical and cognitive symptoms was removed to avoid potential double counting of quality-of-life burden, as these aspects are already reflected in the health state utility values derived from the Hypoparathyroidism Patient Experience Scale (HPES) and the EQ-5D instrument used within the economic model.[22] | The EAG noted that the company focused on outcomes related to the maintenance of calcium levels, and the reduction of calcium treatments.<br><br>Changes in physical and cognitive symptoms were not reported directly, but only through the patient-reported HPES and other quality of life scores. |
| **Economic analysis** | The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. | As per final scope | Not applicable | See Section 4.2.1. |

| | | | | |
|---|---|---|---|---|
| | Costs will be considered from an NHS and Personal Social Services perspective.<br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.<br>The availability and cost of biosimilar and generic products should be taken into account. | | | |
| **Subgroups** | Subgroups based on eGFR and disease severity, if evidence allows. | No subgroups considered | Given chronic HypoPT is a rare disease with limited trial size and that the PaTHway trial represents a subpopulation of the licensed population, it was not appropriate to undertake further subgroup analysis. | The EAG requested these subgroup analyses, as they were assessed in the PaTHway trial.<br><br>The EAG accepts, however, that due to the small number of patients in the subgroups, post-hoc subgroup analyses will have limited value. |
| **Special considerations including issues related to equity or equality** | It is expected that more women than men will be treated with palopegteriparatide; this is because post-surgical HypoPT is more common in women than men (women are more likely to have thyroid disease and hence undergo thyroidectomy).[24] Furthermore, the epidemiology of CKD suggests that women are at a higher risk of developing CKD than men meaning that women with HypoPT may be at a higher risk of impaired renal function than men with HypoPT.[25] | | | Some patients may require help administering palopeg. For example, those with disabilities or who are infirm. Providing support would necessitate daily visits to patients. If this level of provision cannot be supported, it may raise important equity concerns, as it could exclude more vulnerable patients who would otherwise be eligible for treatment. |

**† Company rationale has been edited for brevity. Complete company responses are included in the decision problem table in the CS.**

**Abbreviations:** CKD, chronic kidney disease; CT, conventional therapy; DHSC, Department of Health and Social Care; eGFR, estimated glomerular filtration rate; EAG, External Assessment Group; ESE, European Society of Endocrinology; HPES, Hypoparathyroidism Patient Experience Scale; HypoPT, hypoparathyroidism; MHRA, Medicines and Healthcare products Regulatory Agency; NAC, not adequately controlled; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PTH, parathyroid hormone; rhPTH, recombinant parathyroid hormone; SmPC, summary of product characteristics

# 3 CLINICAL EFFECTIVENESS

## *3.1 Critique of the methods of review(s)*

The company conducted a systematic literature review (SLR) to identify studies on the efficacy and safety of any systemic therapies for adult patients with HypoPT. Details of the SLR are reported in Appendix B of the CS.

***Searches***

The company searches to identify studies for the clinical effectiveness SLR were included within Appendix B of the submission. The searches were designed to retrieve RCTs and Systematic Reviews (SRs) of any interventions for hypoparathyroidism and took place in March 2025.

The EAG found that the company searches had some limitations which may have led to missing relevant studies. The reporting of database searches also lacked transparency as all databases were searched together via Ovid. Appendix Table 29 includes the detailed appraisal of the searches.

***Inclusion criteria***

The SLR eligibility criteria are reported in Table 4 in Appendix B of the CS (p15). The eligibility criteria used in the SLR reported in the CS were broader than those specified in the decision problem; the CS SLR population was HypoPT (i.e. it was not restricted to chronic HypoPT) and any systemic therapies were eligible. However, these would not have resulted in any relevant studies being missed, especially given the company's focus on patients whose disease is not adequately controlled by conventional therapy. No details were reported regarding how study selection was undertaken (e.g. whether this was done by one or two reviewers).

***Critique of data extraction***

Data extraction methods were reported in Appendix B of the CS (p16). Data were extracted by one reviewer and independently checked by a second, senior reviewer with any disagreements resolved through consensus or with a third reviewer.

Very minimal details were presented in the CS on the methods and results of the PaTH Forward open-label extension (OLE) study, the PaTHway OLE study and the PaTH Forward trial. These were requested by the EAG at the clarification stage (Questions A10 and A11). The company supplied reports and publications from these studies, but only minimal data tables, so data may not have been formally extracted from these studies.

***Quality assessment***

The quality assessment of the PaTHway trial was reported in Table 12 of the CS, based on questions on randomisation, blinding, drop-outs and reported outcomes. The CS did not report whether the quality assessment was performed in duplicate and how any disagreements were resolved. Details of the results of the EAGs assessment of the PaTHway trial are reported in Section 3.2.1.

***Evidence synthesis***

No synthesis of studies was performed.

## *3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The CS included two randomised placebo-controlled trials of palopeg: one phase 3 trial called PaTHway (n=84, NCT04701203) and one phase 2 trial called PaTH Forward (n=59).

PaTHway had a blinded phase of 26 weeks followed by a 156-week OLE (Table 19 of the CS reported that 78 patients completed week 52), whereas PaTH Forward had a much shorter 4-week blinded period but an OLE to week 214. Both OLE studies are currently ongoing. The CS focussed on PaTHway, given that it was the pivotal Phase 3 study supporting marketing authorisation.

### 3.2.1 Critical appraisal of the PaTHway trial

#### *3.2.1.1 Risk of bias*

The company considered that patients were adequately blinded to their treatment allocation (see CS Table 12). The EAG acknowledges that palopeg and placebo were provided in identical pens by the site pharmacist, but there were still concerns about blinding given the large difference between the trial arms in the level of independence from calcium and vitamin D (CS Figures 15 and 16); i.e. patients may be likely to know which trial treatment they've been allocated, based on the amount of CT they're taking. This issue can be considered as a type of 'functional unblinding'; this can occur when a treatment's effects are unmistakable such that participants assigned to that treatment would know that they are receiving the active study drug. Functional unblinding was also mentioned as a possible issue in the EMA's EPAR on palopeg.[26] This is an important issue as it can lead to the results for subjective patient reported outcomes, such as quality of life measures, being subject to bias due to a differential (across groups) in patient expectations. Any functional unblinding may have biased the AC state utility values which were derived from EQ-5D PaTHway data. The EAG therefore asked the company to comment on this issue (clarification question A7). The company acknowledged there may have been a degree of functional unblinding, as participants and investigators were aware of the CT doses and/or serum calcium levels but thought any unblinding would have had minimal impact on the

trial results. The EAG did not see any evidence in the company's response to assume that any impact would have been minimal.

Although the company's assessment asked whether there were any unexpected imbalances in dropouts between groups, and whether an intention-to-treat analysis was performed, its assessment did not consider whether any assumptions made about missing outcome data were appropriate. No analyses were reported in the submission based on a conservative approach to imputing missing data – the company's analyses adopted an optimistic 'missing at random' assumption to missing data, which has the potential to overestimate treatment effects if the assumption is not plausible. Therefore, in clarification question A6, the EAG requested analyses of all secondary outcomes using a baseline-observation-carried-forward approach to missing data, but these were not provided.

#### *3.2.1.2 Applicability of the PaTHway results to the NHS setting*

***Population***

The EAG's adviser thought that the criteria for categorising patients as being not adequately controlled were not reflective of NHS practice. He was of the opinion that in NHS practice it is likely that very few patients would need palopeg, since their HypoPT would be adequately controlled by conventional therapy. He noted that the mean baseline calcium and active vitamin D doses in the PaTHway cohort suggest that some patients would likely be considered as having adequately controlled disease (rather than all patients being not adequately controlled, as assumed by the company in its cost-effectiveness analyses).

In clarification question A12, the EAG asked the company to confirm their claim that most of the population in PaTHway met a NAC definition. The response, reproduced in Table 7, shows that [redacted] ([redacted]/82) of the PaTHway population would be classified as NAC, when using the company's definition based on the Guidelines from the Second International Workshop on the evaluation and management of HypoPT.[16] Hypercalciuria (met by [redacted]% of the PaTHway population) was by far the most common reason for being categorised as NAC. The EAG asked their adviser what proportion of his NHS patients had hypercalciuria; he noted that <50% of patients had hypercalciuria in a recent audit where urine calcium was measured.

The adviser also commented that only <5% of patients in his clinic have daily calcium doses ≥2000 mg (this compares with [redacted]% of PaTHway patients, using Table 7 data). Moreover, in NHS practice, these high dose calcium patients would be considered for treatment with thiazide diuretics (which were prohibited in PaTHway) since this often results in reductions in alfacalcidol or calcium doses.

In Table 7, the company uses a definition of 'poor quality of life' based on SF-36 instead of using the disease-specific HPES outcome; the issue with SF-36 is that it will also capture poor quality of life

due to comorbidities which HypoPT treatment cannot address. When defining HypoPT which is NAC, poor quality of life should be based on symptoms of HypoPT because HypoPT treatment cannot improve aspects of quality of life due to any comorbidities. The EAG's adviser also noted that renal impairment and a history of renal complications are quite common so are not very specific to HypoPT so are not a good measure of NAC disease; some definition of *worsening* renal impairment would be a better criterion. Furthermore, the EAG notes that the updated European Society of Endocrinology guidelines, scheduled for publication in October 2025, recommend considering palopeg as a second-line treatment based on five criteria (see Section 2.2.4.2); of note, the criteria on impaired quality of life 'attributable to chronic HypoPT' and renal insufficiency (an eGFR < 60 mL/min/1.73 m²) are more specific than the broader categorisations used by the company.

The EAG notes that if hypercalciuria, poor quality of life and renal insufficiency are excluded from the definition of NAC then the numbers who were NAC might be much lower (perhaps below 50%), but as the company did not provide detailed cross-tabulated data on this, exact numbers are uncertain.

In light of these issues, the EAG concludes that the PaTHway population is not adequately representative of the NHS population likely to receive palopeg (regardless of how small that might be) since many of the patients in PaTHway would be classed as having adequately controlled disease in the NHS setting.

Table 7 'Not adequately controlled' criteria applied to PaTHway baseline ITT population

| **Criteria** | **Frequency (out of 82)** |
|---|---|
| Symptomatic hypocalcaemia (per medical history) | [redacted] |
| Hyperphosphataemia (>1.45 mmol/L) | [redacted] |
| Renal insufficiency (<60 mL/min, renal stone, etc. as per criteria) | [redacted] |
| Hypercalciuria | [redacted] |
| Poor quality of life (SF-36 < 40) | [redacted] |
| High dose of calcium ≥2000 mg daily | [redacted] |
| **Met any of the above** | [redacted] |

**Abbreviations:** SF-36, Short Form-36 Health Survey; NAC, not adequately controlled; mmol/L, millimoles per litre; mL/min, millilitres per minute.

### *Conventional therapy*

The PaTHway trial required all patients in both arms to substantially reduce their active vitamin D dose at the start of the trial. The company stated that this was done based on FDA recommendations and therapeutic guidelines. Calcium dose could vary during the trial, but there was some attempt to down-titrate doses in the CT arm in order to meet the primary outcome of independence from CT. Based on clinical advice, the EAG has substantial concerns that this reduction in active vitamin D and calcium doses mean that the CT arm of the PaTHway trial does not represent how CT would be used in the NHS, and could adversely affect serum calcium levels and quality of life.

The EAG notes that the EMA reached a similar conclusion, with the EPAR stating that standard care in the trial was potentially sub-optimal and consequently patient reported outcomes could therefore not be used in the relevant sections of the SmPC.

Use of thiazide diuretics was also prohibited in PaTHway - p39 of the CSR states: "Subjects taking a thiazide diuretic discontinued at least 4 weeks prior to the baseline Screening 24-hour urine collection scheduled during the week prior to Visit 1". Clinical advice to the EAG suggested that many patients (perhaps half) who were genuinely NAC would be offered thiazide diuretics. In PaTHway 13.4% of patients had some record of prior thiazide diuretic use. The EAG is therefore concerned that exclusion of thiazide diuretics may mean that the PaTHway trial is not representative of standard practice and may be unfairly biasing results against the CT arm.

***Outcomes***

The primary outcome in the PaTHway trial was a composite outcome which was defined as the proportion of patients at week 26 who achieved all the following:

- Albumin adjusted serum calcium levels in the normal range (2.07 to 2.64 mmol/L [8.3 to 10.6 mg/dL])
- Independence from CT is defined as requiring no active vitamin D and ≤ 600 mg/day of calcium supplementation, and
- No increase in prescribed study treatment within 4 weeks prior to week 26

The EAG considers this outcome to be inappropriate for evaluating CT and therefore does not believe that this outcome allows for a fair comparison of the trial interventions. It is relevant only to patients receiving palopeg, since the component on achieving independence from CT (in the short time frame of 26 weeks) does not seem to be a plausible goal for patients taking CT; assuming that this component of the primary outcome could likely only be achieved by spontaneous recovery this component is not actually evaluating the efficacy of conventional therapy. This suggests that the primary outcome was not designed with the evaluation of CT in mind.

The EAG also notes that the primary outcome is a surrogate outcome, since it does not directly measure clinical benefit, although it is expected to predict clinical benefit; for example, it may be expected that the less CT patients need to take, the lower the likelihood of complications such as renal impairment. The EAG's adviser thought that although improvements in renal impairment were plausible, they were yet to be proven. A limitation of the PaTHway trial is that it was not designed to detect clinical benefit in terms of renal outcomes, cardiovascular disease, or other complications (as defined in the cost-effectiveness model). Instead, the company used data on complications from the

CPRD dataset – an approach which has important limitations, given that such a large proportion of patients in the CPRD dataset had non-surgical HypoPT (see Section 4.2.8.2).

The EAG's adviser also had another concern about the applicability of the primary outcome to NHS practice since, in practice, clinicians may try to keep serum calcium a bit low to induce some production of parathyroid hormone which, over time, may gradually increase enough to enable some patients to go into remission. Therefore, for patients on conventional therapy, achieving serum calcium in the normal range is not necessarily a good outcome.

### 3.2.2 Clinical efficacy results of the PaTHway trial

***Baseline characteristics***

Baseline characteristics of the PaTHway cohort were reported in Table 11 of the CS. The EAG's adviser considered that the trial population was applicable to population seen in the NHS in terms of age, sex, and BMI but for the causes of HypoPT, the 85% figure for acquiring HypoPT post-surgery seemed a bit low: the adviser considered that this figure would be likely to be nearer 95% in a typical NHS population.

***Primary outcome***

The CS reported that at week 26, significantly more participants in the palopeg group (79%, 48/61) than in the placebo group (5%, 1/21), achieved normal serum calcium and independence from CT, without an increase in prescribed trial drug over the previous 4 weeks ($p<0.0001$). As discussed in Section 3.2.1, the EAG does not consider that this outcome allows a fair comparison between palopeg and placebo. The EAG requested subgroup analyses (clarification question A15) based on whether patients were deemed to be NAC or AC at baseline and on baseline eGFRs and vitamin D/calcium doses. The company's response is reproduced in Table 8. The results suggest that palopeg may be [redacted] in patients who are more definitively NAC, such as those with eGFRs of 30-60 and in patients taking high dose calcium and high dose vitamin D.

Table 8 Subgroup analyses for responders meeting primary outcomes from baseline to week 26 in the palopeg arm

| Primary outcome components | NAC* | eGFR 30-60 | eGFR >60 | High dose Calcium (>2000mg) | High dose vitamin D |
|---|---|---|---|---|---|
| All criteria | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Normocalcaemia | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| No active vit D | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Calcium ≤600 mg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Stable dose 4 weeks* | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*The total number of NAC patients includes only those in the palopegteriparatide arm of the trial (57 of the 77)
**Abbreviations:** eGFR, estimated glomerular filtration rate ;NAC, not adequately controlled

***Hospital admissions***

The submission did not report on hospital admissions as a whole, although some safety data were reported on hospital visits due to hypercalcaemia or hypocalcaemia (Table 16 of the CS).

***Calcium levels***

Figure 19 and Table 36 of the PaTHway CSR reports a least squares mean change from baseline in serum calcium at week 26 of 0.30 mg/dL in the palopeg group compared with -0.39 mg/dL in the placebo group; the EAG notes that the reduction in the placebo group may be due to the mandated reduction in active vitamin D dose.

***Renal function (eGFR)***

Results for eGFR were not presented in the main submission document, the appendices, nor the CSR. In response to clarification question A1 the company stated that a post-hoc analysis was conducted to examine the impact of palopeg on renal function. This found that from baseline to week 26, mean eGFR increased by 7.9 mL/min/1.73m$^2$ in the palopeg group and decreased by -1.9 mL/min/1.73 m$^2$ in the placebo group ($p<.001$ for the group difference). This was based on one-year PaTHway trial results reported in a paper by Rejnmark et al. 2024.[27] The paper also stated that a clinically meaningful change in eGFR was ≥5 mL/min/1.73 m$^2$. In placebo participants who received open-label palopeg from week 26, the mean eGFR was 7.6 mL/min/1.73 m$^2$ ($p<0.01$) higher at week 52 when compared to baseline.

***Cardiovascular outcomes***

Results for cardiovascular outcomes were not presented in the main submission document, the appendices, nor the CSR. The EAG accessed the full CSR tables from the EMA's clinical data website and found there to have been one ≥grade 3 cardiac arrest in the palopeg arm and no cardiac disorders events in the placebo arm.

***Patient reported outcomes***

The Hypoparathyroidism Patient Experience Scale (HPES) was developed and validated by the company. It has two symptom domains: physical and cognitive, and two impact domains: physical functioning and daily life (physical functioning, daily life, psychological well-being, social life and relationships). These were secondary outcomes in PaTHway. When compared with placebo at week 26, palopeg significantly improved all domains: physical symptoms (p=0.004), cognitive symptoms (p=0.006), physical functioning (p=0.005) and daily life (p=0.006). More results details are reported in Table 14 of the CS.

Statistically significant improvements with palopeg were also reported at week 26 for the Short Form Survey (SF-36) physical functioning subscale (p=0.035), see Figure 14 of the CS.

Some EQ-5D domain data were reported in Table 15 of the CS although the comparisons were not consistent (changes in the proportion of patients reporting 'no problems' were typically presented for palopeg and changes in 'moderate problems' reported for placebo). The EAG accessed EQ-5D results from the EMA's clinical data website; although larger changes from baseline at week 26 in EQ-5D utility scores were seen in the palopeg group than in the placebo group most of the means and medians were notably different and the maximum and minimum values were quite extreme, suggesting significant population heterogeneity in the trial cohort. Given the small group sizes, these outlying data could have an impact on the reliability of the mean results (as illustrated in Table 9).

Table 9 EQ-5D utility scores at Baseline and Week 26 in PaTHway*

| | Palopeg (n=59) | Placebo (n=19) |
|---|---|---|
| **Baseline Mean (SD)** | [redacted] | [redacted] |
| **Baseline Median (Min, Max)** | [redacted] | [redacted] |
| **Observed Week 26 Mean (SD)** | [redacted] | [redacted] |
| **Observed Week 26 Median (Min, Max)** | [redacted] | [redacted] |
| **Change from baseline (in means, SD)** | [redacted] | [redacted] |
| **Change from baseline (in medians, Min, Max)** | [redacted] | [redacted] |

* Data extracted from Table 14.2.4.3 of the CSR from the EMA's clinical data website https://clinicaldata.ema.europa.eu/web/cdp/login. File name is: m5351-tcp-304-p-csr-tfgs.pdf
**Abbreviations:** CSR, clinical study report; ED-5D,EuroQol 5 dimensions ; Min, minimum; Max, maximum; SD, standard deviation

### 3.2.3 PaTH Forward trial

The CS did not present details of the PaTH Forward trial, so it is briefly assessed here, based on the supplied CSR.

PaTH Forward randomised 44 patients to receive palopeg, across three dose groups, and 15 patients were randomised to placebo. It was not clear how many patients would class as NAC using conventional therapy. However, the inclusion criteria were similar to PaTHway and patient characteristics appeared broadly similar to PaTHway, although possibly patients in PaTH Forward had slightly lower initial doses of calcium. The primary outcome was similar to that of PaTHway and included reduction in CT use (For our critique of this as an outcome see Section 3.2.1.2). The EAG notes that, unlike PaTHway, there does not seem to have been any requirement that patients reduce their vitamin D dose at the start of the trial. The blinded period of the trial had a duration of four weeks.

The percentage of patients with serum calcium in the normal range after four weeks was 93.3% (14 of 15) in the placebo arm, and 86.4% (38 of 44) across all palopeg dose arms. In the highest palopeg dose arm (21 µg/day) 93.3% of patients had serum calcium in the normal range. No data for physical

function, cognitive function or renal function outcomes were presented. The EAG notes that PaTH Forward therefore showed no difference between CT and palopeg in terms of maintenance of calcium levels. This differs from PaTHway (see Section 3.2.2) and highlights the EAG's concern that outcomes in PaTHway may have been impacted by the required reduction in Vitamin D dosage (see Section 3.2.1.2).

### 3.2.4 Open-label extension studies

The company presented few data in the CS on the OLEs so the EAG requested further data and reports via clarification question A10. The company provided numerous PDFs covering different follow up durations, although most were reported as conference abstracts, so the data are difficult to critique.

Khan et al 2025 reported 3-year results from the PaTHway OLE study in a conference abstract.[28]At week 156, 89% (73/82) of participants remained in the study; 70/73 (96%) were independent from CT, and 88% had normal albumin-adjusted serum calcium levels. At week 156, the mean increase from baseline in eGFR was 8.8 mL/min/1.73 $m^2$. In the 23 participants with a baseline eGFR <60 mL/min/1.73 $m^2$, the mean increase in eGFR was 14.0 mL/min/1.73 $m^2$.

Palermo et al presented 4-year results from the PaTH Forward OLE study in a conference abstract.[29] At week 214, 95% (56/59) of participants remained in the study; 52/56 (93%) were independent from CT and 98% had normal albumin-adjusted serum calcium levels. The mean increase from baseline in eGFR at week 214 was 7.6 mL/min/1.73 $m^2$.

No data were presented on hospital admissions or cardiovascular outcomes.

In response to clarification question A11 about losses to follow up and missing data, the company reported that 6 patients withdrew from the PaTHway OLE with all except one, due to 'withdrawal by subject'. Where reasons were provided, these were: relocation to another country, wanting to conceive, family emergency, feeling overwhelmed by new clinical situation and wanting to join another clinical study. One patient discontinued the study early due to pregnancy. Two patients withdrew from the PaTH Forward OLE. One was due to 'withdrawal by subject' and the other due to a protocol violation. The company reported that no patients were lost to follow up in both studies.

### 3.2.5 Adverse events and safety data

Treatment-emergent adverse event (TEAE) data were reported in Tabe 16 of the CS; the event rates across all grades (1-4) were similar across the two groups, as were the rates of TEAEs related to hypercalcaemia or hypocalcaemia leading to A&E/urgent care visits and/or hospitalisation. Injection

site reactions were more common in the palopeg group (31%) than in the placebo group (0%). The median duration of injection site reactions was [redacted] hours, ranging from [redacted] to [redacted] hours.

Although hypocalcaemia was more common in the placebo group (43%) than the palopeg group (10%) this result should be viewed in the context of the mandatory large reduction in active vitamin D doses in the PaTHway cohort. Such a reduction would not be seen in clinical practice. The reduction is likely to have increased the risk of hypocalcaemia in the placebo group more than in the palopeg group.

### *3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

No indirect or multiple treatment comparisons were performed. The CS did not present data on any trials of other treatments.

### *3.4 Critique of the indirect comparison and/or multiple treatment comparison*

No indirect or multiple treatment comparisons were performed.

### *3.5 Additional work on clinical effectiveness undertaken by the EAG*

The EAG have not undertaken any further work, given the lack of comparator treatments and limited data on which to perform any further analyses.

### *3.6 Conclusions of the clinical effectiveness section*

The clinical evidence for palopeg is largely based on a single RCT, the PaTHway trial, which included 84 patients randomised to palopeg or CT (active vitamin D and calcium) with a blinded duration of 26 weeks. The primary outcome of the trial showed that patients on palopeg could retain adequate serum calcium levels in the normal range while largely discontinuing conventional therapy. The EAG therefore agrees that palopeg could reasonably be used as an alternative to conventional calcium and vitamin D treatment. However, the EAG has several concerns with the evidence presented that could have a substantial impact on determining whether palopeg is clinically preferrable to, or more cost-effective than, conventional therapy.

The evidence is presented as being in a population whose disease is not adequately controlled on conventional therapy. However, there is no single consistent definition of NAC, and the number of patients in PaTHway who were NAC varied slightly depending on the definition chosen. The trial was not explicitly designed as being only for NAC patients, as this was not part of the inclusion criteria. The high proportion of NAC patients in the trial does not concur with clinical advice to the EAG,

which is that only a minority of NHS patients are NAC with conventional therapy. Consequently, it is unclear whether the trial fairly represents a NAC population.

The trial used independence from CT as part of its primary outcome. The EAG considers this outcome to be inappropriate for evaluating CT because, by definition, independence from treatment is not feasible, at least within the trial time frame. The trial is therefore not adequately comparing palopeg to conventional therapy, which limits its value for this assessment. The primary outcome is also a surrogate outcome, making the assumption that independence from CT with adequate calcium levels is desirable in itself, rather than demonstrating actual clinical benefit of palopeg as the primary outcome.

All trial patients, including those on conventional therapy, were required to substantially reduce their vitamin D dose. This does not match standard practice and so the EAG concludes that the control arm of the PaTHway trial is not a fair representation of conventional therapy. Reduction in vitamin D dose could adversely affect serum calcium levels and quality of life outcomes in patients on conventional therapy, so the results of the PaTHway trial may be overestimating the relative benefits of palopeg. Similarly, use of thiazide diuretics was not permitted in the trial. As patients who are NAC with CT might be offered thiazide diuretics, the control arm of PaTHway appears not to represent NHS practice.

Although the trial was blinded, patients were aware of their calcium dosage and so may have been "functionally unblinded" as they may have deduced what treatment they were receiving. As physical and cognitive function outcomes were based on patient reporting, this functional unblinding could have biased results in favour of palopeg. Patient-reported outcomes using HPES suggests that palopeg improves physical and cognitive function when compared to conventional therapy, but the exact benefit may be overstated.

Renal insufficiency and its consequent harms are a key adverse outcome of conventional therapy, but this was not a protocol-specified outcome in the PaTHway trial. A post-hoc analysis of renal function suggested that palopeg gave some improvement in renal function whereas CT did not, but this should be interpreted with caution as it was not protocol specified.

Overall, the EAG accepts that palopeg can control calcium levels, so could be useful in the management of HypoPT. Although the EAG has concerns with the evidence presented, it also seems plausible that palopeg could be particularly beneficial in patients whose physical and cognitive symptoms are not well managed by conventional therapy, or in patients where there are concerns over renal harm, such as in patients requiring high doses of calcium. The EAG notes, however, that it does

not consider the evidence presented in the submission to be sufficiently robust to be confident that palopeg should be the preferred treatment for such patients.

# 4 COST EFFECTIVENESS

## *4.1 EAG comment on company's review of cost-effectiveness evidence*

The company undertook two SLRs to identify relevant cost-effectiveness studies and health-related quality of life studies for patients with HypoPT. The company provides a detailed report of the methods and results of the SLRs in Appendix E and F of the CS.

### 4.1.1 Search strategy

Appendix E of the CS included the searches to identify both economic evaluations of treatments for hypoparathyroidism and cost and healthcare resource use studies relating to this population. Searches were undertaken in March 2025.

The EAG found that the company searches had some limitations which may have led to missing relevant studies, see Appendix Table 30. The reporting of the database searches also lacked transparency as all databases were searched together via the Ovid interface.

### 4.1.2 Inclusion/exclusion criteria

Studies including adults with HypoPT receiving any treatment including no treatment, were eligible for inclusion. Screening was conducted at both the title/abstract and full-text levels by two independent reviewers, with any disagreements resolved by a third reviewer. Data extraction from included full-text studies was performed using a Microsoft Excel®-based template and independently reviewed by a second, senior researcher.

The EAG considers the selection criteria and the company's methods for study identification and screening to be appropriate and clearly described

### 4.1.3 Identified studies

A total of 41 unique studies were identified from 47 included records in the cost-effectiveness review. The company report that one of the identified studies was a US-based decision analytic approach to evaluate the cost effectiveness of recombinant human parathyroid hormone (rhPTH) compared to usual care in patients with postsurgical HypoPT.

For the HRQL review, 104 reports were included, yielding 73 unique studies. Among the 73 included studies, only two reported preference-based utility values, but both failed to meet the NICE reference case requirements due to the use of non-admissible instruments or valuation sets. The company also stated that no suitable preference-based data were available to quantify cognitive benefits, and any cognitive utility gain is likely to be conservatively represented in the model.

None of the findings from these reviews were used to inform the company's economic model; utility values and cost inputs were derived from other sources.

Although the US rhPTH cost-effectiveness study does not directly inform the cost-effectiveness of rhPTH in other settings, the general approach including model structure, assumptions, and clinical inputs remains relevant. A brief summary of the study is provided below:

The US study evaluated the clinical and cost-effectiveness of rhPTH versus usual care (CT) in adults with postsurgical HypoPT. It was assumed the modelled population consisted of patients without renal disease, stable on CT and without contraindications to rhPTH. A US healthcare system perspective was used, and both costs and outcomes were discounted at 3% per year. The model used an annual cycle length and a ten-year time horizon. Effectiveness was measured in quality-adjusted life years (QALYs).

The model structure comprised a Markov model with health states defined according to treatment received. Substates were also used to account for side effects associated with HypoPT, including renal complications. Model health states captured treatment response, side effects (particularly renal complications), and quality of life. Transition probabilities and utilities were derived from published literature and supplemented with expert opinion. The model incorporated costs of medication, endocrine visits, and complications, based on 2017 Medicare data.

In the base case, rhPTH was more effective but substantially more costly than UC, with an ICER of $804,378/QALY—far exceeding the $100,000 willingness-to-pay (WTP) threshold. Sensitivity analyses identified key drivers of cost-effectiveness as the utilities of rhPTH and UC and the incidence of rhPTH-related side effects. Probabilistic sensitivity analysis confirmed that UC was preferred in all model iterations at the stated WTP. Threshold analysis indicated that rhPTH would become cost-effective if its annual cost fell below $18,737. The model did not identify scenarios in which rhPTH was cost-effective at current pricing, except potentially in patients with poor response or high risk of complications under UC.

#### 4.1.4 Interpretation of the review.

The CS did not identify any previous cost-effectiveness analyses assessing palopeg. The company also did not make any statements as to the appropriateness of the studies identified for other interventions to inform the modelling of palopeg.

Although the EAG considers the company's model to provide the most relevant evidence for the cost-effectiveness of palopeg, the US study evaluating rhPTH provides an important basis for comparing key structural assumptions, data sources and parameter uncertainties.

## *4.2 Summary and critique of the company's submitted economic evaluation by the EAG*

### 4.2.1 NICE reference case checklist

Table 10 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 10 NICE reference case checklist

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | QALY benefits for treated individuals were considered. |
| Perspective on costs | NHS and PSS | NHS and PSS costs were considered. |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | Fully incremental cost-utility analysis was implemented. |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | The economic model evaluates patients until 100 years of age, commensurate with a lifetime horizon. |
| Synthesis of evidence on health effects | Based on systematic review | The company undertook a systematic review to identify relevant data sources. Modelled effects on complication rates and mortality are based on an assumed surrogate relationship. |
| Measuring and valuing health effects | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | EQ-5D-5L data were collected in the PaTHway trial. These data were cross-walked to EQ-5D-3L using the Hernández-Alava et al. [30] mapping algorithm. |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | EQ-5D data was directly obtained from patients in the PaTHway trial. |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | Yes |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| Evidence on resource use and costs | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | Costs based on UK sources, including BNF and NHS reference costs. Resource use and costs applied to health states were based on the CPRD and clinical advice. This included resource use and costs not directly attributable to HypoPT. This is inconsistent with the reference case, which stipulates that only costs directly related to the condition of interest should be included in the economic evaluation. |
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | Costs and benefits were discounted at 3.5% per annum. |

**Abbreviations:** BNF, British national formulary; CPRD, Clinical Practice Research Datalink; EQ-5D, EuroQol 5-Dimension scale standardised instrument for use as a measure of health outcome; eMIT, electronic market information tool; HRQL, health related quality of life; PSS, personal social services; QALYs, quality-adjusted life years;

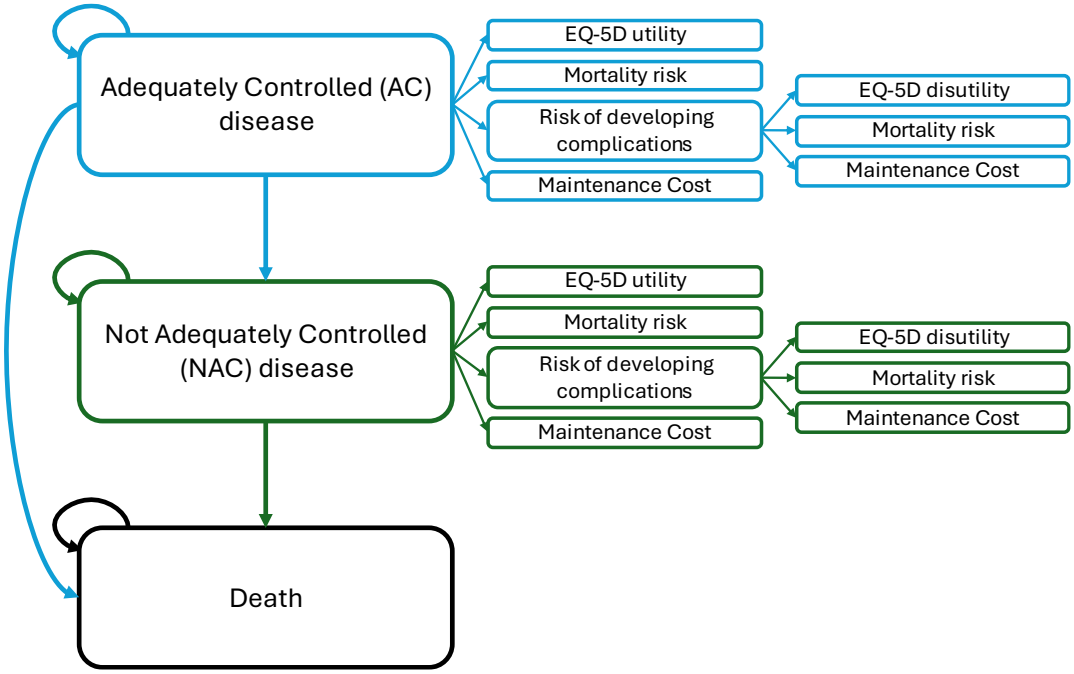
### 4.2.2 Model structure

The company submitted a three-health state model, comprising the health states AC, NAC, and death (see, Figure 2). The company describe the model as an on/off treatment model, with health state occupancy determined by treatment status (on/off palopeg). Patients enter the model in the AC or 'on treatment' health state if initiating palopeg, or in the NAC of 'off treatment' health state if initiating CT. In each 28-day cycle, patients in the AC (on treatment) state may discontinue palopeg treatment and move to NAC (off treatment) state. No transitions from NAC to AC are permitted in the model. Death is an absorbing state, and patients in any health state may die, based on age- and state-specific mortality risks.

A linked event-based sub-model captures long-term complications of chronic HypoPT, including CKD, CVD, nephrolithiasis, and other relevant events. These are modelled as repeatable events, with risks stratified by health state using CPRD-based hazard ratios (HR). Event-level costs and mortality were excluded in the base case to prevent double counting with health-state-level estimates.

Hypocalcaemia and hypercalcaemia were modelled separately as treatment-related adverse events, based on exposure-adjusted rates from PaTHway. Each was assigned a cost, disutility, and duration of effect.

Figure 2: Palopegteriparatide model structure




**Abbreviations:** AC = Adequately Controlled; NAC = Not Adequately Controlled; EQ-5D = EuroQol 5-Dimension questionnaire.

**Source:** CS, Figure 18.

Due to the on/off treatment structure, the modelled treatment effect does not relate to the (composite) primary outcome of PaTHway or any other clinical outcome. Instead, health benefits are directly attributed to treatment with palopeg, with the modelled treatment effect based on observed differences in HRQL between the palopeg and CT arms of the PaTHway trial.

#### *4.2.2.1 Points for critique*

***Conceptual limitations of model structure***

The model structure adopts an approach in which health states are defined by treatment received rather than by a clinical endpoint. As a result, QALY gains are primarily inferred from observed differences in HRQL between treatment arms in the PaTHway trial and are not directly linked to the trial's primary outcome or any other clinical endpoint. While this approach is valid and is consistent with existing cost-effectiveness studies in this indication. [31] It represents a conceptually weak foundation that has several important limitations. Firstly, it decouples the model structure from the underlying pathophysiology of the condition, reducing clinical interpretability of the model. Secondly, this approach obscures the mechanisms by which health benefits are generated, as treatment allocation is a proxy rather than a direct measure of health.

The limited evidence available from the PaTHway trial, both in terms of the range of outcomes collected and the absence of clear disease severity measures in HypoPT, restricts the alternative modelling options available to the company. However, one viable alternative would be to use the primary outcome as a measure of treatment response and define health states accordingly. This approach offers two key advantages. First, achievement of the primary outcome is directly linked to clinically relevant outcomes. Namely, achieving normal serum calcium and becoming independent from CT. Second, this structure would allow for the inclusion of an assessment period in the model, for example after six months, during which treatment response could be evaluated and non-responders would discontinue therapy. This method of response-based assessment is commonly used for high-cost treatments in chronic conditions, and clinical advice to the EAG indicated it would be feasible in clinical practice.

In their clarification response, the company rejected this alternative, arguing that benefits are delivered irrespective of whether a patient meets the primary endpoint. They maintained that the on/off treatment framework better reflects both real world clinical practice and the benefits of palopeg observed in the trial evidence.

***Equivalence of 'on treatment' and adequate control***

A fundamental assumption in the company's model is that all patients receiving palopeg are assumed to be in the AC state, whereas all patients receiving CT are assumed to be in the NAC state. This assumption is important because the NAC heath state is associated with substantially worse outcomes,

not only in terms of HRQL, but also higher complication rates, AE rates, mortality, and increased healthcare resource utilisation. These outcomes are central to the company's value proposition; indeed, the majority of the benefits attributed to palopeg are not due to direct improvements in HRQL, but rather to the reduced costs associated with patients in the AC health state. It is, however, not clear that this assumption is appropriate for several reasons:

First, in the context of the target population, it is not clear that all CT-treated patients can reasonably be considered NAC. As discussed in Section 2.3.1, the eligibility criteria include patients with renal complications and those classified as high resource users. However, these criteria do not necessarily reflect poor response to CT. Patients may therefore be well-controlled on CT and still be within the target population. More restrictive eligibility criteria solely based on either symptom burden or dosing CT may imply a failure of CT, in which case, the term NAC may be appropriate to apply to the target population. However, this is not what has been put forward by the company.

Second, a substantial proportion of patients in the CT arm of the PaTHway trial had normal serum calcium levels at 26 weeks (47.6%). While normal serum calcium is not necessarily synonymous with disease control, it is a relevant and important treatment aim. The fact that many CT patients maintain normal serum calcium undermines the assumption that all CT patients are NAC. Moreover, not all patients receiving palopeg achieved normal serum calcium at 26 weeks (80.3%), suggesting that some patients treated with palopeg may not meet the criteria for being AC either.

Third, the model assumes that patients who are NAC on CT will remain permanently in that state. However, clinical input to the EAG indicated that patients (with surgical aetiology) on CT often taper their doses with the long-term aim of achieving CT independence. Furthermore, the PaTHway trial reported at least one patient who was able to maintain normal serum calcium while becoming independent from CT, suggesting that transitions between states may be possible, see Table 13 of CS.

***Reliance on surrogate relationships***

As noted above, higher complication rates, AE rates, mortality, and increased healthcare resource utilisation are key drivers of cost-effectiveness linked to health state occupancy in the model. Except for AE rates, none of the modelled benefits associated with palopeg are based on directly observed outcomes from the PaTHway trial. This reflects limitations in the trial design, namely, the short follow-up period and the single-arm design of the OLE, as well as its focus on intermediate outcomes, such as serum calcium levels and CT independence.

Instead of relying on direct evidence, the model is structured around a chain of assumptions that links intermediate outcomes (in particular, treatment allocation) to final outcomes, including survival, complications, and healthcare utilisation. However, the CS does not fully justify these assumptions.

Specifically, it does not provide adequate evidence to support a causal or surrogate relationship between treatment allocation (or any intermediate outcome) and final outcomes. The justification is limited to indirect and largely unquantified claims.

The EAG considers this a significant omission. The NICE methods manual [32] clearly states:

*"When using 'final' clinical end points is not possible and data on other outcomes are used to infer the effect of the technology on mortality and health-related quality of life, evidence supporting the outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling."*

In response to clarification requests, the company acknowledged the use of surrogate relationships and cited biological plausibility grounded in the mechanistic understanding of disease. While the EAG accepts this biological rationale and agrees that improved disease control may lead to downstream benefits (e.g., reduced complications, mortality, and healthcare utilisation), the company did not provide any empirical evidence to quantify these effects. Instead, it highlighted the absence of long-term data due to the rarity of the condition and the limited duration of available trial evidence.

Without either direct evidence or a well-supported surrogate relationship to quantify these benefits, it is difficult to confidently attribute the modelled benefits to palopeg. The EAG emphasises that the reliance on surrogate relationships represents a significant area of uncertainty, as many of the claimed benefits of palopeg are based on strong, unproven assumptions about its impact on final outcomes. One important example is the predicted reduction in healthcare resource use which represent a major driver of cost-effectiveness. This assumption is based on categorising patients in the CPRD dataset using the following criteria:

- AC or 'on treatment': ≤5 outpatient visits and <1 inpatient admissions per patient per year
- NAC or 'off treatment': >5 outpatient visits and ≥1 inpatient admission per patient per year

These thresholds are based purely on the frequency of healthcare encounters and are not linked to any clinical indicators of disease severity, such as symptom burden, CT dosing, or serum calcium levels. The implied high resource burden associated with patients classified as NAC is therefore entirely driven by the definition, which presumes this to be the case. Limited evidence has been provided in the company's submission to support the conceptual link between the clinical concept of NAC and increased resource use with model assumptions principally relying on clinical opinion and single study by Chen et al.[33] which demonstrated modest differences in some elements of resource use between NAC and AC patients. Moreover, considering the comorbidities and complex clinical context of the HypoPT population, it is not clear that such a relationship would necessarily exist. For a more detailed discussion of these concerns, see Section 4.2.8.2.

### 4.2.3 Population

As outlined in Section 2.2.4, the proposed position of palopeg is as a second-line treatment option in patients with chronic HypoPT who are NAC on CT. This population is narrower than the marketing authorisation, which covers all patients with HypoPT.

The modelled population is based upon the PaTHway study (n=82), which informs several of the modelled treatment effects and HRQL values used in the model, see Section 4.2.6 and Section 4.2.7 respectively for details. The company assumes that the population recruited to the PaTHway trial are generalisable to the narrower population of patients whose chronic HypoPT is NAC. The baseline characteristics of the modelled population included age and sex, which were used to inform general population mortality rates as well as to age-adjust the utility values used in the model. These values were informed by the PaTHway trial and assumed an average starting age of 48.56 years and that 78% of the cohort were female.

#### *4.2.3.1 Points for critique*

***Deviation from NICE scope***

The EAG considers the company's focus on a narrower population of HypoPT patients in greatest need to be reasonable. As discussed in Section 2.3.1 , the majority of HypoPT patients are well-controlled on CT and can maintain normal blood calcium and phosphate levels while adequately balancing the risks of treatment-related complications. Clinical advice to the EAG therefore clarified that the use of palopeg in the full population would not be appropriate.

***Target population and generalizability of the PaTHway trial***

As discussed in Section 2.3.1, the EAG has several concerns regarding the appropriateness of the target population defined by the company and the proposed eligibility criteria. While high-dose CT may be a reasonable criterion, other proposed criteria are less clearly appropriate and may be difficult to apply in clinical practice. In brief, symptom burden is inherently subjective, and increased resource use may not necessarily be attributable to HypoPT. Moreover, renal impairment and a history of renal complications are relatively common in HypoPT and do not necessarily indicate severe or uncontrolled disease.

It is also unclear whether the population recruited to the PaTHway trial is representative of the proposed NHS target population. The eligibility criteria used in the trial do not align with those now proposed to define the target population. These uncertainties are significant, as the PaTHway trial population forms the basis of the modelled population and informs several of the clinical effectiveness parameters used in the economic model. Therefore, if the PaTHway trial population is not generalisable to the target population, the results of the economic analysis may also lack generalisability.

### 4.2.4 Interventions and comparators

As described in Section 2.2.3, palopeg is a parathyroid hormone replacement therapy indicated for adults with chronic HypoPT. The marketing authorisation granted on 24th April 2024, permits the use of 3 alternative pre-filled pens containing either 168 micrograms/0.56 mL, 294 micrograms/0.98 mL or 420 micrograms/1.4 mL of palopeg solution for injection.

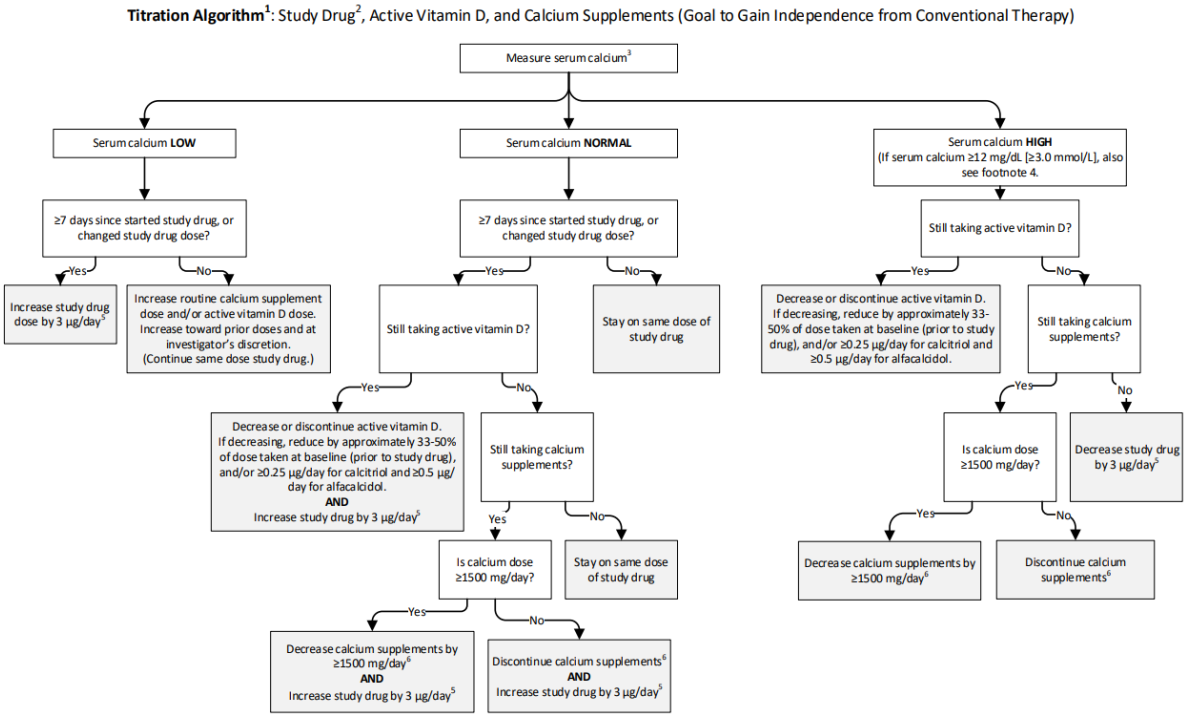
Palopeg is administered as a once-daily subcutaneous injection for self-administration. The recommended starting dose is 18 mcg daily. Dose adjustments are made in 3 mcg increments, with a minimum 7-day interval for increases and 3-day interval for decreases (if hypercalcaemia occurs). The dose range is 6–60 mcg/day. The goal is to achieve a maintenance dose that keeps serum calcium normal without active vitamin D or therapeutic calcium, though dietary calcium supplementation may continue. Figure 3 outlines the titration algorithm. Patients requiring daily doses of more than 30 mcg will need to use two separate pens per day, with the dose administered as two injections at different sites. Recommended dose combinations and corresponding pen summarised in Table 3 of the PaTHway CSR. Each pre-filled pen must be discarded 14 days after first use.

During the double-blind phase of the PaTHway trial (up to Week 26), the mean daily dose of palopeg was 20.1 mcg, range (9.7 to 34.1 mcg). At week 26, 10% of patients are receiving a daily dose of between 6 and 12 mcg, 51.7% between 15 and 21 mcg, and 36.7% between 24 and 30 mcg. Only 1.7% of patients received more 30 mcg, indicating that a single patient required two injections daily. Mean daily of palopeg thereafter increases. By Week 110 of the OLE, 1.7% of patients were receiving a daily dose of between 6 and 12 mcg, 32.8% between 15 and 21 mcg and 48.3% between 24 and 30 mcg. The proportion of patients receiving more than 30 mcg also increases to 17.1%

In the economic model, patients receiving palopeg are assumed to continue concomitant CT, comprising oral calcium and alfacalcidol. Dosing in palopeg arm is based on observations from the PaTHway trial up to Week 26.

The SmPC does not outline any specific criteria for permanent discontinuation of palopeg. It recommends temporary interruption and reassessment in cases of severe hypercalcaemia, but continued treatment with dose adjustment is generally advised. The company states that 6 out of 79 patients discontinued treatment by Week 156 in the open-label extension of the PaTHway trial, yielding an annualised discontinuation rate of 2.6%. This discontinuation rate was extrapolated throughout the model time horizon.

Figure 3 Titration algorithm




**Source:** PaTHway CSR, Figure 3.

The comparator outlined in the NICE scope is established clinical management without palopeg, which may include teriparatide, rhPTH, vitamin D analogues (e.g. alfacalcidol or calcitriol), calcium and magnesium supplements, and thiazide diuretics.

The company included only active vitamin D analogues and calcium, defined as CT. A simplifying assumption is made to represent CT using alfacalcidol and calcium. The company states that per trial protocol, all participants reduced their active vitamin D dose by 33% to 50% at the start of the blinded treatment period. The model used the doses of active vitamin D (0.618 µg/day) and calcium (1,847 mg/day) based on mean observed dose throughout the blinded period of the of the PaTHway trial.

Other potential comparators such as teriparatide, rhPTH 1-84, magnesium supplements, and thiazide diuretics were excluded. The company justified these exclusions on the following basis. Teriparatide is not licensed for HypoPT, used off-label in a small proportion of patients, and limited by safety concerns and duration of use. rhPTH 1-84 has not been appraised by NICE and is being withdrawn from the market. Magnesium and thiazides are used only as adjuncts in a minority of patients and are not considered relevant comparators.

#### *4.2.4.1 Points for critique*

***Modelled comparators***

As described in Section 2.3.2, the EAG considers the exclusion of teriparatide, rhPTH 1-84, magnesium supplements as comparators to be appropriate. However, the exclusion of thiazide diuretics may not be appropriate. Thiazides were explicitly prohibited in the PaTHway trial, clinical expert opinion consulted by the EAG, however, suggests this restriction does not reflect usual clinical practice. In the UK, thiazide diuretics are used as an adjunctive therapy in some (5% of all patients) patients with chronic or refractory HypoPT. As such, while the EAG agrees with the company that thiazides do not represent a separate comparator they should have been included as part of the basket of treatments that make CT. Their exclusion may result in an incomplete representation of CT in clinical practice.

***Dosing of calcium and vitamin D in the CT arm***

The dosing of vitamin D and calcium based observed dosing in the CT arm of the PaTHway trial may not reflect practice. This is because the trial protocol mandated that all participants reduce their active vitamin D dose by 33% to 50% at the start of the blinded treatment period. In addition, subsequent dose reductions followed the same titration protocol as the intervention arm. As such, all patients were titrated based on serum calcium levels, with the protocol aiming to reduce or discontinue active vitamin D and calcium. Both the mandatory initial reduction and subsequent titration are unlikely to represent routine clinical practice for CT and it is notable that mean doses of vitamin D in the CT arm were substantially reduced compared to their base line values, see Figure 16 of the CS. While this has only a small impact on overall acquisition costs the EAG conducts scenario analysis in Section 6 to explore using the base line doses of calcium and vitamin D to inform acquisition costs.

### 4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide, [32] the company's analysis adopted an NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5% per annum. The impact of a 0% discount rate (no discounting) was also explored in scenario analysis. A lifetime horizon was chosen for the base case analysis in which patients remained in the economic model to the age of 100. At the end of the time horizon, the model predicts <0.1% will remain alive. A lifetime horizon is therefore considered appropriate by the EAG to account for the claimed impact of palopeg.

### 4.2.6 Treatment effectiveness and extrapolation

#### *4.2.6.1 Efficacy of palopegteriparatide*

As outlined in Section 4.2.2, the company's revised base case defines health states according to treatment status, specifically whether patients are receiving palopeg or not. The efficacy of palopeg is

therefore represented through differential utility values assigned to the AC and NAC health states. In line with this structure, all patients initiating treatment with palopeg are assumed to enter the model in the AC health state (100 percent), while all patients receiving CT are assumed to begin in the NAC health state (100 percent). Patients in the AC health state are assumed to remain in that state for the duration of the model's time horizon, which reflects lifetime treatment with palopeg, conditional on continued treatment and survival.

***Points for critique***

*Durability of the treatment effect*

An implicit assumption of the economic analysis is that the treatment effects observed at 26 weeks are extrapolated over the entire time horizon of the model. Accordingly, patients are assumed to retain 100% of the observed treatment effect while remaining on palopeg, with no waning. The company justifies this assumption by citing both its biological plausibility and consistency with available evidence. It emphasises that, as a hormone replacement therapy, palopeg restores normal calcium regulation by addressing the underlying hormonal deficiency and directly re-establishes physiological calcium metabolism. The company further notes that long-term data from the PaTHway and PaTH Forward OLE studies demonstrate sustained treatment benefits over follow-up periods of 156 and 216 weeks, respectively. Additionally, it references supportive data for Natpar (which shares the same mechanism of action as palopeg) showing no attenuation of treatment effects over five years, supporting long-term durability of treatment benefits.[34]

The EAG concurs with the company that available evidence and biological mechanisms for palopeg support the underlying assumption of durable treatment effect. The EAG, however, notes that OLE studies provide only limited follow-up (maximum 216 weeks) and that neither study provides comparative evidence. As such, there remains a degree of residual uncertainty regarding the durability of the treatment effect, and it is important to acknowledge that the current evidence is being extrapolated over a very long time period (more than 50 years in the base case). Additionally, it is important to emphasise that the evidence cited by the company pertains to the maintenance of treatment benefits as defined by the primary clinical outcome, rather than to the modelled improvements in HRQL. However, evidence from EQ-5D data collected throughout the OLE shows that the initial improvements in HRQL are sustained, supporting the assumption of a permanent treatment effect.

#### *4.2.6.2 Discontinuation rates*

Patients initiating treatment with palopeg may discontinue at any time and are assumed to transition immediately to the 'off treatment' health state. A constant discontinuation rate is applied across the model time horizon, based on the observed rate from the PaTHway OLE study. This results in a per-cycle discontinuation rate of [redacted].

The company explores the possibility of differential discontinuation rates in a scenario analysis, considering scenarios where the discontinuation rate is halved and doubled.

***Points for critique***

Discontinuation rates are not a major driver of cost-effectiveness. The EAG is satisfied that the base case assumptions are appropriate.

#### *4.2.6.3 Complication rates*

The company's model incorporates several complications associated with HypoPT which are assumed to occur with reduced frequency while on treatment with palopeg. Each complication is assumed to impact HRQL through the application of specific disutilities; however, no direct costs are attributed to these complications. See Section 4.2.7.3 for a detailed discussion of the disutilities applied to each complication.

The list of complications included in the model was identified through a targeted literature review and subsequently validated by clinical experts. Complications were included if they were common in real-world settings and if their incidence was likely to differ between patients with and without adequate disease control. See Table 22 of the CS for a full list of complications included in the model. Complication rates were linked to health state occupancy, with higher rates associated with the NAC health state.

Incidence rates for each complication were estimated using data from the CPRD. A three-stage approach was employed: first, underlying incidence rates for all included complications were estimated in a matched general population cohort. Second, HR were calculated for each complication, stratifying HypoPT patients by disease control status (AC vs. NAC). Third, estimated HR were then applied to age stratified incidence rates for each complication to generate age (band) specific complication rates.

***Points for critique***

*Lack of direct evidence to support reduced complications*

The EAG has concerns about the evidence underpinning the modelled complications and the inferences that are being drawn from the CPRD analysis.

Firstly, while the EAG recognises the biological potential for palopeg to reduce complication rates through reduced reliance on CT, the inferred complication rates are not supported by the available clinical evidence. The PaTHway trial does not show any meaningful differences in the rates of complications, nor has the company provided evidence from the OLE indicating reductions in the rates of complications.

Secondly, the classification of patients in the CPRD analysis is based on resource use and relies on surrogate relationships that have not been adequately justified. In the specific case of complication rates, the company makes two key assumptions. First, it assumes that treatment with palopeg (via improved disease control) reduces resource use. Second, it assumes that resource use serves as a proxy for complication rates, implying that reductions in resource use will correspond directly to reductions in complication rates. However, neither of these assumptions is well-supported. As detailed in Section 4.2.8.2, resource use is likely to be heavily dependent on comorbidities not associated with disease control. Moreover, while it may be plausible that resource use is associated with complication rates, there is no reason to believe that palopeg would reduce complication rates to those observed in the AC CPRD population.

Given the above concerns the EAG prefers to set the rates of complications in both arms to zero removing this treatment benefit from the model.

*All complications are repeatable*

The company's approach assumes that all complications are repeatable. This makes sense for some complications, such as respiratory tract infection, but it is not clear that this is appropriate for more serious complications such CVD or CKD, which would be more likely non-reversible complications which impact quality of life on an ongoing basis. The EAG recognises the complexity of modelling such one-off complications in the context of a cohort model where individual patients are not tracked but the EAG is concerned that this approach may not accurately capture the risks of these one-off complications.

#### *4.2.6.4 Mortality*

The company models a survival benefit for patients treated with palopeg by modelling health state-specific mortality rates. This was implemented in the model by estimating HR that compare mortality in HypoPT patients stratified by disease control status to matched controls. These HR are then applied to general population life tables using general population mortality. Table 26 of the CS reports the HR applied to each health state.

***Points for critique***

*Lack of direct evidence to support reduced mortality*

The critique of the company's approach to modelling mortality parallels the concerns raised earlier regarding complication rates. The PaTHway trial does not provide direct evidence of improved survival. Instead, the company relies on a surrogate relationship between resource use and mortality using the CPRD dataset. As with complication rates, the EAG acknowledges the potential for palopeg to improve survival, possibly through a reduction in HypoPT-related complications, but considers the assumed proxy relationships to be inadequately justified. Although it is reasonable to expect higher

mortality among patients with high resource use, there is no clear justification for assuming that any mortality benefit associated with palopeg would reflect the differences in mortality between high and low resource use groups.

*Generalisability of mortality rates*

The EAG is concerned that the modelled excess mortality attributable to HypoPT appears substantially overstated. The HR of approximately 5 used in the model suggests a life expectancy of around 69 years for HypoPT patients, 14 years shorter than that of the general population. While the EAG acknowledges that HypoPT may be associated with increased mortality, it considers the magnitude of risk applied in the model to be excessive. The HR used is notably higher than those reported in several recent studies, including one sponsored by the company. For instance, a Scottish study of 280 HypoPT patients reported an HR of 2.15 (95% CI: 1.71 to 2.71),[35] while a 2022 CPRD-based study sponsored by the company estimated an HR of 2.89 (95% CI: 1.85 to 4.51).[36] It is unclear why there is such a disparity in the estimates provided by the company as part of their submission and the those reported in the literature. The EAG explores the use of alternative value in Section 6.

#### *4.2.6.5 Adverse event rates*

The model includes treatment-emergent adverse events related to hypercalcaemia or hypocalcaemia of any grade, based on observed rates in the PaTHway trial (see Table 25, p144 of CS). Adverse events impact both costs and QALYs in the model and are applied on a per-cycle basis. These are summarised in Section 4.2.7, Health-related quality of life (for the QALY reductions) and Section 4.2.8, Resource use and costs (for the cost increases).

Table 11: Adverse event incident rate per cycle

| Adverse event | Palopegteriparatide | CT |
|---|---|---|
| Hypercalcaemia | [redacted] | [redacted] |
| Hypocalcaemia | [redacted] | [redacted] |

**Source:** Table 25 of the CS

***Points for critique***

*Inconsistency in modelled AE rates*

Modelled event rates are a key driver of cost-effectiveness in the company's base case analysis. This is due to the substantial numerical difference in hypocalcaemia and hypercalcaemia rates between treatment arms, as well as the significant costs associated with these adverse events. Consequently, the lower overall incidence of AEs applied in the palopeg model arm results in very substantial cost savings ([redacted] in the company base case).

The EAG is, however, concerned about a potential disconnect between the modelled AE rates, which are based on any-grade events, and the modelled utility decrements and costs, which assume an

emergency hospital stay. At the clarification stage the EAG request the company further justify their assumptions. The company's response outlined that the model uses any grade of calcium-related adverse events from the PaTHway trial to estimate rates of hypocalcaemia and hypercalcaemia, as these provide a fuller picture of biochemical instability, even if not all events are severe. They further highlight that in trials, close monitoring helps catch issues early, meaning that observed rates are likely to be lower than the real clinical practice where such monitoring is less feasible. The company therefore considers the applied AE rate reflect the clinical burden and costs associated with hypocalcaemia and hypercalcaemia that would likely arise outside a trial setting.

While the EAG acknowledges that trial participants may benefit from more intensive monitoring, potentially enabling earlier intervention, it considers it unlikely that this would materially alter AE rates to the extent implied by the company's model. The company's argument assumes that all grade 1/2 events would escalate to a level requiring hospital-based care, which the EAG finds implausible. Moreover, the EAG considers the company's argument almost entirely speculative. No supporting evidence from a real-world setting is provided to support the high frequency of hypocalcaemia and hypercalcaemia AE assumed in the base case. The EAG also notes that this approach departs from established precedent in previous NICE appraisals, where AE modelling is generally limited to more serious events, with costs and utility decrements applied accordingly.

For consistency, the EAG prefers to use the rate of hypercalcaemia or hypocalcaemia AE leading to A&E/urgent care visit and/or hospitalisation from PaTHway, aligning the modelled AE rates with modelled disutilities and costs. The EAG also notes that the values used in the company base case do not align with those reported in Table 16 of the CS. These are corrected in Section 6.

### 4.2.7 Health related quality of life

#### *4.2.7.1 Health-related quality-of-life studies*

An SLR was conducted to identify relevant HRQL data to inform the model. Electronic database searches were conducted on 21 December 2023, 08 July 2024, and 27 March 2025. [37] 73 unique studies from 104 reports were identified and included for data extraction. Only two studies were identified that reported preference-based utility values, and neither aligned with the NICE reference case requirements.

- Weycker et al 2016, a post hoc analysis of the REPLACE trial of rhPTH 1-84 mapped observations from SF-36 to health utilities index-2 (HUI2) to determine health state utility change. [38]
- Siggelkow 2020, the EQ-5D-5L index instrument was administered to patients with HypoPT and the UK value set reported by Devlin (2018). [6] [39] (a violation of the NICE reference case)

***Points for critique***

The EAG is satisfied that the utility values obtained from the PaTHway trial (see below) represent the most appropriate source given the structure of the model and studies identified in the HRQL review.

Appendix F of the CS included the company searches to identify HRQL studies in patients with HypoPT. The EAG found the searches were generally appropriate, although some limitations were identified which may have affected optimal retrieval of relevant studies for this SLR. These limitations are detailed in Table 31.

*4.2.7.2 Health-related quality of life from clinical trials*

In the PaTHway trial, patient-reported outcomes were assessed by the generic SF-36, EQ-5D-5L and by the disease-specific HPES tool. EQ-5D data was deemed the most appropriate for informing the model.

The EQ-5D-5L data collected during the PaTHway clinical trial was mapped to the EQ-5D-3L descriptive system to calculate utility values by health state. The base case analyses utilised the mapping function created by Hernandez-Alava et al. (2023) in line with the NICE reference case. [30] [32]

The week 26 EQ-5D-3L change from baseline was estimated using the ANCOVA-adjusted least squares (LS) mean between-treatment difference for the ITT population of PaTHway (palopeg vs placebo: [redacted](Table 12).

Table 12: EQ-5D-3L utility score at baseline vs week 26 ITT (based on Table 28 of the CS)

| Baseline | Treatment group (palopegteriparatide) | Control group (placebo) |
|---|---|---|
| Baseline | | |
| N | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] |
| SD, SE | [redacted] | [redacted] |
| Observed at week 26 | | |
| N | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] |
| SD, SE | [redacted] | [redacted] |
| ANCOVA model | | |
| N | [redacted] | [redacted] |
| LS Mean (SE) | [redacted] | [redacted] |
| 95% CI for LS mean | [redacted] | [redacted] |
| Difference in LS means (SE) | [redacted] | [redacted] |

**Source:** Table 28 of the CS

The utility values used in the company's base case were derived from the ANCOVA analysis described above and are summarised in Table 13. Age-gender adjustments were made to health state

utilities to ensure demographic adjustment over the lifetime horizon of the model were captured using Hérnandez Alava et al. (2022) (Table 13). [40]

Table 13: Health state utilities

| Health state | Utility value |
|---|---|
| AC/on treatment | [redacted] |
| NAC/off treatment | [redacted] |

**Abbreviations:** AC, adequately controlled disease; NAC, not adequately controlled disease; Source: PaTHway trial [41]
**Source:** Table 29 of the CS

***Points for critique***

*Appropriateness of ANCOVA model*

The EAG is concerned that company analysis approach which uses an ANCOVA. At the clarification state the EAG requested that the company provide a detailed overview of the EQ-5D collected as part of PaTHway trial and OLE with the aim of better understanding the justification for using an ANCOVA model. In their response the company outlines that within the blinded phase of the PaTHway trial EQ-5D data was collected at baseline and study visit around week 10, week 20 and week 26. The data set available to the company therefore includes repeat assessments of participants within the blinded phase of the PaTHway trial. Given this data structure the EAG does not consider the use of ANCOVA model appropriate and considers that Mixed Model for Repeated Measures (MMRM) is more appropriate. The ANCOVA model used by the company only considers the values reported at baseline and a week 26 and ignores the data available from both weeks 10 and week 20 meaning. A MMRM analysis is able to use this data and therefore represent a more efficient estimator increasing power and reducing standard errors. Moreover, an MMRM is less vulnerable to attrition bias as it is able to use all available data where ANCOVA models require a complete case analysis or imputation of missing values.

At clarification the EAG also requested to justify the use of an ANCOVA model noting that the EAG typically prefers to use a MMRM analysis. The company's response outlined that they consider the ANCOVA model more appropriate because at intermediate time points duration of palopeg treatment is insufficient for the HRQL impact of treatment to be fully realised. The EAG does not consider this argument credible. The HRQL data provided in response to clarification question B9 clearly shows a substantial increase in EQ-5D values at week 10 in line with the magnitude of those observed at week 26. Moreover, the economic model assumes an instantaneous improvement in HRQL which is inconsistent with the company's argument.

Given the clear advantages of the MMRM analysis the EAG prefers to use the MMRM analysis of the PaTHway EQ-5D data and present scenario analysis in Section 6 incorporating utility values generated from the MMRM analysis into the economic model.

*Uncertainty in the magnitude of the modelled HRQL improvements*

As outlined in Section 3.2, the EAG has several concerns regarding the design of the PaTHway trial that may have led to an overestimation of modelled HRQL benefits.

There were substantial differences between trial arms in participants' reliance on calcium and vitamin D supplementation. This raises the concern that participants may have been able to infer their treatment allocation based on their use of CT, resulting in functional unblinding. This is an important issue, as it may introduce bias into subjective patient-reported outcomes, such as EQ-5D, due to differing expectations between treatment groups. In this context, any functional unblinding may have increased the difference utility values derived from EQ-5D data in the PaTHway trial.

The protocol-mandated reduction in active vitamin D dosing in the CT arm is not reflective of standard clinical practice and may have adversely impacted HRQL among participants in control arm of the PaTHway trial. This could have contributed to an overestimation of the treatment effect. The EAG notes that HRQL in the CT arm declined over the 26-week duration of the PaTHway trial (see Table 12). While this finding is not conclusive, particularly given the small sample size (n=19), it is noteworthy. In most clinical trials of chronic fluctuating conditions such as HypoPT, regression to the mean and placebo effects typically result in at least modest (within group) improvements in both clinical and patient reported outcomes. The absence of such improvement may therefore suggest bias introduced by the suboptimal management of CT required by the trial protocol.

#### *4.2.7.3 Complication related disutilities*

Complication disutilities were assumed to apply for a duration of one cycle. The applied disutilities and the source for each complication are provided in Table 14

Table 14: Complication disutility

| **Complication** | **Details** |
|---|---|
| Neurological complications (seizure) | The parameter estimates of adult patients with epilepsy having one seizure daily (0.130) versus those seizure free (0.800) were combined. [42] |
| Cataract | From Andayani 2022, the weighted disutility of cataract patients (-0.346) with moderate or worse visual acuity was compared to those with mild visual acuity impairment (0.926).[43] |
| Cardiovascular disease | (0.337) calculated from composite events disutilities from Dyer 2010 (Myocardial Infarction and Heart Failure) and Golicki 2015 (Stroke) weighted by incidence from Conrad 2024 (expanded below). [44] [45] [46] |
| Chronic Kidney Disease | The EQ-5D utility score of all CKD stages combined (0.74) versus the stage G1/G2 utility score (0.85) from Jesky 2016. [47] |
| Mental health | Excluded from base case |

| | |
|---|---|
| Bone fracture | From the catalogue of EQ-5D scores in chronic disease assembled by Van Wilder et al., the disutility of those with vertebral fracture (-0.490) was compared to the healthy age-matched population norm (0.810).[48] |
| Urinary tract infection | The TTO utility decrement of mild to moderate UTI in type 2 diabetes (T2DM, 0.090) was compared to the mean utility score for uncomplicated T2DM of 0.920. [49] |
| Upper respiratory tract infection | From the Van Wilder catalogue the utility of any respiratory tract disease (0.71) was compared with age-matched population norm of 0.85 to derive disutility. [48] |
| Lower respiratory tract infection including pneumonia | |
| Nephrolithiasis | From Eryildrim 2015, the mean EQ-5D index of 0.72 was compared against the age-gender population norm of 0.910 to calculate disutility.[50] |
| Nephrocalcinosis | |

**Abbreviations:** CKD, chronic kidney disease; EQ-5D, EuroQoL 5 Dimensions; T2DM, type 2 diabetes mellitus; TTO, timed trade-off; UTI, urinary tract infection; VAS, visual analogue scale.
**Source:** Table 31 of the CS

As no relevant source for CVD disutility was identified by the company, alternative sources were identified to model CVD disutility namely Dyer (2010) and Golicki (2015). [45, 46] An incidence-weighted composite acute disutility for CVD was calculated.

***Points for critique***

The disutilities used for complications come from heterogeneous populations which are not closely related to chronic HypoPT. For example, the disutility value for acute CVD was based on an incidence-weighted composite calculation from a range of cardiovascular subgroups and stroke patients. [45, 46] It is not possible for the EAG to verify this calculation.

#### *4.2.7.4 Adverse events*

Table 15 presents the disutilities applied for hypocalcaemia and hypercalcaemia in the company's base case. The disutility for both adverse events assumed the need for emergency hospital admission and was informed by a study by Lin et al. (2020),[51] which assessed quality of life in elderly patients hospitalised for acute illness. The specific values applied were based on the difference between median EQ-5D utility scores at admission (0.440) and discharge (0.648). A 7-day duration was assumed for each adverse event, in line with the drug titration period observed in the PaTHway study.

Table 15: Adverse event disutility

| **Adverse event** | **Disutility (Lin 2020) [51]** | **Duration** |
|---|---|---|

| | | |
|---|---|---|
| Hypercalcaemia | 0.21 | 7.00 |
| Hypocalcaemia | 0.21 | 7.00 |

**Source:** Table 32 of the CS

***Points for critique***

*Relevance of disutility values applied*

The EAG has concerns regarding the relevance of the disutility values applied in the company's base case. The source of these values, Lin et al. (2020), is based on a population comprising exclusively patients aged 65 years and older who were admitted to a geriatric ward. Importantly, the study does not specifically relate to HypoPT, hypercalcaemia, or hypocalcaemia. Rather, it reports on HRQL in elderly patients hospitalised for acute illness more generally. The EAG therefore questions the appropriateness of applying these disutility values in this context.

However, the EAG acknowledges that the specific disutility values applied have only a limited impact on the overall ICER, due to the short duration of adverse events (seven days). This impact is further diminished when the adverse event rates in the model are more appropriately restricted to those requiring hospitalisation, see Section 4.2.6.5. The EAG therefore does not consider this issue further.

### 4.2.8 Resources and costs

The company's model includes costs relating drug acquisition and administration costs, management of adverse events, complication costs, mortality costs and routine monitoring and care costs.

The company extracted and synthesised data from 41 unique studies reporting resource use and cost data. Full details of the resource use are provided in Appendix G of the CS. None of the studies were considered by the company to be relevant to the current decision problem. A critique of the searches is included in Section 4.1.1.

#### *4.2.8.1 Drug acquisition and administration costs*

Palopeg is available in three pack sizes (168 mcg/0.56 mL, 294 mcg/0.98 mL, and 420 mcg/1.4 mL), each pack contains two pre-filled disposable injection pens. All pack sizes are priced equally at £7,406.00 per pack, reflecting a flat pricing structure. Acquisition costs applied in the model for palopeg were inclusive of a confidential PAS discount of [redacted] off the list price reducing the per pack costs to [redacted]

As outline in Section 4.2.4 doses of palopeg exceeding 30 mcg/day to require injections per day implying the need for two packs per 28-day cycle. The proportion of patients requiring two packs was derived from the PaTHway and OLE trials, see Table 16. After cycle 40, (which corresponds with the end of OLE) the proportion of patients using two packs is fixed high-dose patients is fixed at [redacted] and maintained for the remainder of the model time horizon.

Table 16 Percentage of double pen patients

| Cycles | Value |
|---|---|
| 1 to 6 | [redacted] |
| 7 to 13 | [redacted] |
| 14 to 26 | [redacted] |
| 27 to 39 | [redacted] |
| 40+ | [redacted] |

**Source:** Company economic model

The model assumes no wastage of palopeg and a real dose intensity (RDI) of [redacted], is used to adjust drug costs based on the compliance rate observed in the PaTHway trial.

Drug costs for CT were obtained from the British National Formulary (BNF) list prices and were applied in line with dosing for calcium carbonate and alfacalcidol observed in the PaTHway trial. Patients in the palopeg arm are assumed to also receive CT during the first year based with doses similarly based those observed in the PaTHway trial. Thereafter patients on palopeg are assumed to be completely independent of CT while they remain on palopeg treatment and no drug acquisition or administration costs are applied. For patients who discontinue palopeg, the CT dose reverts to those applied in the CT arm.

Table 17 summarises the drug acquisition costs applied in the model.

Table 17 Drug unit costs, doses, and dose intensity

| Treatment | Cost per pack, £ | Pack size | Dose | Dosing schedule | Mean RDI (%) | Drug cost per 28 days (cycle), £ |
|---|---|---|---|---|---|---|
| **Palopeg arm** | | | | | | |
| Palopgeteriparatide | 7,406.00 with PAS discount: [redacted] | 28-day pack | 168 mcg/0.56 mL, 294 mcg/0.98 mL, and 420 mcg/1.4 mL | Started with [redacted] SC once daily | [redacted] | [redacted] |
| Calcium carbonate | 9.33 | 100 tablets | 500 mg | [redacted] orally once daily | 100 | [redacted] |
| Alfacalcidol | 4.56 | 30 capsules | 0.25 mcg | [redacted] orally once daily | 100 | [redacted] |
| **CT arm** | | | | | | |
| Calcium carbonate | 9.33 | 100 tablets | 500 mg | [redacted] orally once daily | 100 | [redacted] |
| Alfacalcidol | 4.56 | 30 capsules | 0.25 mcg | [redacted] orally once daily | 100 | [redacted] |

**Abbreviations:** CT, conventional therapy; RDI, relative dose intensity; PAS, patient access scheme
**Source:** Adapted from CS Table 33 and company economic model

The drug administration cost for palopeg includes a one-off cost associated with the initial titration period, with no ongoing administration costs thereafter. The assumption of a 4-week titration phase is based on that the majority of dose titration occurred within the first 4 weeks of the 10-week titration period in the double-blind phase of the PaTHway trial. The initial titration period is assumed one consultant-led OP appointment, two Band 7 specialist nurse-led outpatient visits, and three serum calcium assays (conducted at the consultant appointment and both nurse follow-ups). The total administration cost at initiation for palopeg is £299.

For CT, administration costs consist of monthly pharmacy dispensing fees and a GP repeat prescription consultation every 84 days.

Table 18 summarises the drug administration cost applied in the model.

Table 18 Summary administration costs for palopegteriparatide and CT

| | Administration (initial year) | Administration (subsequent years) |
|---|---|---|
| Palopegteriparatide | £ 525.11 | £ 0 |
| CT | £ 226.11 | £ 226.11 |

**Abbreviations:** CT, conventional therapy; palopeg', palopegteriparatide.
**Source:** Adapted from Table 35 of the CS

***Points for critique***

*Wastage assumptions*

The EAG is concerned that the company has not accounted for drug wastage associated with dose adjustments and considers the assumption of no wastage to be unrealistic. As highlighted in Section 4.2.4, patients receiving palopeg in the PaTHway trial and the OLE continued to undergo dose modifications throughout the follow-up period. When these dose changes exceed the minimum or maximum dose deliverable by their current pen, patients must switch to a new pack size, implying wastage of unused pens.

Further the EAG notes that the company adjusts drug costs based on the RDI observed in the PaTHway trial. However, given the requirement that pens must be used within 14 days, the EAG considers it implausible that dose reductions or skipped doses would translate into lower drug acquisition costs. As such, the EAG does considers the adjustment of drug costs based on RDI to be inappropriate.

The failure to account for drug wastage and the adjustment of costs based on RDI both contribute to an underestimation of drug acquisition costs in the palopeg arm. The EAG explores the impact of these assumptions in Section 6.

*Omission of administration costs*

The EAG notes the omission of any administration costs for palopeg and the implicit assumption that all patients will be able self-administer. Consultation with clinical advisor to the EAG suggests that this is not a reasonable assumption and that it is likely that a proportion of patients will not be able to self-administer. This may be for a range of reasons. For example, people with physical or mental disabilities, the elderly or those who have a phobia of needles may not be able to self-administer. The EAG further notes that in the appraisals of monoclonal antibodies for migraine (which are similarly administered subcutaneously via preloaded pen) the committee concluded it was unlikely that everyone would be capable of self-administering treatment for the reasons outlined above.[52-54] In these appraisals it was agreed that applying an administration cost for 10% of people was reasonable, though this proportion was subject to uncertainty. For parity with these previous appraisals, the EAG implements an exploratory scenario in Section 6 applying an administration cost for 10% of palopeg patients.

An important difference between these appraisals and the current appraisal, is that monoclonal antibodies for migraine require only monthly dosing. It is unclear whether NHS services could support the administration of daily or bi-daily subcutaneous injection in the same way. To the extent such provision could not be supported by the NHS this may represent important equity issue as this would exclude more vulnerable patients who are otherwise eligible for treatment.

#### *4.2.8.2 Health state unit costs and resource use*

Health state costs were estimated using a micro-costing approach, whereby the frequencies of individual resources were estimated for the AC and NAC health states. This was informed by an analysis of CPRD from 2021 in patients with HypoPT. The analysis quantified the following elements of care: primary care consultations, outpatient attendances, inpatient admissions, emergency visits, and kidney replacement therapy.

The CPRD data set does not include any relevant clinical measures of disease severity for HypoPT patients, and therefore, patients were classified into the AC and NAC categories based on the following criteria:

- AC: ≤5 outpatient visits and <1 inpatient admissions per patient per year
- NAC: >5 outpatient visits and ≥1 inpatient admission per patient per year

Total per-cycle costs applied in the AC health state were [redacted] and [redacted] in the NAC health state. The significant disparity in health state costs between the AC and NAC is a major driver of cost-effectiveness, and in the base case analysis, as palopeg is predicted to generate [redacted] of cost savings.

***Points for critique***

*Predicted cost savings*

The EAG has substantive concerns regarding the company's approach to modelling health state costs. As outlined above, the classification of patients into the AC and NAC health states is made without reference to any clinical criteria. Rather, the company applies a circular rationale in which patients are stratified based on healthcare resource utilisation, and this stratification is subsequently used to infer a causal relationship between resource use and disease severity. No empirical evidence is provided to demonstrate a direct association between disease severity and resource use.

While the EAG considers it plausible that improved disease control may result in modest reductions in healthcare resource use, the magnitude of cost savings projected by the company's model is not considered credible. In clinical practice, HypoPT frequently arises as a secondary condition, most commonly following thyroid surgery, and is often accompanied by multiple co-morbidities. Consequently, elevated healthcare utilisation among this patient population may reflect the burden of these comorbid conditions rather than the severity of HypoPT itself.

Moreover, the EAG considers the company's approach to be inconsistent with the NICE Methods Guide. [32] Specifically, Section 4.4.11 states that only costs directly related to the condition of interest should be included in the economic evaluation, and that costs unrelated to the condition or the

technology under assessment should be excluded. However, the company's analysis of the CPRD dataset does not differentiate between healthcare costs directly attributable to HypoPT and those arising from unrelated background comorbidities. As a result, the cost estimates may overstate the economic burden of HypoPT and is likely to overstate the cost savings resulting from improved disease control.

At the clarification stage, the EAG requested justification for the company's assumptions regarding health state costs. In response, the company referred to one study (Chen et al. 2019)[33] and stated that the assumptions underpinning the base-case analysis had been reviewed by three clinical advisors but provided only clinical opinion as justification for these substantial assumptions. The EAG does not consider clinical opinion alone to constitute sufficient justification, particularly given the magnitude of the associated impact on cost-effectiveness outcomes. Moreover, the study by Chen et al. shows only modest difference in resource use for some items and does not correspond with the model benefits. The EAG highlights that the cost savings projected in the company's base case are equivalent to a health benefit exceeding 5 QALYs, assuming a willingness-to-pay threshold of £20,000 per QALY. In the EAG's view, benefits of this magnitude warrant a robust evidentiary foundation, equivalent to that required for clinical benefits of similar scale.

Given the lack of evidence to support the differential health state costs applied in the model the EAG prefers to remove the health state costs applied to the AC and NAC health states. This removes the health state relate cost savings implied by the company's base case model.

*Inflation index*

The company applies the Consumer Price Index (CPI) to inflate costs from 2021 to 2025 price levels. However, this approach is inconsistent with best practice and, arguably, with the NICE Methods Guide. Specifically, Section 4.4.12 of the Guide advises that "costs from previous years should be adjusted to present value using inflation indices appropriate to the cost perspective, such as the NHS cost inflation index and the PSS pay and prices index."

The EAG considers the NHS cost inflation index to be more appropriate for inflating healthcare costs and notes that this method has been used in the vast majority of previous technology appraisals. Due to the small impact of this assumption, the EAG, however, does not pursue this issue further.

*Aetiology of CPRD cohort*

The CPRD data used to inform estimates of resource use and costs associated with the AC and NAC health states are derived from a cohort of patients with HypoPT of mixed aetiology, encompassing both surgical and non-surgical patients. Within this dataset, non-surgical cases constitute the majority,

accounting for 77% of the cohort. This distribution stands in contrast to that observed in the PaTHway trial, where 85% of patients had HypoPT of surgical origin.

Clinical expert advice provided to the EAG indicates that, in the NHS, the vast majority of HypoPT cases are of surgical aetiology and they considered the PaTHway trial representative of NHS clinical practice in this regard. The EAG is uncertain why the CPRD cohort does not reflect this distribution and is concerned that this inconsistency may limit the generalisability of the CPRD data to the NHS HypoPT population.

Moreover, the EAG notes that differences in the clinical management and care needs of surgical versus non-surgical HypoPT patients may lead to variation in healthcare resource utilisation and associated costs. As such, the application of aggregate CPRD-based estimates may not accurately reflect the resource use patterns relevant to the NHS population. At clarification, the EAG therefore requested that the company provide separate analyses of CPRD data for surgical and non-surgical patients, enabling reweighting in line with the aetiological distribution observed in the PaTHway trial. Analysis incorporating these revised health state costs is presented in Section 6.

#### *4.2.8.3 Adverse event costs*

Two AE were modelled by the company hypocalcaemia and hypercalcaemia, with each assumed to incur an emergency hospital admission per event. Costs were informed by Ward et al. (2023), [55] a cost-effectiveness of patiromer for the treatment of hyperkalaemia in patients with chronic kidney disease. The values from Ward et al. were uplifted to current prices using the CPI index. The Ward study is, however, not the original source of the cost applied, and the EAG believes it instead to be a HRG code EB03H hospitalisation for heart failure from 2010/2011 NHS reference costs.

***Points for critique***

*Source of AE costs*

The EAG does not consider that using the HRG code for heart failure is suitable for capturing the costs of hypocalcaemia and hypercalcaemia. Even if it were suitable, the costs should be based on the most recent NHS cost collection data rather than uplifted from older versions of these costs. Currently, there is no specific HRG code for hypocalcaemia and hypercalcaemia in the NHS cost collection data. The EAG considers the codes HRG KC05 Fluid or Electrolyte Disorders, assuming a non-elective short stay admission, to be the most relevant and performs scenario analysis in Section 6, updating AE costs in line with this data. The EAG notes that using this HRG code significantly reduces the costs associated with these adverse events, thereby lowering the overall cost savings attributed to palopeg.

#### *4.2.8.4 Confidential pricing arrangements*

There are no commercial arrangements in place for any of the drugs comprising the comparator regimen or any subsequent treatments. The treatment acquisition costs used in the analyses presented in the company submission and the EAR (Section 6), therefore represent the prices there reflect all relevant confidential pricing agreements. The EAG, however, notes that the company used the BNF to inform the costs of CT and that costs can also be obtained from the electronic market information tool (eMIT). This provides information on the average price paid by the NHS for pharmaceuticals, which can differ from the list prices listed in the BNF and is seen as a more accurate and up to date indicator of costs. The EAG considers eMIT to be a more appropriate source of drug acquisition costs, where available, and presents a scenario analysis in Section 6 using these values.

# 5 COST EFFECTIVENESS RESULTS

## *5.1 Company's cost effectiveness results*

The results of the company's revised base case following the clarification response are summarised in this section (cost-effectiveness model version 3.2, dated 26 June 2025). The results presented in the following sections are inclusive only of the PAS discount for palopeg. Results do not include commercial arrangements available for CT (active vitamin D analogues such as alfacalcidol and calcium carbonate).

### 5.1.1 Deterministic Results

The incremental cost effectiveness ratio (ICER) is the ratio of expected additional total costs to those of expected additional QALYs compared with alternative technologies, at a willingness-to-pay (WTP) threshold. The company use a WTP threshold of £30,000 per QALY gained.

The company base case results are presented below, Table 19. The results show that palopeg is associated with increased costs (cost difference of [redacted] and greater health benefits (incremental QALYs of [redacted]) compared with CT. The company's base case ICER comparing palopeg with CT is £19,895 per QALY gained.

Table 19 Revised company base case results: deterministic

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER vs baseline (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Palopeg vs CT** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,895 |

**Abbreviations**: CT: Conventional therapy; ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Within the cost-effectiveness model, results are broken down by what is labelled 'outcomes' (see Table 20). These are essentially disaggregated lifetime costs. Table 21 shows that the benefit of palopeg is in cost savings, namely, resource use and adverse events.

Table 20 Outcomes as per revised company base case results

| Outcomes | Palopeg | CT | Incremental | Incremental (%) |
|---|---|---|---|---|
| Palopeg drug costs | [redacted] | [redacted] | [redacted] | [redacted] |
| CT drug costs | [redacted] | [redacted] | [redacted] | [redacted] |
| Administration costs | [redacted] | [redacted] | [redacted] | [redacted] |
| Complications | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| Resource use | [redacted] | [redacted] | [redacted] | [redacted] |
| Adverse events | [redacted] | [redacted] | [redacted] | [redacted] |
| End of life | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations**: CT: Conventional therapy

In addition, within the cost-effectiveness model, Table 21 shows the costs per health state with the differences between palopeg and CT are in the savings from patients not entering the NAC health state.

Table 21 Health state costs as per revised company base case results

| Health state costs | Palopeg | CT | Incremental | Incremental (%) |
|---|---|---|---|---|
| AC | [redacted] | [redacted] | [redacted] | [redacted] |
| NAC | [redacted] | [redacted] | [redacted] | [redacted] |
| End of life | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations**: AC, adequately controlled; CT: Conventional therapy; NAC, not adequately controlled

### 5.1.2 Probabilistic Results

The EAG performed a probabilistic sensitivity analysis (PSA) on the revised company base case model, running 10,000 iterations for the fully incremental comparison. The mean probabilistic ICER for palopeg compared to CT are presented below in Table 22.

Table 22 Company base case results: probabilistic pairwise analysis

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER vs baseline (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Palopeg vs CT** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,217 |

**Abbreviations**: CT: Conventional Therapy; ICER: incremental cost effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

The PSA scatter plot, presented in Figure 4, shows that palopeg is more effective and more costly compared to CT. Results were relatively stable at this point with [redacted] of ICERs between palopeg and CT in the north-east quadrant of the cost-effectiveness plane. A multi-way cost-effectiveness acceptability curve for both interventions is also shown Figure 5.

Palopeg has a [redacted] probability of being cost-effective at a threshold of £20,000 per QALY, and an [redacted] probability of being cost-effective at a threshold of £30,000 per QALY (Figure 5).

Figure 4 Cost-effectiveness plane (generated from company model)

Figure 5 Multi-way cost-effectiveness acceptability curve (generated from company model)

### *5.2 Company's deterministic sensitivity analyses*

The company conducted a series of one-way deterministic sensitivity analyses (DSAs) to identify variables with the greatest effects on the ICER for palopeg compared to CT. The DSA for the comparison between palopeg and CT, presented in Figure 6, suggests that the health state maintenance costs in the NAC health state, symptomatic hypocalcaemia in the CT adverse event, and symptomatic hypocalcaemia adverse event cost per event were the most influential parameters on the ICER.

Figure 6 Tornado diagram: palopeg versus CT (generated from company model)

[redacted]

### *5.3 Company's additional scenario analyses*

In the company submission explored several alternative scenario analyses considering alternative model assumptions and parameter input values. At the clarification stage, the EAG posed some questions that resulted in the company presenting additional scenario analyses with the results also presented. The results of both of these sets of scenario analysis are presented in Table 23.

Table 23 Company's additional scenario analysis (deterministic): CT vs palopeg (inclusive of palopeg PAS)

| # | Parameter varied | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|
| | **CT vs Palopeg** | | | |
| | Base case | [redacted] | [redacted] | £19,895 |
| 1 | Undiscounted | [redacted] | [redacted] | £ 21,916 |
| 2 | Trial primary endpoint response (discontinue immediately) | [redacted] | [redacted] | £ 27,892 |
| 3 | Trial primary endpoint response (discontinue rate) | [redacted] | [redacted] | £ 29,596 |
| 4 | Half discontinuation | [redacted] | [redacted] | £ 15,708 |
| 5 | Double discontinuation | [redacted] | [redacted] | £ 18,988 |
| 6 | Responder patients utility | [redacted] | [redacted] | £ 22,630 |
| 7 | Complication costs | [redacted] | [redacted] | £ 11,133 |
| 8 | Dose distribution none | [redacted] | [redacted] | -£ 4,027 |
| 9 | Dose distribution 26-weeks | [redacted] | [redacted] | -£ 1,530 |
| 10 | Dose distribution 52-weeks | [redacted] | [redacted] | £ 12,725 |
| 11 | Dose distribution 104-weeks | [redacted] | [redacted] | £ 15,968 |
| 12 | No mortality benefit | [redacted] | [redacted] | £ 17,034 |
| 13 | Use lower bound mortality (both) | [redacted] | [redacted] | £ 19,904 |
| 14 | Use upper bound mortality (both) | [redacted] | [redacted] | £ 19,712 |
| 15 | Complications excluded | [redacted] | [redacted] | £ 20,806 |
| 16 | Adverse events - half the impact of costs | [redacted] | [redacted] | £ 20,548 |
| 17 | Adverse events - half the impact of utilities | [redacted] | [redacted] | £ 46,328 |
| 18 | End of life costs excluded | [redacted] | [redacted] | £ 20,008 |
| 19 | Palopegteriparatide price erosion | [redacted] | [redacted] | -£ 25 |

| # | Parameter varied | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|
| **Based on company clarification response, Table 8** | | | | |
| 20 | HPES moderate/severe | [redacted] | [redacted] | £12,452 |
| **Based on company clarification response, Table 18** | | | | |
| 21 | CPRD: PS with complications | [redacted] | [redacted] | £37,209 |
| 22 | CPRD: PS without complications | [redacted] | [redacted] | £38,998 |
| 23 | CPRD: NS with complications | [redacted] | [redacted] | £16,915 |
| 24 | CPRD: NS without complications | [redacted] | [redacted] | £17,746 |
| 25 | CPRD: Weighted with complications | [redacted] | [redacted] | £32,788 |
| 26 | CPRD: Weighted without complications | [redacted] | [redacted] | £34,389 |

**Abbreviations**: CPRD, Clinical Practice Research Datalink; CT, Conventional therapy; HPES, Hypoparathyroidism Patient Experience Scale; NS, non-surgical; PS, Post-surgical ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life-years

## *5.4 Model validation and face validity check*

The company performed model technical validation in which the internal validity and stress testing of the model was assessed. The internal validity check consisted of internal quality control processes included independent cross-checking of formulas, review of logic and flow, and audit of data inputs against source references. Stress testing of models was performed through scenario and sensitivity analyses. An independent external modeller conducted a full technical review of the model to verify transparency, structural logic, and appropriateness of implementation.

#### 5.4.1.1 *Validation undertaken by the EAG*

As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing

Following an initial validation of the model, several errors were identified prior to calcification step and were corrected by the company in an updated model. The EAG, however, identified three additional coding errors following clarification. The first error related to the implementation of age adjustment cells (F229:F311, 'inputs sheet') which did not rescale the adjustment factor to take into account the starting age of the cohort. The second error relates to the calculation of mortality and state occupancy in the palopeg arm. This impacts cells O37:R1103, 'Yorvipath Trace'. The third error relates to the AE rates applied in the model. The EAG is unable to verify how these have been estimated and the values applied do not align with those reported in Table 16. The CS states that exposure-adjusted utility AE rates were applied in the model, but it is unclear why this adjustment increases the estimated hypocalcaemia risk from approximately a fourfold difference (CS Table 16) to a nineteen-fold difference (CS Table 25). Furthermore, the EAG does not understand why the two trial arms have different treatment exposure durations, given that they are drawn from the same trial

and had a low number of dropouts. This error impacts cells E89:F90, ‘inputs sheet’. The EAG’s proposed correction uses the rates from Table 16 and has a very large impact on the results of the economic analysis increasing the ICER by approximately £30,000 per QALY.

All identified errors were corrected by the EAG, and a revised model was supplied to the company with altered cells highlighted to aid verification. These corrections lead to a modest reduction in the company base case ICER. Revised results are presented in Section 6.

# 6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section4. The EAG presents several alternative scenarios where an alternative approach was considered more appropriate, or where it was considered important to explore the impact of uncertainty. The EAG includes several further scenarios in the following section to demonstrate the impact of alternative assumptions on the EAG base case.

Descriptions of the exploratory analyses are presented in Section 6.1 and the impact of these analyses on the revised company's base case are presented in Section 6.2 and Section 6.3, along with the EAG's preferred base case.

## *6.1 Exploratory and sensitivity analyses undertaken by the EAG*

The following deterministic exploratory analyses were conducted by the EAG following corrections to the (company's revised base case) as described in Section 5.4. These addressed calculation errors associated with the dosing of alfacalcidol in the palopeg arm and the implementation of age adjustment.

1. MMRM derived health state utilities

The EAG prefers to use a MMRM to analyse the EQ-5D data from the PaTHway trial rather than an ANCOVA model preferred by the company as this more appropriately accounts for repeat measures and attrition in the data set. The utility values applied in the model are therefore updated in line with Table 24.

Table 24 Summary of health state utility values

| Health state | ANCOVA model (company preferred) | MMRM (EAG preferred) |
|---|---|---|
| AC | [redacted] | [redacted] |
| NAC | [redacted] | [redacted] |

**Abbreviations:** AC, adequately controlled; EAG, evidence assessment group; MMRM, mixed model for repeated measures; NAC, not adequately controlled

2. Complication rates set to zero

The PaTHway trial does not provide direct evidence to support the modelled reduction in complication rates. Moreover, the magnitude of the reduction is based on a proxy relationship between treatment with palopeg, resource use, and subsequent complication rates, a relationship that is not sufficiently substantiated. This scenario therefore sets the complication rates applied in the model to zero.

3a. Survival benefits removed

The modelled survival benefits in the company's base case are not supported by direct evidence from the PaTHway trial. As with complication rates, the modelled reduction in mortality is based on a proxy relationship between treatment with palopeg, resource use, and mortality, which is not adequately justified. In this scenario, the HR applied in the model is set to 4.99 in both arms, thereby removing the modelled survival benefits.

3b. Survival benefits informed by published values

The EAG is concerned that the HR applied to represent excess mortality associated with HypoPT is too high and inconsistent with values reported in the literature. The EAG therefore explores a scenario in which a HR of 2.89 is applied in both model arms, based on the company-sponsored study by Reddy et al. (2025).[36]

4. Revise AE rates

The EAG considers it inappropriate to model any grade of AE rates while applying utility decrements and costs associated with more serious AE requiring hospital care. The EAG therefore explores a scenario in which AE rates are informed by hypercalcaemia or hypocalcaemia AE leading to hospital care.

5. Revise AE costs

The AE costs applied to the two modelled AEs hypocalcaemia and hypercalcaemia related to hospitalisation for heart failure. The EAG considers this inappropriate, and that cost would be more accurately reflect by applying the HRG code KC05 Fluid or Electrolyte Disorders, assuming a non-elective short stay admission. Costs are estimated weighting the relevant cost codes in line with the number of reported episodes reported in the NHS cost collection data 2022/23 data uplifted to 2023/2024 prices (Note the EAG had to use an older version of reference costs as the 2023/2024 data was temporally unavailable). This reduces the AE costs applied for hypocalcaemia and hypercalcaemia from £3,315.25 per event to £563.63.

6a. Set RDI to 100%

This scenario sets RDI to 100% for palopeg as missed doses/dose reductions cannot reasonably result in reduced drug acquisition costs due to the requirement that pens be used for maximum of 14 days.

6b. Include wastage based on observed dose band changes

The company's base case does not account for drug wastage resulting from patients moving between pack sizes as result of transitions between dosing bands. The EAG considers this assumption unrealistic and instead uses reported data on dose adjustments from PaTHway and its OLE to apply drug wastage in cycles 6, 13, 21, and 27 (approximately equivalent to weeks 26, 52, 84, and 110). Drug wastage is assumed to amount to half a pack of palopeg, based on the assumption that transitions to new pack size occur midway through a cycle on average.

6c. Extrapolate wastage from last period over the model time horizon

This scenario revises scenario 6b by assuming that drug wastage is applied throughout the entire model time horizon. This is implemented by assuming that the proportion of patients moving between dose bands, as observed between weeks 84 and 110 of the OLE phase, will continue indefinitely. Drug wastage costs are therefore applied every seventh model cycle after cycle 27 (i.e., cycles 34, 41, 48, and so on). As in scenario 6b, drug wastage is assumed to amount to half a pack of palopeg.

7. Revise CT dosing

The PaTHway trial mandated a reduction in vitamin D. Participants also followed a titration protocol aimed at reducing or discontinuing active vitamin D and calcium. This approach does not reflect UK clinical practice in patients receiving CT and may result in an underestimation of CT dosing in the trial, with implications for the estimated drug acquisition costs. In this scenario, the baseline doses of vitamin D (alfacalcidol) and calcium (calcium carbonate) are used to estimate the drug acquisition costs applied in the CT arm of the model.

8. Drug acquisition costs for alfacalcidol from eMIT

Drug acquisition costs for alfacalcidol were calculated using BNF list prices. However, alfacalcidol prices are also available from eMIT. The EAG considers eMIT to provide a more representative estimate of NHS drug expenditure. This scenario therefore uses the eMIT price instead of the BNF list price, reducing the pack price of alfacalcidol from £4.56 to £1.14.

9a. Remove Health state costs

The EAG considers the company's approach to modelling health state costs associated with the management and monitoring of HypoPT to be inconsistent with the NICE reference case as they include costs unrelated to HypoPT. Moreover, the substantial cost saving predicted by the company model are not supported by any compelling evidence. The EAG expects that some health state costs to

be applicable but in the absence of evidence to inform these sets applied health state costs to zero, thereby removing all (health state related) cost savings associated with palopeg.

9b. Revise health state costs to use trial weight of surgical/non-surgical patients

The health state costs applied in the model are based analysis of a CPRD dataset in which the mix of surgical to non-surgical patients is skewed in favour of non-surgical patients. This does not align with the patient mix recruited to the PaTHway trial or expected NHS practice where the vast majority of patients are of surgical aetiology. This scenario therefore reweights the applied health state costs and mortality HR to align with the mix of surgical to non-surgical patients in the PaTHway trial.

9c. Revise health state costs to use company alternative weight of surgical/non-surgical patients

In the clarification response, the company presented a scenario analysis in which health state costs and mortality HR generated from the CPRD analysis assume a 75% to 25% mix of surgical and non-surgical patients. This scenario replicates this analysis.

10. Palopeg administration cost in those need assistance

The company's base-case analysis assumes that all patients are able to self-administer palopeg. This scenario explores an alternative in which 10% of patients require assistance with administration, consistent with assumptions made in previous appraisals of monoclonal antibodies for migraine. [52-54] An administration cost of £29 per visit is applied, based on the PSSRU unit cost for a home visit following discharge from an acute medical unit.[56] For patients requiring twice-daily dosing, this results in two visits per day.

## *6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

The results of the scenario analyses described in Section 6.1 are presented in Table 25. These results include the PAS discount for palopeg.

Table 25 EAG Exploratory scenario analyses (deterministic)

| Scenario | | Technology | Total | | Incremental | | ICER |
|---|---|---|---|---|---|---|---|
| | | | Costs | QALYs | Costs | QALYs | |
| Company base case | | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £19,895 |
| Company base case, inclusive of EAG suggested calculation corrections | | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £52,602 |
| 1 | Utility values (MMRM) | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £59,925 |
| 2 | Exclude complication rates | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £54,815 |
| 3a | No survival benefit | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £56,396 |
| 3b | Use survival HR from literature | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £56,802 |
| 4 | Use AE rate that results in hospitalisation | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £66,553 |
| 5 | Alternative AE costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £64,404 |
| 6a | Set RDI to 100% | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £57,920 |
| 6b | Include wastage based on trial dose band changes | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £52,917 |
| 6c | Extrapolate wastage from last period over the model time horizon | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £53,161 |
| 7 | CT dosing | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £50,381 |
| 8 | eMIT costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £53,214 |
| 9a | Remove health state maintenance costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £126,697 |
| 9b | Reweigh PS/NS health state maintenance costs to PaTHway trial | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £67,145 |
| 9c | Use alternative company weighting of PS/NS health state maintenance costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £65,455 |
| 10 | Nurse visit for 10% of chronic HypoPT patients | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £61,127 |

**Abbreviations**: AE, adverse event; CT, conventional therapy; CPRD, Clinical Practice Research Datalink; EAG, evidence assessment group; eMIT, electronic market information tool; HR, hazard ratio; HypoPT, hypoparathyroidism; ICER,

incremental cost effectiveness ratio; MMRM, mixed models for repeated measures; NHS, National Health Service; NS, non-surgical; PAS, patient access scheme; PS, post -surgical; QALY, quality-adjusted life-year; RDI, relative dose intensity.

### *6.3 EAG's preferred assumptions*

The cumulative impact of the EAG's preferred assumptions is presented in Table 26 below. These results include the PAS discount for palopeg. The EAG base case adopts the following scenarios described in Section 6.1 Section on top of the corrections previously described:

- Scenario 1: MMRM derived health state utilities
- Scenario 2: Complication rates set to zero
- Scenario 3b: Survival benefits informed by published values
- Scenario 4: Revise AE rates
- Scenario 5: Revise AE costs
- Scenario 6a. Set RDI to 100%
- Scenario 6b: Include wastage based on observed dose band changes
- Scenario 7: Revise CT dosing
- Scenario 8: Drug acquisition costs for alfacalcidol from eMIT
- Scenario 9a: Remove Health state costs
- Scenario 10: Palopeg administration cost in those need assistance

Table 26 EAG's base case (Deterministic)

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| **Palopeg vs CT** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £225,502 |

**Abbreviations**: CT, conventional therapy; EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life-years

Probabilistic results for the EAG's base case are presented in Table 27. The model was set to the EAG's preferred assumptions and run with 10,000 iterations. The ICER for Palopeg was £226,101 in the probabilistic EAG base case, with a [redacted] probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000.

Table 27 EAG's base case (Probabilistic)

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER vs baseline (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Palopeg vs CT** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £226,101 |

**Abbreviations:** CT, conventional therapy; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life-years

## *6.4 Conclusions of the cost effectiveness section*

The EAG considers the submitted evidence to broadly reflect the decision problem outlined in the final scope. However, the submitted analyses do not fully adhere to the requirements of the NICE reference case, particularly in relation to the modelling of health state costs. The NICE methods guide states that only costs directly related to the condition of interest should be included in the economic evaluation, and that costs unrelated to the condition or the technology under assessment should be excluded. However, the company's analysis (based on CPRD) does not differentiate between healthcare costs directly attributable to HypoPT and those arising from unrelated background co-morbidities. This is likely to be significant issue given the burden of comorbidities in HypoPT patients, which frequently arises as a secondary condition. As a result, the health state cost estimated by the company are very likely to overstate the economic burden of HypoPT and to overstate the cost savings resulting from improved disease control.

Beyond this issue the EAG has identified several important areas of uncertainty that materially affect the reliability of the cost-effectiveness estimates.

The first major area of uncertainty concerns the conceptual foundation of the model structure. The company' model structure use two health states AC and NAC which are based on treatment allocation rather than clinical outcomes or disease severity, i.e. all palopeg treated patients are assumed AC and all CT treated patients are assumed to be NAC. This approach results in treatment effects being inferred from differences in HRQL between arms of the PaTHway trial, without being directly linked to the trial's primary endpoint or any other clinical measure of disease control. While this structure is a valid, the EAG considers it conceptually weak, as it limits clinical interpretability. The model structure also precludes the evaluation of response-based stopping rules, which may be clinically appropriate.

The second related uncertainty is the assumption that treatment allocation is synonymous with disease control. Specifically, all patients receiving palopeg are assumed to be in the AC state, while all

patients receiving CT are assumed to be NAC. This assumption is central to the company's value proposition, as most of the modelled benefits derive not from direct improvements in HRQL but instead on surrogate relationships to estimate downstream benefits. The model assumes reduced complications, mortality, and healthcare utilisation based on stratification of patients in the CPRD dataset by inferred disease control status. However, the criteria used to define AC and NAC in the CPRD are based solely on healthcare utilisation thresholds, not clinical indicators. This circular reasoning, using healthcare use to define health state, then claiming reductions in healthcare use from health state changes, substantially undermines confidence in the modelled benefits. Furthermore, the lack of direct evidence to support these assumptions means that many of the projected benefits of palopeg are not substantiated by trial or real-world data. Moreover, the use of surrogate or proxy relationships to model several key benefits of palopeg, without appropriate justification is contrary to the expectations of the NICE reference case.

A third area of uncertainty relates to the representativeness of the trial population. As discussed in the clinical sections of the report, the EAG has significant concerns regarding the appropriateness and clinical applicability of the target population defined by the company, particularly the proposed eligibility criteria beyond high-dose CT. Criteria such as symptom burden, increased healthcare utilisation, and renal impairment are either subjective, non-specific to HypoPT, or common in the condition without necessarily indicating uncontrolled disease. Additionally, the PaTHway trial population may not be representative of this proposed target group, as the trial's inclusion criteria differ from those used to define the modelled population. Given that the trial informs key clinical effectiveness inputs, any lack of generalisability between the trial and target populations introduces substantial uncertainty into the economic analysis.

A fourth area of uncertainty relates to the modelled health state utilities which make up the vast majority of modelled QALY gains. The EAG is concerned by the analysis approach taken by the company that uses an ANCOVA model using EQ-5D values measured only at baseline and week 26. This approach excludes intermediate data collected at weeks 10 and 20 and the EAG prefers to use MMRM analysis which is a more efficient model and would allow this data to be utilised. An MMRM approach is also a more robust estimator and less vulnerable to attrition bias. The EAG is also concerned that weaknesses in the PaTHway trial design may have impact the internal validity of observed differences in EQ-5D scores. The PaTHway protocol mandated reductions in active vitamin D for the control arm, which diverges from clinical practice and may have contributed to the observed decline in EQ-5D utility within this group in that group. Further, substantial differences between trial arms in participants' reliance on calcium and vitamin D supplementation may have led to functional unblinding that could influence patient-reported outcomes.

A final important area of uncertainty relates to the modelling of AE which represent a major source of cost-saving in the company's base case. The company model focuses on two hypocalcaemia and hypercalcaemia which are assumed to result in hospital care. The EAG is, however, concerned about a potential disconnect between the modelled AE rates, which are based on any-grade events, and the modelled utility decrements and costs, which accordingly assume an emergency hospital stay. This approach is very likely to overestimate the HRQL, and cost burden associated with these AE and the EAG is concerned that no supporting evidence from a real-world setting is provided to support the high frequency of hypocalcaemia and hypercalcaemia AE assumed in the base case.

Taken together, these issues introduce substantial uncertainty into the economic model. While the EAG has explored alternative assumptions in its scenario analyses (see Section 6), it is important to recognise that the modelled cost-effectiveness of palopeg is highly sensitive to structural assumptions, many of which are not well-supported by the available evidence. In particular, the reliance on surrogate relationships and broad categorisations of disease control status drive a large proportion of the modelled benefits.

# 7 SEVERITY MODIFIER

The company provided a severity modifier QALY shortfall analysis in their submission. The expected total QALYs for the general population were based on the 2021-23 National life tables for England and Wales from the ONS. [57] The population EQ-5D-3L data adjusted by age and sex were derived from the Health Survey from England (HSE) 2014, as recommended by the NICE DSU. [40].

The results of the company's QALY shortfall analysis are presented in Table 28, alongside the values generated in the EAG's preferred base case in Table 26. These findings were sense-checked using the DSU calculator to ensure accuracy. The analysis indicates that the absolute QALY shortfall is below 12, and the proportional shortfall is less than 0.85. Based on these results, a severity modifier of 1 is applicable to this population.

Table 28 Summary of QALY shortfall analysis

| | **Expected total QALYs for the general population** | **Total QALYs that people living with a condition would be expected to have with current treatment** | **Absolute QALY shortfall** | **Proportional QALY Shortfall** |
|---|---|---|---|---|
| **Company base case** | | | | |
| CT | 16.1 | [redacted] | 8.6 | 0.53 |
| **EAG base case** | | | | |
| CT | 16.1 | [redacted] | 6.2 | 0.39 |

**Abbreviations:** CT, conventional therapy; EAG, evidence assessment group; QALY, quality-life adjusted-years

# 8 REFERENCES


1. Sardella A, Bellone F, Morabito N, Minisola S, Basile G, Corica F, Catalano A. The association between hypoparathyroidism and cognitive impairment: a systematic review. *J Endocrinol Invest* 2021;**44**:905-19.

2. Sinnott BP. Hypoparathyroidism – review of the literature 2018. *Journal of Rare Disorders: Diagnosis & Therapy* 2018;**04**.

3. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *J Bone Miner Res* 2013;**28**:2570-6.

4. Ascendis Pharma. *[Data on File]: Chronic Hypoparathyroidism Report*; 2024.

5. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine CM. Low health-related quality of life in hypoparathyroidism and need for PTH analog. *Endocr Connect* 2022;**11**:e210379.

6. Siggelkow H, Clarke BL, Germak J, Marelli C, Chen K, Dahl-Hansen H, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. *Clinical Endocrinology* 2020;**92**:159-68.

7. Astolfi D, Murphy D, Sanders B, Gulley L, Knoefler A, Park M, et al. *The voices of hypopara survey: Journey of patients living with hypoparathyroidism*. n.d. Available from: https://ascendispharma.com/wp-content/uploads/2020/10/hp_survey_poster_2020_asbmr.pdf [accessed 23 July 2025]

8. Sikjaer T, Eskildsen SF, Underbjerg L, Østergaard L, Rejnmark L, Evald L. Hypoparathyroidism: changes in brain structure, cognitive impairment, and reduced quality of life. *J Bone Miner Res* 2024;**39**:855-66.

9. Brod M, Waldman LT, Smith A, Karpf D. MON-LB092 understanding the patient-centered impact of hypoparathyroidism on functioning and well-being. *J Endocr Soc* 2019;**15**.

10. Waldman LT, Brod M, Smith A, Karpf D. PDB115 Impacts of hypoparathyroidism on patient work productivity and out-of-pocket costs. *Value Health* 2019;**22**:S159.

11. Ascendis Pharma. *[Data on File]: People with hypoparathyroidism (hypoPT): Treatment burden survey*; 2024.

12. Ascendis Pharma. *[Data on File]: Retrospective analysis of healthcare resource utilization and cost associated with chronic hypoparathyroidism in England - CPRD study: Version 8*; 2025.

13. Ascendis Pharma. *[Data on File]: KOL summary report*; 2025.

14. Karpf DB, Pihl S, Mourya S, Mortensen E, Kovoor E, Markova D, Leff JA. A randomized double-blind placebo-controlled first-in-human phase 1 trial of TransCon PTH in healthy adults. *J Bone Miner Res* 2020;**35**:1430-40.

15. Ascendis Pharma. *Yorvipath: Summary of product characteristics*. 2024. Available from: https://products.mhra.gov.uk/substance/?substance=palopegteriparatide [accessed 23 July 2025]

16. Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Gittoes NJ, Pasieka JL, et al. Evaluation and management of hypoparathyroidism summary statement and guidelines from the second international workshop. *J Bone Miner Res* 2022;**37**:2568-85.

17. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of hypoparathyroidism: Summary statement and guidelines. *Int J Clin Endocrinol Metab* 2016;**101**:2273-83.

18. Bollerslev J, Rejnmark L, Zahn A, Heck A, Appelman-Dijkstra NM, Cardoso L, et al. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in

pregnancy: recommendations of the ESE educational program of parathyroid disorders (PARAT 2021). *Eur J Endocrinol* 2022;**186**:R33-R63.

19. Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ, Shaha AR, Shindo ML, et al. American Thyroid Association statement on postoperative hypoparathyroidism: Diagnosis, prevention, and management in adults. *Thyroid* 2018;**28**:830-41.

20. Stack BC, Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, et al. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: postoperative hypoparathyroidism - definitions and management. *Endocr Pract* 2015;**21**:674-85.

21. Takeda. *Direct healthcare professional communication: Natpar (parathyroid hormone rDNA) 100/75/50/25 micrograms/dose powder and solvent for solution for injection: Discontinuation of manufacturing at the end of 2024 and update on 100mcg shortage*. 2022. Available from: https://assets.publishing.service.gov.uk/media/638358738fa8f56ea9d462e3/natpar.pdf [accessed 23 July 2025]

22. Ascendis Pharma. *[Data on File]: Briefing book for patient reported outcome instruments included in the phase 3 clinical trial of palopegteriparatide in adults with hypoparathyroidism*; n.d.

23. Takeda. *Takeda to discontinue manufacturing of Natpar® / Natpara® for patients with hypoparathyroidism at the end of 2024*. 2022. Available from: https://www.takeda.com/en-us/newsroom/statements/2022/takeda-to-discontinue-manufacturing-of-natpar-natpara [accessed 23 July 2025]

24. Mannstadt M, Bilezikian JP, Thakker RV, Hannan FM, Clarke BL, Rejnmark L, et al. Hypoparathyroidism. *Nat Rev Dis Primers* 2017;**3**:17055.

25. Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013;**346**:f324-f.

26. European Medicines Agency. *Assessment report: Yorvipath - International non-proprietary name: palopegteriparatide. Procedure No. EMEA/H/C/005934/0000*. Amsterdam: EMA; 2023.

27. Rejnmark L, Gosmanova EO, Khan AA, Makita N, Imanishi Y, Takeuchi Y, et al. Palopegteriparatide treatment improves renal function in adults with chronic hypoparathyroidism: 1-year results from the phase 3 PaTHway trial. *Adv Ther* 2024;**41**:2500–18.

28. Khan A, Clarke B, Rubin M, Schwarz P, Shoback D, Gagnon C, et al. *[Data on File]: Efficacy and safety of palopegteriparatide treatment in adults with hypoparathyroidism: 3-year results from the phase 3 PaTHway trial*; 2025.

29. Palermo A, Khan A, Rubin M, Schwarz P, Clarke B, Pagotto U, et al. *[Data on File]: Long-term efficacy and safety of palopegteriparatide treatment in adults with chronic hypoparathyroidism: 4-year results from the phase 2 PaTH forward trial*; 2025.

30. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. *Pharmacoeconomics* 2023;**41**:199-207.

31. Chomsky-Higgins KH, Rochefort HM, Seib CD, Gosnell JE, Shen WT, Duh QY, Suh I. Recombinant parathyroid hormone versus usual care: Do the outcomes justify the cost? *World J Surg* 2018;**42**:431-6.

32. National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual. Process & methods [PMG36]*; 2022.

33. Chen K, Krasner A, Li N, Xiang CQ, Totev T, Xie J. Clinical burden and healthcare resource utilization among patients with chronic hypoparathyroidism, overall and by adequately vs not adequately controlled disease: a multi-country chart review. *J Med Econ* 2019;**22**:1141-52.

34. Abouzid M, Riad M, Singh J, Zaidi S, Yadav R, Rendón M, Dueñas J. Abstract #989981: Three cases of hypoparathyroidism treated successfully with daily recombinant human parathyroid hormone rhPTH (1-84; Natpara) subcutaneous injections, with improvement in the quality of life and reduction in daily calcium and vitamin D requirements. *Endocr Pract* 2021;**27**:S86.

35. Vadiveloo T, Donnan PT, Leese CJ, Abraham KJ, Leese GP. Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study. *Clin Endocrinol (Oxf)* 2019;**90**:285-92.

36. Reddy NL, Rice CT, Carvalho SJ, Davidson JA, Glenister E, Sibley CT, et al. Estimating complications and mortality in patients with post-surgical chronic hypoparathyroidism in England: A retrospective matched cohort study. *Endocr Metab Sci* 2025;**19**:100258.

37. Ascendis Pharma. *[Data on File]: Health-related quality of life systematic literature review to support TransCon PTH in hypoparathyroidism*; 2025.

38. Weycker D, Chen K, Vera-Llonch M, Bornheimer R, Oster G. Phase III trial of recombinant human parathyroid hormone in hypoparathyroidism: A post-hoc analysis of change in health-state utility among responders. *Value Health* 2016;**19**:A677-A8.

39. Devlin NJ, Shah KK, Feng Y, Mulhern B, Van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ* 2018;**27**:7-22.

40. Hernández Alava M, Pudney S, Wailoo A. *Estimating EQ-5D by age and sex for the UK. NICE DSU; 2022*; 2022. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/DSU%20Age%20based%20utility%20-%20Final%20for%20website.pdf

41. Ascendis Pharma. *[Data on File]: Analysis of utility data from a clinical trial for hypoparathyroidism technical report*; 2024.

42. Wester V, De Groot S, Versteegh M, Kanters T, Wagner L, Ardesch J, et al. Good days and bad days: Measuring health-related quality of life in people with epilepsy. *Value Health* 2021;**24**:1470-5.

43. Andayani TM, Kristina SA, Hidayaturahmah R. Comparison and validation of EuroQol-5 dimension level and short form-6 dimension in cataract patients. *Pharmacy Education* 2022;**22**:236-41.

44. Conrad N, Molenberghs G, Verbeke G, Zaccardi F, Lawson C, Friday JM, et al. Trends in cardiovascular disease incidence among 22 million people in the UK over 20 years: population based study. *BMJ* 2024:e078523.

45. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes* 2010;**8**:13.

46. Golicki D, Niewada M, Buczek J, Karlińska A, Kobayashi A, Janssen MF, Pickard AS. Validity of EQ-5D-5L in stroke. *Qual Life Res* 2015;**24**:845-50.

47. Jesky MD, Dutton M, Dasgupta I, Yadav P, Ng KP, Fenton A, et al. Health-related quality of life impacts mortality but not progression to end-stage renal disease in pre-dialysis chronic kidney disease: A prospective observational study. *PLoS One* 2016;**11**:e0165675.

48. Van Wilder L, Rammant E, Clays E, Devleesschauwer B, Pauwels N, De Smedt D. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. *Qual Life Res* 2019;**28**:3153-61.

49. Shingler S, Fordham B, Evans M, Schroeder M, Thompson G, Dewilde S, Lloyd AJ. Utilities for treatment-related adverse events in type 2 diabetes. *J Med Econ* 2015;**18**:45-55.

50. Eryildirim B, Sahin C, Tuncer M, Sabuncu K, Cetinel C, Tarhan F, Sarica K. Effect of medical expulsive therapy on the health-related quality of life of patients with ureteral stones: a critical evaluation. *Int Urol Nephrol* 2015;**47**:1271-5.

51. Lin C-F, Huang Y-H, Ju L-Y, Weng S-C, Lee Y-S, Chou Y-Y, et al. Health-related quality of life measured by EQ-5D in relation to hospital stay and readmission in elderly patients hospitalized for acute illness. *Int J Environ Res Public Health* 2020;**17**:5333.

52. National Institute for Health and Care Excellence. *Galcanezumab for preventing migraine [TA659]*. London: NICE; 2020.

53. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine [TA764]*. London: NICE; 2022.

54. National Institute for Health and Care Excellence. *Erenumab for preventing migraine [TA682]*. London: NICE; 2021.

55. Ward T, Lewis RD, Brown T, Baxter G, De Arellano AR. A cost-effectiveness analysis of patiromer in the UK: evaluation of hyperkalaemia treatment and lifelong RAASi maintenance in chronic kidney disease patients with and without heart failure. *BMC Nephrol* 2023;**24**:47.

56. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. *Unit costs of health and social care 2023 manual*. Kent: Personal Social Services Research Unit & Centre for Health Economics; 2024. Available from: https://kar.kent.ac.uk/id/eprint/105685

57. Office for National Statistics. *National life tables: UK*. n.d. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [accessed 23 July 2025]

# 9 APPENDIX

Table 29 EAG appraisal of clinical evidence identification

| Topic | EAG response | Note |
|---|---|---|
| Is the report of the search clear and comprehensive? | PARTLY | Useful information about the searches was missing from Appendix B however was provided in the company response to the PfCs.<br><br>As all databases were searched together via the Ovid interface it was unclear if all relevant subject headings had been included in the search strategy. |
| Were appropriate sources searched? | PARTLY | Appendix B did not report searches of the International HTA database or searching of HTA websites. However, in the company response to PfCs a list of HTA websites, including the International HTA database, were reported as search sources.<br><br>A database search strategy for the International HTA database was not provided. |
| Was the timespan of the searches appropriate? | YES | |
| Were appropriate parts of the PICOS included in the search strategies? | PARTLY | Population: Hypoparathyroidism AND Study design: RCTs OR SRs<br><br>The above structure was not appropriate for searches of the Cochrane Database of Systematic Reviews (CDSR), CENTRAL, DARE and the Health Technology Assessment (HTA) database. These databases are prefiltered by study design and should have been searched using population terms only. |
| Were appropriate search terms used? | PARTLY | Searches of the keyword field were missing for the population part of the search.<br><br>Subject headings were searched appropriately in MEDLINE, Embase and CENTRAL, but it was unclear if relevant subject headings were searched for the other databases searched via Ovid. |
| Were any search restrictions applied appropriate? | NO | Inappropriate exclusion of letters and case reports from search results. Studies can be reported as letters, and case reports can be a useful source for locating adverse events data.<br><br>Inappropriate limit to humans used at line 47, table 3, page 14. This limit removes studies that are about humans but have not yet been indexed as humans (i.e. recent studies added to the database which have not yet had indexing applied).<br><br>Inappropriate limitation to RCTs and SRs in CDSR, CENTRAL, DARE, and the HTA database. These databases are prefiltered by study design and should have been searched using population terms only. |
| Were any search filters used validated and referenced? | PARTLY | Search strategies designed by NICE rather than externally validated search filters were used to limit retrieval to RCTs or SRs. Externally validated search filters to limit to RCTs and SRs are available but were not used. |

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 30 EAG appraisal of evidence identification for SLR of cost-effectiveness

| **Topic** | **EAG response** | **Note** |
|---|---|---|
| Is the report of the search clear and comprehensive? | PARTLY | - Useful information about the searches was missing from Appendix B however was provided in the company response to the PfCs.<br><br>- As all databases were searched together via the Ovid interface it was unclear if all relevant subject headings had been included in the search strategy. |

| | | |
|---|---|---|
| Were appropriate sources searched? | YES | - A range of relevant databases, conference proceedings, and HTA websites were searched along with reference checking of relevant systematic reviews.<br><br>- The company clarified that the International HTA database was searched in their response to the PFCs, however did not provide a full search strategy for this database. |
| Was the timespan of the searches appropriate? | YES | |
| Were appropriate parts of the PICOS included in the search strategies? | PARTLY | Population: Hypoparathyroidism AND Study design: economic evaluations OR cost and resource use studies<br><br>- The above structure was appropriate for searches of MEDLINE and Embase.<br><br>- The above structure was inappropriate for searches of the CENTRAL, NHS EED and the Health Technology Assessment (HTA) database. These databases are prefiltered by study design and should have been searched using population terms only. In addition, EconLit should have been searched using population terms only. |
| Were appropriate search terms used? | PARTLY | - Searches of the keyword field were missing for the population part of the search.<br><br>- Subject headings were searched appropriately in MEDLINE, Embase and CENTRAL.<br><br>- Both NHS EED and the HTA database have subject headings available in the Ovid interface, however it appears they were not included in the search strategy. |
| Were any search restrictions applied appropriate? | NO | - Inappropriate exclusion of letters from search results. Economic evaluations and other study types can be reported as letters.<br><br>- Inappropriate limit to humans used at line 47, table 10, page 43. This limit removes studies that are about humans but have not yet been indexed as humans (i.e. recent studies added to the database which have not yet had indexing applied).<br><br>- Inappropriate restriction to economic evaluations or cost and resource use studies applied in CENTRAL, NHS EED and the HTA database. These databases are prefiltered by study design and should have been searched using population terms only. In addition, EconLit should have been searched using population terms only. |
| Were any search filters used validated and referenced? | UNCLEAR | Clarification was sought from the company about the inclusion of study design search filters within the search strategy in Table 10. From their response it appeared that several search lines from two search filters (by CADTH and SIGN) along with additional terms were incorporated into the strategy. URL links to the filters rather than references were provided. |

Table 31 EAG appraisal of evidence identification for SLR of HRQL studies

| Topic | EAG response | Note |
|---|---|---|
| Is the report of the search clear and comprehensive? | PARTLY | - Useful information about the searches was missing from Appendix B however was provided in the company response to clarification.<br><br>- All databases were searched together via the Ovid interface with one strategy presented for all databases. This reduced the transparency of the search methods. |
| Were appropriate sources searched? | YES | A range of relevant databases, conference proceedings, and HTA websites were searched along with reference checking of relevant systematic reviews and selected studies. |
| Was the timespan of the searches appropriate? | YES | Conducted in March 2025 |
| Were appropriate parts of the PICOS included in the search strategies? | YES | Databases: Population - hypoparathyroidism AND Outcomes - Quality of life<br><br>Conference proceedings and HTA websites: Population - hypoparathyroidism |
| Were appropriate search terms used? | PARTLY | - Searches of the keyword field were missing for the population part of the search.<br><br>- Subject headings were searched appropriately in MEDLINE, Embase and CENTRAL.<br><br>- Unclear if subject headings were searched appropriately for the other databases. |
| Were any search restrictions applied appropriate? | NO | - Inappropriate exclusion of letters from search results. Research studies can be reported as letters.<br><br>- Inappropriate limit to humans used at line 33, table 16, page 59. This limit removes studies that are about humans but have not yet been indexed as humans (i.e. recent studies added to the database which have not yet had indexing applied). |
| Were any search filters used validated and referenced? | UNCLEAR | - Two search filters (by CADTH and SIGN) were used to restrict retrieval to quality of life or utility studies along with some further search terms representing related concepts. It is unclear how well this combination of search filters with additional terms would have performed for the retrieval of all relevant quality of life or utility studies, but terms appeared to be comprehensive.<br><br>- The search filters were not referenced, however a URL was provided. |

**Abbreviations:** HTA, Health Technology Assessment; CADTH, Canadian Agency for Drugs and Technologies in Health; SIGN, Scottish Intercollegiate Guidelines Network.

# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Report
# Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

## *EAG addendum: review of Adverse event rate data*


| | |
|---|---|
| **Produced by** | CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD |
| **Authors** | Sumayya Anwer, Research Fellow, CRD, University of York<br>Joy Chen, Research Fellow, CRD, University of York<br>Mark Corbett, Research Fellow, CRD, University of York<br>Diarmuid Coughlan, Research Fellow, CRD, University of York<br>Melissa Harden, Senior Information Specialist, CRD, University of York<br>Mark Simmonds, Senior Research Fellow, CRD, University of York<br>Robert Hodgson, Senior Research Fellow, CRD, University of York |
| **Correspondence to** | Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD |
| **Date completed** | 12/09/2025 |



**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR170273.


**Declared competing interests of the authors**

None

**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

**Note on the text**

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

# Table of Contents

Table of Tables 3
1 Background 4
2 Description and critique of NEW EVIDENCE 4
2.1.1 Points for Critique 6
3 Updated Economic analysis 6

# Table of Tables

Table 1: Exposure-adjusted treatment emergent adverse events (per patient per year) ..... 5
Table 2: Grade 1-4 Adverse event exposure adjusted event rates ..... 5
Table 3 Grade 3-4 Adverse event exposure adjusted event rates ..... 5
Table 4 Company corrected base case (Deterministic) ..... 7
Table 5 EAG Exploratory scenario analyses (deterministic) ..... 8
Table 6 EAG's base case ..... 9

# 1 BACKGROUND

In the evidence assessment report (EAR), concerns were raised regarding the adverse event rates used in the model, noting that it was unclear how these had been calculated and that the rates applied differed significantly from those reported in the clinical sections of the company's submission. This was important as AE rates are a key driver of cost-effectiveness. Due to this uncertainty, the EAG recommended a correction to the company's base case analysis using AE rates estimated from the data in the company submission and the clinical study report for the PaTHway trial.

To help resolve this uncertainty and clarify the company's position the company has provided additional information on its approach to modelling AE rates and the methodology used to derive them. This addendum reviews this new information and presents a revised economic analysis incorporating this evidence.

# 2 DESCRIPTION AND CRITIQUE OF NEW EVIDENCE

The company reported that the AE rates applied in the model were derived from the incidences of exposure-adjusted hypocalcaemia (including paraesthesia) and hypercalcaemia observed in the PaTHway trial. To estimate AE rates for conventional therapy (CT), the company used data from the double-blind phase (week 26). For the palopegteriparatide (palopeg) arm, AE rates were estimated using data from both the double-blind and open-label extension (OLE) phases, incorporating patients initially randomised to palopeg as well as those who crossed over from CT to palopeg in the OLE phase.

Modelled AE rates were based on grade 1-4 symptomatic events, with per-cycle rates estimated by dividing annualised rates by 13. Table 1 summarises the exposure-adjusted treatment-emergent adverse events from the PaTHway trial, with the values used to inform the model highlighted in bold. Table 2 presents the AE rates applied in the company's base case, derived from the values in Table 1, which match those reported in Table 33 of the CS.

**Table 1: Exposure-adjusted treatment emergent adverse events (per patient per year)**

| Arm | Exposure adjusted TEAE | Week | | | |
|---|---|---|---|---|---|
| | | 26 | 52 | 104 | 156 |
| **Symptomatic hypocalcaemia** | | | | | |
| Palopeg arm | Paraesthesia | [redacted] | [redacted] | [redacted] | [redacted] |
| | Hypocalcaemia | [redacted] | [redacted] | [redacted] | [redacted] |
| | Total events per person year | [redacted] | [redacted] | [redacted] | [redacted] |
| CT arm* | Paraesthesia | [redacted] | [redacted] | [redacted] | [redacted] |
| | Hypocalcaemia | [redacted] | [redacted] | [redacted] | [redacted] |
| | Total events per person year | [redacted] | [redacted] | [redacted] | [redacted] |
| Combined | Paraesthesia | - | [redacted] | [redacted] | [redacted] |
| | Hypocalcaemia | - | [redacted] | [redacted] | [redacted] |
| | Total events per person year | - | [redacted] | [redacted] | [redacted] |
| **Symptomatic hypercalcaemia** | | | | | |
| Palopegteriparatide arm | Hypercalcaemia | - | - | - | [redacted] |
| CT arm* | Hypercalcaemia | - | - | - | [redacted] |

Source: PaTHway clinical trial *Note, patients on the CT arm cross-over to treatment with palopegteriparatide after 26-weeks i.e. weeks 52 to 156, represent treatment with palopegteriparatide for 26 to 130 weeks.

**Table 2: Grade 1-4 Adverse event exposure adjusted event rates**

| Adverse event | Rate adjusted for cycle | |
|---|---|---|
| | Palopeg | CT |
| Symptomatic hypercalcaemia | [redacted] | [redacted] |
| Symptomatic hypocalcaemia | [redacted] | [redacted] |

Source: PaTHway clinical trial

In addition, to support the Evidence Assessment Group (EAG) in conducting scenario analyses, the company provided exposure-adjusted rates for grade 3-4 adverse events only, as shown in Table 3. This reflects the EAG's preferred approach of focusing on higher-grade events, since the costs and utility decrements in the model are based on hospitalisations for hypercalcaemia and hypocalcaemia. However, the company noted that it does not agree with this approach, as the results show no difference in hypocalcaemia between treatment groups which the company argues is inconsistent with what would be expected in clinical practice.

**Table 3 Grade 3-4 Adverse event exposure adjusted event rates**

| Adverse event | Rate adjusted for cycle | |
|---|---|---|
| | Palopeg | CT |
| Symptomatic hypercalcaemia | [redacted] | [redacted] |
| Symptomatic hypocalcaemia | [redacted] | [redacted] |

Source: PaTHway clinical trial

### 2.1.1 Points for Critique

The EAG thanks the company for providing the additional data and for clarifying its approach to deriving AE rates in the base-case analysis. The EAG is largely satisfied that the event rates applied in the base case have been correctly calculated and therefore does not consider the correction proposed in the EAR to be necessary.

While the EAG is satisfied that the company's base-case calculations are broadly appropriate, it remains concerned about the company's approach to deriving AE rates. The EAG continues to consider it appropriate to use grade 3-4 AE rates, consistent with the costs and utility decrements applied in the model (see Section 4.2.6.5 of the EAR for full discussion). The EAG also considers it inappropriate to incorporate OLE data to model AE rates only in the palopeg arm, as this approach breaks randomisation and does not provide a fair comparison with CT. In particular, it introduces long-term data for palopeg that are not available for CT. It is also plausible that AE rates in the CT arm would have decreased with longer follow-up, especially given that CT therapy in the blinded phase of the PaTHway trial was suboptimal due to the titration protocol used.

Reflecting the new data provided by the company, the EAG prefers to use the exposure-adjusted grade 3-4 AE rates reported in Table 3. The EAG considers that the model should be based on adverse event rates observed in the first phase of the PaTHway trial, as these represent the only randomised and blinded comparison between palopeg and CT. The EAG notes that it is unclear whether the rates in the palopeg arm were derived using OLE data. As such, this revision to the EAG base case may not fully align with the EAG's preference to use grade 3-4 AE rates from the double-blind phase only. Updated economic analyses are presented in Section 3.

# 3 UPDATED ECONOMIC ANALYSIS

Table 4 reports a new correct company base, including the EAG's calculation corrections. These incorporate changes to the way in which age adjustment is applied, the calculation of mortality and state occupancy in the palopeg arm as well as the new correction in which AE rates applied are re-estimated by dividing annualised rates by 13.04 (28/365.25). Results are inclusive of the PAS discount for palopeg.

**Table 4 Company corrected base case (Deterministic)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| **Company base case** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,895 |
| **Company base case with calculation errors corrected** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £17,578 |

Table 5 reports the EAG scenario analysis using the new company corrected base case as the reference analysis. The scenarios presented all match those described in the EAR except for scenario 4, which now incorporates the exposure-adjusted grade 3-4 AE rates provided by the company.

**Table 5 EAG Exploratory scenario analyses (deterministic)**

| Scenario | | Technology | Total | | Incremental | | ICER |
|---|---|---|---|---|---|---|---|
| | | | Costs | QALYs | Costs | QALYs | |
| Corrected company base case | | | [redacted] | [redacted] | | | |
| | | | [redacted] | [redacted] | [redacted] | [redacted] | £17,578 |
| 1 | Utility values (MMRM) | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £19,915 |
| 2 | Exclude complication rates | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £18,287 |
| 3a | No survival benefit | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £15,155 |
| 3b | Use survival HR from literature | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £15,486 |
| 4 | Use AE rate that results in hospitalisation | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £68,131 |
| 5 | Alternative AE costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £56,252 |
| 6a | Set RDI to 100% | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £22,686 |
| 6b | Include wastage based on trial dose band changes | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £17,880 |
| 6c | Extrapolate wastage from last period over the model time horizon | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £18,115 |
| 7 | CT dosing | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £15,445 |
| 8 | eMIT costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £18,166 |
| 9a | Remove health state maintenance costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £88,738 |
| 9b | Reweigh PS/NS health state maintenance costs to PaTHway trial | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £30,109 |
| 9c | Alternative company weighting of PS/NS health state maintenance costs | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £28,956 |
| 10 | Nurse visit for 10% of chronic HypoPT patients | CT | [redacted] | [redacted] | | | |
| | | Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | £25,765 |

**Abbreviations**: AE, adverse event; CT, conventional therapy; CPRD, Clinical Practice Research Datalink; EAG, evidence assessment group; eMIT, electronic market information tool; HR, hazard ratio; HypoPT, hypoparathyroidism; ICER,

The cumulative impact of the EAG's preferred assumptions is presented in Table 6 below. The EAG base case adopts the following scenarios described in Section 6.1:

- Scenario 1: MMRM derived health state utilities
- Scenario 2: Complication rates set to zero
- Scenario 3b: Survival benefits informed by published values
- Scenario 4: Revise AE rates (updated from EAR)
- Scenario 5: Revise AE costs
- Scenario 6a. Set RDI to 100%
- Scenario 6b: Include wastage based on observed dose band changes
- Scenario 7: Revise CT dosing
- Scenario 8: Drug acquisition costs for alfacalcidol from eMIT
- Scenario 9a: Remove Health state costs
- Scenario 10: Palopeg administration cost in those need assistance

**Table 6 EAG's base case**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| **EAG base case (Deterministic)** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £226,468 |
| **EAG base case (Probabilistic)** | | | | | | | |
| CT | [redacted] | [redacted] | [redacted] | | | | |
| Palopeg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £ 227,450 |

**Single Technology Appraisal**

**Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 4th August 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

The company wants to point out that “corrected company base case” is not aligned with the actual base case in the submission, so naming of it is misleading and factually inaccurate. Additionally, the company believes two out of three corrections made by the EAG are incorrect, and full explanation on why it is inaccurate is provided below, within the table. Since the base case forms the basis of the explanatory analysis, base case accuracy and relevance are critical to this submission. Therefore, we are asking for both issues, mistakes made in the 'corrected base case' and the naming of it to be addressed.

**Suggested modelling errors and corrected company base case**

| **Description of problem** | **Description of proposed amendment** | **Justification for amendment** | **EAG Response** |
|---|---|---|---|
| In section 1.6 (Table 2) and section 6.2 (Table 25), the EAG presents the “Corrected company base case” as a scenario. The company believes this to be misleading as the company has had no input on any changes made by the EAG, and, as set out below, believes the changes made are incorrect or unnecessary. | Please change the name of this scenario to remove “company” or any suggestion that the base case has been presented by the company. Given the scenarios were conducted on the “corrected company base case”, please update these scenarios to be on the company base case. | The current label implies that the scenario reflects the company’s submitted position, which is not the case. A more appropriate and neutral label—such as “EAG revised base case”—would avoid misrepresenting the company’s input and maintain clarity regarding scenario ownership. | Given that the company does not agree with our proposed calculation corrections, we have changed this to say, “Company base, inclusive of EAG suggested calculation corrections.”<br>The revisions implemented in this scenario refer only to calculation errors. It is therefore important to retain the word Company in the name as this does reflect the company’s submitted position regards model assumptions and parameter values, not the EAG’s. |

| | | | |
|---|---|---|---|
| In section 5.4.1, the EAG states: “The first error related to the implementation of age adjustment cells (F229:F311, ‘inputs sheet’) which did not rescale the adjustment factor to take into account the starting age of the cohort”. The company believes this change is unnecessary as the age of the population was accounted for in the “Yorvipath/CT Trace” sheets in C37:C1103. | Please remove this statement as an identified model error and adjust the EAG adjusted company base case and exploratory analyses. | The model already incorporates the starting age of the cohort through the age progression in the “Yorvipath/CT Trace” sheets (C37:C1103). These cells ensure that age-dependent parameters are correctly aligned with patient age over time. As such, additional adjustment or rescaling in the input sheet is not required, and this should not be considered a model error. | Not a factual error.<br>The company’s model applies age adjustment to utility values incorrectly. When implementing age adjustments, the adjustment factor should be rescaled to the cohort’s starting age, such that the factor equals 1 in the first cycle. This is necessary because the PaTHway utility values already capture the HRQL impact of age for the target population. Specifically, they reflect the HRQL of HypoPT patients with a mean age of approximately 48 years, incorporating both the condition-specific decrement and the effect of being, on average, 48 years old. We also note that this correction reduces the ICER in the company base case. |
| In section 5.4.1, the EAG states: “The third error relates to the AE rates | Please remove this point as an identified model error and instead clarify that the adverse event rates | The AE rates used in the model were derived as exposure-adjusted event rates, calculated | The EAG remains unclear as to how the “exposure-adjusted” event rates have |

| | | | |
|---|---|---|---|
| applied in the model. The EAG is unable to verify how these have been estimated and the values applied do not align with those reported in Table 16. This impacts cells E89:F90, 'inputs sheet'. This latter error has a very large impact on the results of the economic analysis increasing the ICER by approximately £30,000 per QALY as the values used by the company significantly overestimate the AE rates in the CT arm of the model." The company does not agree with this assessment as the values used are correct. | applied in the model are based on exposure-adjusted event rates and were not expected to match the unadjusted rates presented in Table 16 of the CS. Please also adjust the EAG adjusted company base case and exploratory analyses. | by dividing the number of symptomatic hypo- and hypercalcaemia events by time on treatment. This approach was taken for three key reasons:<br>• Patients in the CT and palopeg arms had different durations of treatment exposure, necessitating adjustment to ensure comparability.<br>• The rate of hypocalcaemia events decreased over time in the palopeg arm, making a point estimate based on raw proportions misleading.<br>• Given the continuous nature of these events across the model time horizon, a rate-based approach is more appropriate than using a fixed probability.<br>Table 16 presents unadjusted event probabilities, which were | been calculated from the PaTHway trial data, as this has not been explained in either this FAC or the CS.<br>We are unclear as to how a 4-fold difference in hypocalcaemia risk in PaTHway (CS Table 16) becomes a 19-fold difference in risk after adjustment (Model and CS Table 25).<br>We do not follow how the two arms had different duration of treatment exposure, given they are from the same trial. Perhaps only the double-blind phase was used for CT, but the OLE was used for palopeg? The EAG is concerned that, if so, that could lead to an unfair favouring of palopeg, because the rate of event is |

| | | | |
|---|---|---|---|
| | | not intended to be used as direct model inputs. Therefore, the company's approach should not be considered an error. | allowed to decline over time on palopeg but not on CT.<br><br>The EAG would need more information on exactly how the exposure-adjusted event rates used in the model were derived from PaTHway data to clarify this point. We have suggested to the NICE technical team that the company provide additional details and that this be reviewed by the EAG as an addendum to our report, ensuring this issue is fully resolved before the initial committee meeting.<br><br>To acknowledge the uncertainty regarding this issue, we have added additional details to Section 5.4.1.1 outlining our concerns. |

**Issue 1** **<u>Uncertain definition of the "Not Adequately Controlled" population</u>**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In section 2.3.1 page 28, the EAG states 'The company focused their decision problem population on the NAC subpopulation as they claim this population will show the biggest clinical benefit as well as drive the cost-effectiveness.' Which is only partially correct as it misses out key information. | Please reword this section to include the following;<br>'The company focused their decision problem population on the NAC subpopulation, as they claim this population will show the biggest clinical benefit, driving cost-effectiveness, from a second-line treatment perspective with PTH replacement therapy following treatment with CT which failed to achieve adequate control.' | The correction is needed as it improves the clarity and precision of the company's rationale and treatment pathway by explicitly identifying palopeg intention as a second-line treatment following CT. This reduces ambiguity, avoiding any misinterpretation of the intended population and treatment positioning. | Not a factual inaccuracy.<br><br>The EAG thinks our text is a reasonable precis of the company position. |
| In section 2.3.1 (page 28), the EAG states: "The definitions broadly agree that high-dose CT, inadequate calcaemic control, renal complications and high resource use define NAC (see Section | Please amend the statement to include context on how the NAC criteria were generated—specifically, that the criteria were informed by a review of published literature and clinical guidelines including European Society of | The NAC criteria used in the submission were not arbitrarily selected but were based on a review of the most relevant and recent published sources. The European Society of Endocrinology 2022 (Bollerslev et al, 2022) and Second | Not a factual inaccuracy.<br><br>This sentence is summarising what is included in the NAC definitions and is not criticizing |

| | | | |
|---|---|---|---|
| 2.2.4.3). However, none of these criteria independently determine whether patients have NAC." The company believes this statement lacks important context regarding how the NAC criteria were derived. | Endocrinology 2022 (Bollerslev et al, 2022), Second International Workshop 2022 (Khan et al, 2022) and Chen et al, 2019. | International Workshop 2022 (Khan et al, 2022) publications provide clinical guidance on the characteristics of patients with chronic HypoPT who may be inadequately controlled on CT, while Chen et al. (2019) offers real-world evidence on clinical and healthcare resource use patterns in such patients. Including this context would clarify the rationale for the criteria and reflect that the definition was grounded in available clinical evidence and expert guidance. | the company's identification of them. |

| | | | |
|---|---|---|---|
| In section 2.3.1 (page 28), the following statement by the EAG is not factually accurate: 'For instance, the guidelines from the Second International Workshop in the company's clarification response were different from those included in the company submission; neither of which were explicitly stated in the publication referenced.' | Please consider removing the sentence. | The guideline criteria referenced in the company submission and the clarification response are consistent however to apply the criteria to the baseline demographics from the trial it was necessary to specify how these would present in patients e.g. a history of hypercalciuria or high dose calcium. This is how they were presented (in a table) in the clarification response. The criteria are also contained in the Second International Workshop publication (Khan et al, 2022) under the section on PTH replacement (pg 2576). | Not a factual inaccuracy.<br><br>The EAG considers that there are clear differences between the discussion of the "Second International Workshop" criteria between Table 6 of the CS and Table 4 of the company response to clarification.<br>Page 2576 of Khan et al does not provide a precise definition of NAC; only a summary of who might be eligible for PTH therapy. |

**Issue 2** **<u>Use of sub-optimal conventional therapy in the PaTHway trial</u>**

| **Description of problem** | **Description of proposed amendment** | **Justification for amendment** | **EAG Response** |
|---|---|---|---|
| In section 2.3.2 page 30, the EAG states: 'The company also excluded magnesium supplements and thiazide diuretics from the decision | Please reword/amend including the following information for transparency. Thiazide diuretics are also infrequently used. | Similar to magnesium supplements, thiazide diuretics were excluded as a relevant comparator as they are an adjunct rather than a | Not a factual inaccuracy.<br><br>The EAG notes that clinical advice supplied to the EAG was that thiazide diuretics |

| | | | |
|---|---|---|---|
| problem, as they were considered adjunct to CT rather than part of it', which is correct, however misses out key information as to why they were excluded. | | replacement to CT and are infrequently used. This is reinforced by the audit data presented in the CS Table 1 (page 15). Amending the wording to reflect this reasoning would be more accurate. | would be used in some NAC patients, plausibly before palopeg. |
| In section 3.2.1.2 page 37, the EAG states: 'The PaTHway trial required all patients in both arms to substantially reduce their active vitamin D dose at the start of the trial. The company stated that this was required to maintain a standardised titration algorithm across both trial arms', which misses out some key information. | Please amend/reword this statement to include reasons behind the reduction in Vitamin D doses. It was recommended by therapeutic guidelines, FDA recommendations, and in line with the national clinical practice reported by clinical experts (Clarification response, page 7). This was explained in the company's clarification responses (Question A3). | This amendment is vital to clarify that the reduction in Vitamin D dose at the start of the trial was not to maintain a standardised titration algorithm across both trial arms. It was a requirement of regulatory agencies to demonstrate the safety and efficiacy of the product and therefore not just a company made decision. | The end of the last sentence has been amended to read: "….this was done based on FDA recommendations and therapeutic guidelines". |

**Issue 3** **Primary outcome in PaTHway trial does not permit a fair comparison with conventional therapy**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In section 3.2.1.2 page 38, the EAG states: 'A limitation of the PaTHway trial is that it was not designed to detect clinical benefit in terms of renal outcomes.' This is not entirely true as renal function was measured at baseline, week 26 and week 52 as provided in the company's response to clarification questions *(*Question A1). A post-hoc analysis was conducted to examine the impact of palopegteriparatide treatment on renal function in adult with chronic HypoPT in PaTHway trial. | Please reword or remove the statement that 'the trial was not designed to detect clinical benefit in terms of renal outcomes' as it is factually incorrect. This outcome has been captured within the trial. | The current statement is a misrepresentation of the clinical trial which indicates that there are no clinical benefits reported in terms of renal outcomes. As shown through the baseline, week 26 and week 52 results for renal function, these have all been captured and it shows clinical benefit within the trial. | Not a factual inaccuracy.<br><br>Only part of this sentence has been quoted by the company. It was stated in the context (see p38) of renal outcomes "as defined in the cost-effectiveness model". PaTHway data on incidence rates of chronic kidney disease were not presented and were not used in the cost-effectiveness model. |

**Issue 4 Model Structure**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In section 4.2.2 (page 51), the EAG states: "…the eligibility criteria include patients with renal complications and those classified as high resource users. However, these criteria do not necessarily reflect poor response to CT". While there is no clear consensus on how NAC patients should be defined, the criteria used by the company were based on sources considered the most appropriate available guidance for identifying patients with chronic hypoPT who are NAC (Khan et al. 2022; Bollerslev et al. 2022; Chen et al. 2019). While there is no established consensus on how to | Please amend the statement to include context on how the NAC definition was derived. The criteria were informed by a review of published literature and clinical guidelines including European Society of Endocrinology 2022 (Bollerslev et al, 2022), Second International Workshop 2022 (Khan et al, 2022) and Chen et al, 2019, all of which describe similar indicators of inadequate disease control.<br><br>Additionally, patients within the PaTHway clinical trial often met multiple criteria to be identified as NAC. For instance, of the 36 patients identified as NAC due to renal classification using the Second International Workshop 2022 (Khan et al, 2022) criteria (Clarification Question A12, Table 4), 35 also met at least one other NAC criterion, reinforcing the | The current statement does not acknowledge the published sources used to inform the NAC definition, which could give the impression that the criteria were arbitrarily defined by the company. Including reference to Second International Workshop 2022 guidelines (Khan et al, 2022) and other supporting literature strengthens the validity of the approach and demonstrates alignment with expert consensus on features of inadequately controlled HypoPT. In addition, the fact that nearly all patients classified as NAC using the Second International Workshop 2022 criteria also met at least one additional NAC criterion supports the internal consistency and clinical relevance of the classification. | Not a factual inaccuracy.<br><br>The statement accurately reflects the EAG's concern that the company's definition of NAC includes elements unrelated to either the severity of chronic HypoPT or a patient's ability to adequately control symptoms with CT. |

| | | | |
|---|---|---|---|
| define NAC HypoPT, the company believes this statement lacks important context regarding how the criteria were derived. | consistency and clinical relevance of the classification. | | |
| In section 4.2.2 (page 51), the EAG states: "…the model assumes that patients who are NAC on CT will remain permanently in that state. However, clinical input to the EAG indicated that patients (with surgical aetiology) on CT often taper their doses with the long-term aim of achieving CT independence. Furthermore, the PaTHway trial reported at least one patient who was able to maintain normal serum calcium while becoming independent from CT, suggesting that transitions between states may be possible, see Table 13 of CS." The Khan et al. 2022 guidelines | Please amend or qualify the statement to reflect the definition of chronic HypoPT as per clinical guidelines (i.e. Second International Workshop, Khan et al, 2022), where spontaneous recovery is considered unfeasible after 12 months. Alternatively, remove the statement or provide clinical evidence supporting the claim that transitions to CT independence are expected in the target patient population (palopeg as a second line treatment for chronic HypoPT patients who are NAC on CT).<br><br>Also, please provide context that the one patient on the CT arm who was able to maintain normal serum calcium while becoming independent from CT did crossover to the palopeg arm of the trial at week 26 (as per | The current statement lacks clinical context and risks misrepresenting the chronic HypoPT population modelled by the company. Referencing isolated recovery cases without clarifying their relevance to the modelled population may be misleading. Including relevant guideline-based definitions or removing the statement would improve accuracy and clarity. | Not a factual inaccuracy.<br><br>Spontaneous recovery is not the same as moving from NAC to AC. Further, this statement is primarily reporting clinical advice to the EAG that long-term adequate control may be feasible with CT in patients who are currently NAC. |

| | | | |
|---|---|---|---|
| define post-surgical HypoPT as permanent if it persists for more than 12 months, at which point independence from CT is considered extremely unlikely except in rare cases of spontaneous recovery. This guidance underpins the company's model assumption. Therefore, the EAG's statement appears to reflect incident HypoPT rather than the company's target population of chronic HypoPT. | protocol) and remains on treatment with palopeg. | | |

**Issue 5** **<u>Lack of direct evidence for complication and mortality benefits</u>**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In section 4.2.2 (page 52), the EAG states: "No evidence has been provided in the company's submission to support a link between the clinical | Please amend the statement to acknowledge that evidence was submitted in the CS and clarification responses to support the association between NAC status and increased resource | The current wording implies that no evidence was provided, which is factually inaccurate. Acknowledging the submitted evidence and expert validation would provide a | The EAG has revised the text to better reflect the evidence provided in the CS acknowledging the data reported in Chen and clinical expert opinion. |

| | | | |
|---|---|---|---|
| concept of NAC and increased resource use. Moreover, considering the comorbidities and complex clinical context of the HypoPT population, it is not clear that such a relationship would necessarily exist. For a more detailed discussion of these concerns, see Section 4.2.8.2." The company considers this statement to be factually incorrect, as both the CS and, more clearly, the clarification question responses (Question B7 and B14) reference Chen et al. 2019, which assessed healthcare resource use in AC vs NAC patients and reported increased use in NAC patients. In addition, clinical validation of this association was provided in the KOL report, where all three clinical experts confirmed that NAC | use, including data from Chen et al. 2019 and clinical validation from the KOL summary report (Question 5). | more accurate and balanced representation of the company's submission. | Text edited to state: "Limited evidence has been provided in the company's submission to support the conceptual link between the clinical concept of NAC and increased resource use with model assumptions principally relying on clinical opinion and single study by Chen et al.[33] which demonstrated modest differences in some elements of resource use between NAC and AC patients". |

| | | | |
|---|---|---|---|
| patients are expected to require higher levels of resource utilisation. | | | |
| In section 4.2.6 (page 59), the EAG states: “First, it assumes that treatment with palopeg reduces resource use. Second, it assumes that resource use serves as a proxy for complication rates, implying that reductions in resource use will correspond directly to reductions in complication rates.” The first statement omits the link that treatment with palopeg is assumed to shift patients from NAC to AC, with reduced resource use resulting from adequate control—not directly from treatment itself. The second statement similarly overlooks that resource use is used in the model as a proxy for control status (AC/NAC), from | Please amend the text to clarify that treatment with palopegteriparatide restores functional PTH and calcium homeostasis, from which the biological rationale for assuming that patients achieve adequate disease control (i.e. AC status) while on treatment is derived.<br><br>Lower healthcare resource use is assumed to result from this improved disease control, and from this, resource usage was used as proxy to identify AC/NAC patients. Therefore, the difference in complication rates was not due to the difference in resource usage, but due to AC/NAC status. | The current wording implies direct and unqualified assumptions between treatment, resource use, and complications, which misrepresents the model structure. Adding this context ensures the assumptions are interpreted correctly. | Not a factual error<br><br>For clarity, the EAG has added text to explicitly state that reduced resource use results from improved disease control.<br><br>The EAG does not agree that the second point is factually inaccurate. It considers the company’s description to convey essentially the same concept, but with an additional intermediate step: resource use is treated as a proxy for AC/NAC, which in turn affects complication rates. The EAG’s explanation more directly and succinctly reflects the underlying assumptions applied in the model. |

| | | | |
|---|---|---|---|
| which differences in complication rates are applied. | | | |
| In section 4.2.6 (page 59), the EAG states: “As with complication rates, the EAG acknowledges the potential for palopeg to improve survival, possibly through a reduction in HypoPT-related complications, but considers the assumed proxy relationships to be unjustified.” The company considers the use of the term “unjustified” to be factually incorrect, as the CS provided a clear rationale for using resource use as a proxy for control status (AC/NAC), which is then linked to differential survival. | Update the wording of “unjustified” to use softer language such as “inadequately justified”. | The term “unjustified” implies that no rationale or evidence was provided, which is not accurate. The CS includes a reasoned explanation for the proxy relationship. Using softer language such as “inadequately justified” more accurately reflects the EAG’s view that the justification was not sufficient, without implying it was entirely absent. | The EAG has amended as suggested. |

**Issue 6 Modelling of adverse event rates and costs**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In section 4.2.6, the EAG states: “The EAG also notes that the values used in the company base case do not align with those reported in Table 16 of the CS. These are corrected in Section 6.” The company considers this statement to be factually incorrect, as the incidence values used in the CEM were not expected to match those in Table 16, which reports unadjusted adverse event probabilities. | Please remove this statement as an identified error and adjust the EAG adjusted company base case to reflect the correct use of exposure-adjusted incidence values. | The incidence values used in the CEM are based on exposure-adjusted event rates (see pages 82, 85-86, and 94 of the CS), calculated by adjusting the number of symptomatic hypo- and hypercalcaemia events for time on treatment. This approach was used because these adverse events were expected to occur continuously across the time horizon, rather than as isolated or one-off events. In contrast, Table 16 reports unadjusted event probabilities and was not intended as a direct input to the model. Therefore, the company base case is correct as submitted, and this point should not be treated as an error. | Please see response to the Issue on modelling errors above. |

**Issue 7** **Non–reference case approach to healthcare resource use**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In Section 4.2.8 (pages 70–71), the EAG states:<br>"Moreover, the EAG considers the company's approach to be inconsistent with the NICE Methods Guide. Specifically, Section 4.4.11 states that only costs directly related to the condition of interest should be included in the economic evaluation, and that costs unrelated to the condition or the technology under assessment should be excluded. However, the company's analysis of the CPRD dataset does not differentiate between healthcare costs directly attributable to HypoPT and those arising from unrelated background | Please amend the statement to acknowledge that efforts were made to minimise confounding in the CPRD analysis by:<br>• Matching patients with chronic HypoPT to a general population comparator cohort (matched by age, sex, and GP practice);<br>• Excluding individuals with prior cardiovascular disease and chronic kidney disease in both cohorts; and<br>• Demonstrating that the annual costs observed in the matched general population comparator were approximately 10% of those in the NAC group.<br>This supports the conclusion that the majority of observed costs are likely attributable to disease-specific | The company believes this statement does not fully reflect the methodological steps taken to align with the NICE Methods Guide. Specifically:<br>• Patients with confirmed chronic HypoPT were matched 1:10 to general population controls by age, sex, and surgery date (for post-surgical cohort), and length of follow-up.<br>• Individuals with prior CVD or CKD were excluded from both groups to reduce the influence of unrelated high-cost comorbidities.<br>• The results demonstrated a marked difference in cost between patients with HypoPT and matched | Not a factual inaccuracy<br><br>The EAG acknowledges the company's effort in providing a matched general population cohort. However, this does not resolve the underlying concern regarding potential confounding from comorbidities, as these were not accounted for in the matching process. The EAG therefore considers that the CPRD analysis does not adequately distinguish healthcare costs directly attributable to hypoPT from those arising from unrelated background comorbidities. |

| | | | |
|---|---|---|---|
| comorbidities. As a result, the cost estimates may overstate the economic burden of HypoPT and is likely to overstate the cost savings resulting from improved disease control.” | burden rather than unrelated comorbidities. | general population controls. For example, the mean annual cost in the uncontrolled NAC group was [redacted], compared to [redacted], in the matched general population—approximately [redacted], of the NAC cost. This strongly suggests that the majority of the incremental cost burden is disease-specific.<br><br>This context supports that the company took reasonable and transparent steps to isolate HypoPT-related healthcare costs and that the analysis aligns with the principles of the NICE Methods Guide. The company believes including this clarification would provide a more balanced and accurate interpretation of the evidence. | |

**Issue 8 Modelling of healthcare resource use**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| In section 4.2.8 (page 71), the EAG states: "At the clarification stage, the EAG requested justification for the company's assumptions regarding health state costs. In response, the company stated that the assumptions underpinning the base-case analysis had been reviewed by three clinical advisors but provided only clinical opinion as justification for these substantial assumptions. The EAG does not consider clinical opinion alone to constitute sufficient justification, particularly given the magnitude of the associated impact on cost-effectiveness outcomes." The company considers this statement to be factually inaccurate, as both clinical | Please amend the statement to reflect that the justification for health state cost assumptions included both expert clinical opinion and supporting evidence from Chen et al. (2019) (Question B14), which reported increased healthcare resource use in the NAC population. | In addition to input from three clinical advisors, the company referenced Chen et al. (2019), which provides empirical evidence of increased resource use in NAC patients with chronic HypoPT. The use of both clinical and published sources reflects a reasonable approach to informing model assumptions in the absence of a direct link between trial and cost data. Amending the statement to acknowledge both sources of justification would improve factual accuracy and provide appropriate context. | Text amended to acknowledge the Chen et al. 2029 reference.<br><br>Text now states: At the clarification stage, the EAG requested justification for the company's assumptions regarding health state costs. In response, the company referred to one study (Chen et al. 2019)[33] and stated that the assumptions underpinning the base-case analysis had been reviewed by three clinical advisors but provided only clinical opinion as justification for these substantial assumptions. The EAG does not consider clinical opinion alone to constitute |

| | | | |
|---|---|---|---|
| opinion and published evidence were provided in support of the assumptions. | | | sufficient justification, particularly given the magnitude of the associated impact on cost-effectiveness outcomes. Moreover, the study by Chen et al. shows only modest difference in resource use for some items and does not correspond with the model benefits. The EAG highlights that the cost savings projected in the company's base case are equivalent to a health benefit exceeding 5 QALYs, assuming a willingness-to-pay threshold of £20,000 per QALY. In the EAG's view, benefits of this magnitude warrant a robust evidentiary foundation, equivalent to that required for clinical benefits of similar scale. |

**General**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| Throughout the EAG report, the EAG uses 'HypoPT' instead of 'chronic HypoPT' | Please amend mentions of HypoPT to include 'chronic'. | The intended treatment is for use in patients with chronic HypoPT who are not adequately controlled on CT. Therefore, by removing 'chronic' this changes the intended patient population group. | The EAG thinks that no meaningful confusion arises from using HypoPT without "chronic".<br>We note that the CS repeatedly uses "HypoPT" without "chronic". |
| In section 1.4 (page 18), the EAG states: "administration of daily or twice-daily subcutaneous injections". The company believes this statement is misleading. | Remove "or twice-daily" from the sentence. | In cases where the full dose cannot be delivered in a single injection (due to volume limits), the dose may be split into two sequential injections given at the same time, not administered as twice-daily injections. The current phrasing could be misinterpreted as implying a need for more frequent, ongoing dosing, which does not reflect the intended clinical use. | Amended as suggested |
| In section 2.2.1 (page 23), the EAG states: "non-surgical patients are younger and have had | Remove the line "and have had HypoPT their entire lives". | While many non-surgical patients are diagnosed at a younger age and experience longer disease duration compared to surgical | This has been amended to: "may have had HypoPT for many years." |

| | | | |
|---|---|---|---|
| HypoPT their entire lives". The company believes this statement is misleading. | | patients, it is not accurate to state that they have had HypoPT their entire lives. Non-surgical HypoPT can present at various ages, including adolescence and adulthood, and some cases may remain undiagnosed for extended periods. The current wording overgeneralises and may misrepresent the variability in disease onset among non-surgical patients. | |
| In Section 2.2.2 (page 24), the EAG states: "In the study, the company defined patients with NAC HypoPT as those who had more than 5 outpatient appointments and at least one inpatient appointment per year (Table 5 in the CS)." The company considers this statement to be inaccurate. | Amend the statement to clarify that the >5 outpatient and ≥1 inpatient visits per year were used as a proxy to categorise patients into NAC and AC groups, rather than as a definition of NAC HypoPT. | The company did not define NAC HypoPT as having more than 5 outpatient appointments and at least one inpatient appointment per year. Rather, these thresholds were used to categorise patients within the CPRD dataset in a way that reflects clinical differentiation between NAC and AC HypoPT, based on feedback from clinical experts. The intention was to align the data categorisation with real-world clinical patterns, not to create a strict operational definition of NAC. Updating the wording would more accurately | This section has been amended to clarify that appointments were used as a proxy for NAC. |

| | | | |
|---|---|---|---|
| | | reflect the purpose and context of the analysis. | |
| In section 2.3.3 (page 30), the EAG states: 'The EAG found that the company focused on outcomes related to the maintenance of calcium levels, and reduction of calcium treatments (which don't necessarily indicate an improvement in disease control) rather than change in physical and cognitive outcomes.' While physical and cognitive outcomes were not primary outcomes, these changes were still considered in the CS section 2.6.2 for weeks 26 and 52. Therefore, the company considers this statement to be factually incorrect. | Please amend this statement to acknowledge efforts were made to include changes and results of both physical and cognitive outcomes within the CS as well as the other primary outcomes relating to the maintenance of calcium levels. | Correcting this statement ensures an accurate representation of the evidence submitted by the company. It prevents the undervaluing or overlooking of physical and cognitive outcome data, which are clinically important for understanding the full impact of treatment on patient quality of life. | Not a factual inaccuracy.<br><br>The EAG is simply making the point that the maintenance of calcium levels, and reduction of calcium treatments were the primary outcomes, rather than actual physical or cognitive symptoms. |
| In Section 3.2 (page 35), the EAG states: "The CS focussed on PaTHway, | Amend the statement to reflect that PaTHway was the pivotal Phase 3 trial used to support | While the PaTHway trial did include a longer blinded phase than PaTH Forward, it was also | Sentence ending amended to …. given that it was the pivotal |

| | | | |
|---|---|---|---|
| given that its blinded phase was much longer than PaTH Forward's." The company believes this statement is missing important context. | regulatory approval and the primary evidence base for the CS, not solely because of its longer blinded phase. | selected as the focus of the company submission because it is the pivotal Phase 3 study supporting marketing authorisation for palopegteriparatide. As such, it was designed and powered to demonstrate the efficacy and safety of the intervention and represents the most robust and relevant clinical evidence available. Including this rationale would provide a more accurate explanation for its central role in the CS. | Phase 3 study supporting marketing authorisation. |
| In section 3.2.2 page 40, the EAG states: 'Results for cardiovascular outcomes were not presented in the main submission document, the appendices, nor the CSR. The EAG accessed the full CSR tables from the EMA's clinical data website and found there to have been one ≥grade 3 cardiac arrest in the palopeg arm and no | Please remove statement 'Results for cardiovascular outcomes were not presented in the main submission document, the appendices, nor the CSR.' | As stated in the CS section 2.10.1 page 69: 'One death of a 74-year-old male with multiple cardiac risk factors occurred during the blinded period of the trial in the palopegteriparatide group due to cardiac arrest' Therefore updating or removing the wording would accurately capture what was included within the CS. | Not a factual inaccuracy.<br><br>Information on one cardiac adverse event in the submission's adverse events section is not presentation of results on the separate scope outcome of "cardiovascular outcomes". |

| | | | |
|---|---|---|---|
| cardiac disorders events in the placebo arm'. Company considers this statement to be factually inaccurate as there is mention of this in the CS | | | |
| In Section 2.2.1 (page 50), the EAG states: "A fundamental assumption in the company's model is that all patients receiving palopeg are assumed to be in the AC state, whereas all patients receiving CT are assumed to be in the NAC state. This assumption is important because the NAC health state is associated with substantially worse outcomes, not only in terms of HRQL, but also higher complication rates, AE rates, mortality, and increased healthcare resource utilisation". The company believes this | Amend the statement to clarify that patients receiving CT are assumed to be in the NAC state because this reflects the target population for palopegteriparatide, consistent with clinical expert input and trial inclusion criteria. | The assumption that patients receiving CT are in the NAC health state reflects the intended use and positioning of palopegteriparatide, which is targeted at patients whose disease is not adequately controlled with conventional therapy. This is consistent with both the clinical expert feedback used to inform model development and the inclusion criteria of the PaTHway trial, which enrolled patients with persistent disease burden despite standard treatment. Clarifying this context would help ensure accurate interpretation of the model structure and assumptions. | Not a factual error.<br>This is an accurate description of the model assumptions. |

| | | | |
|---|---|---|---|
| statement lacks important context. | | | |

**Typographical errors**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG Response |
|---|---|---|---|
| Section 1.1, Table 1 (page 10): Typographical error | Please amend “not attributable to HypotPT” to “not attributable to HypoPT” | Typographical error | Thank you for identifying these. All typographical errors have been corrected. |
| Section 1.4 Issue 6 (page 16): Typographical error | Please amend “Removing morality benefits” to “Removing mortality benefits” | Typographical error | Amended as suggested |
| Section 2.2.2, page 24: Typographical error | Please amend “they needed to be interpretated” to “they needed to be interpreted” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 31): Typographical error | Please amend “indicators of poor diease control” to “indicators of poor disease control” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 31): Typographical error | Please amend “the manufactering of all strengths” to “the manufacturing of all strengths” | Typographical error | Amended as suggested |

| | | | |
|---|---|---|---|
| Section 2.3.4, Table 6 (page 31): Typographical error | Please amend “exclusion of magenesium supplements” to “exclusion of magnesium supplements” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 31): Typographical error | Please amend “teriparatide and recombinanat parathyroid hormone” to “teriparatide and recombinant parathyroid hormone” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 31): Typographical error | Please amend “thiazide diureticcs may be given” to “thiazide diuretics may be given” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 32): Typographical error | Please amend “could make it a viable as a second-line treatment” to “could make it viable as a second-line treatment” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 32): Typographical error | Please amend “reference case stipulates that the cost of effectiveness of treatments” to “reference case stipulates that the cost-effectiveness of treatments” | Typographical error | Amended as suggested |
| Section 2.3.4, Table 6 (page 33): Typographical error | Please amend “Some patients may require help adminstering palopeg” to “Some patients may require help administering palopeg” | Typographical error | Amended as suggested |

| | | | |
|---|---|---|---|
| Section 3.2.1.2, page 38: Repetition of words | Remove the duplicate of the word in the sentence “This suggests that that..” | Repetition | Now deleted |
| Section 4.1.4, page 47: Typographical error | Please amend “analyses assessing palplopeg” to “analyses assessing palopeg” | Typographical error | Amended as suggested |
| Section 4.2.3, page 53: Typographical error | Please amend “patients with chronic HypoPT who NAC on CT.” to “patients with chronic HypoPT who are NAC on CT.” | Typographical error | Amended as suggested |
| Section 4.2.4, page 54: Typographical error | Please amend “permits the use 3 alternative” to “permits the use of 3 alternative” | Typographical error | Amended as suggested |
| Section 4.2.4, page 55: Typographical error | Please remove extra space from following sentence “teriparatide, rhPTH, vitamin D analogues” | Typographical error | Amended as suggested |
| Section 4.2.6.5, page 60: Repetition of words | Please amend repetition of words “substantial numerical difference in hypocalcaemia and hypocalcaemia” | Repetition | Changed to hypercalcemia |
| Section 4.2.7.1, page 62: Typographical error | Please amend/remove mention of Table 31, as it is not linked to any content | Typographical error | This has been corrected |

| | | | |
|---|---|---|---|
| Section 4.2.7.2, page 63: Typographical error | Please amend “the EAG also requested the justify the use” to “the EAG also requested to justify the use” | Typographical error | Amended as suggested |
| Section 4.2.7.4, page 65: referencing error | Please correct the referencing error “Lin et al. (2020), {Lin, 2020 #298 | Referencing error | This has been corrected |
| Section 4.2.8.1, page 67: Typographical error | Please amend “no wastage of palopeg and an real dose intensity” to “no wastage of palopeg and a real dose intensity” | Typographical error | Amended as suggested |
| Section 4.2.8.1, page 67: Typographical error | Please reword the following sentence as it’s grammatically incorrect “Thereafter palopeg are assumed to be” to “Thereafter patients on palopeg are assumed to be” | Typographical error | This has been corrected. |
| Section 4.2.8.1, page 67: Typographical error | Please reword the following sentence as it’s grammatically incorrect “and no drug acquisition of administration costs are applied” to “and no drug acquisition or administration costs are applied” | Typographical error | This has been corrected. |
| Section 5.3, page 77: Typographical error | Please amend “several alternative scenario considering” to “several alternative scenario analyses considering” | Typographical error | Amended as suggested |

| | | | |
|---|---|---|---|
| Section 5.4.1.1, page 78: Typographical error | Please amend heading “Validation undertake by the EAG” to “Validation undertaken by the EAG” | Typographical error | Amended as suggested |
| Section 6.0, page 80: Typographical error | Please amend “These issues are identified and critiqued in Section 0.” to relevant Section number once updated | Typographical error | Corrected to the relevant section. |
| Section 6.3, page 85: Typographical error | Please amend “EAG’s preferred assumptions is presented in Table # below.” to relevant Table number once updated | Typographical error | Corrected to the relevant Table. |