Palopegteriparatide for treating chronic hypoparathyroidism

For screen, confidential information redacted

Technology appraisal committee A [7 October 2025]

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Company: Ascendis Pharma

Palopegteriparatide for treating chronic hypoparathyroidism

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

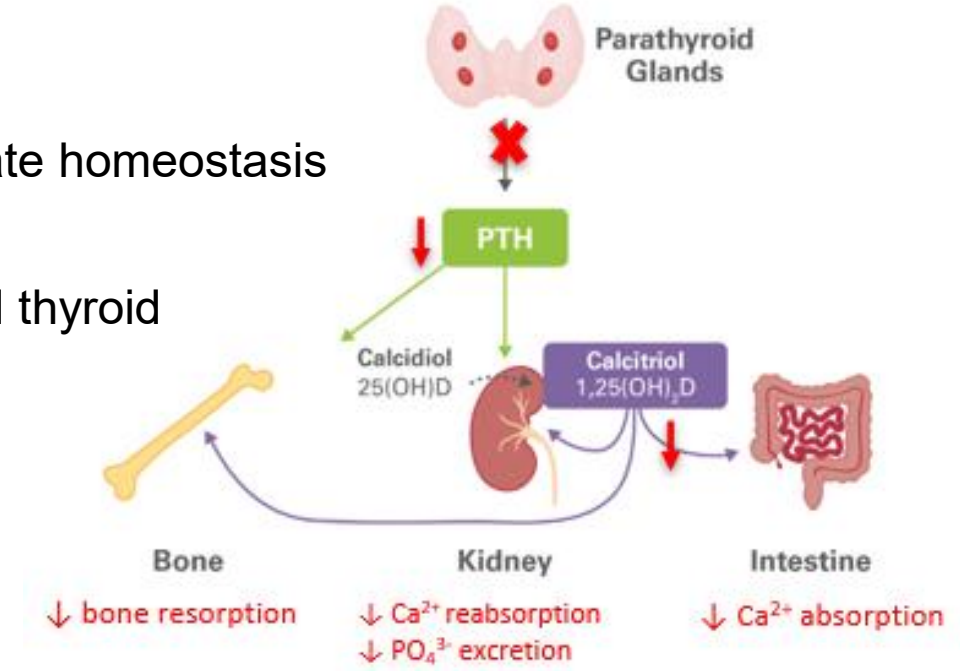
NICE National Institute for Health and Care Excellence

Chronic hypoparathyroidism (HypoPT) background

Overview + epidemiology

- Chronic HypoPT caused by insufficient parathyroid hormone
  - ↳ 75% post-surgical – accidental damage to parathyroid glands
  - ↳ 25% non-surgical – autoimmune, genetic, idiopathic
- Parathyroid hormone (+ vit. D) key regulator of calcium + phosphate homeostasis
- Estimated UK prevalence: 21 per 100,000
- Post-surgical aetiology more common in females due to increased thyroid disease risk; no sex difference in non-surgical aetiology

Mechanism of chronic HypoPT



Diagnosis + classification

- Diagnosed by lack of parathyroid hormone, or by hypocalcaemia
- ‘Chronic’ = persists longer than 6 months

Symptoms + complications

- Symptoms: can affect multiple organ systems, causing physical and cognitive symptoms including paraesthesia (‘pins + needles’), pain, muscle cramps, fatigue, brain fog, anxiety and depression
- Complications include hypocalcaemia, renal impairment, urinary tract infections, cardiovascular disease

NICE HypoPT, hypoparathyroidism.

Patient and clinical perspectives

Parathyroid UK

- Chronic HypoPT is a lifelong challenge to maintain calcium homeostasis and prevent life-threatening crises from developing
- Quality-of-life impact due to high symptom burden and unpredictability
- Caregiver burden – 24-hour care, severe cases require help with daily living
- Conventional treatment is inadequate – most patients have frequent symptoms + poor symptom control, and it can cause short- and long-term complications
- Palopeg. will make a significant difference to patients' lives and wellbeing

'My condition is unbearable, debilitating on every level of physical and mental well-being, unable to work, unable to socialise or function… causing endless health issues'

Clinical expert statements and NHS England

- Main aims of treatment include:
  - ↳ Maintain serum calcium in lower part of normal range
  - ↳ Reduce symptoms and improve quality of life
- Pathway of care not well defined and significant inter-individual variation in care
- No UK-specific guidelines – currently follow European and international guidelines
- More people likely to achieve biochemical and symptom control with palopeg. – meaning less difficult to manage 10 to 15% of cases with frequent emergency admissions with disturbances of calcium balance

'Offering palopeg. would be a step change and will be addressing an unmet need of this patient population'

Palopegteriparatide (Yorvipath®, Ascendis Pharma)

Marketing authorisation	• 'Parathyroid hormone replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism' • MHRA marketing authorisation granted April 2024
Mechanism of action	• Palopegteriparatide is a prodrug of parathyroid hormone, becomes active parathyroid hormone when exposed to physiological temperature and pH

Administration	• Once-daily subcutaneous administration
	• Recommended starting dose: 18 mcg once daily
	  ○ Dose adjustments in 3 mcg increments thereafter
	  ○ Dose range is 6 to 60 mcg per day

Price	• List price: £7,406 (for 2 pens, 28 days of treatment) • Annual cost: £96,278 (based on 13 packs per year) • A patient access scheme is available

Equality considerations

At scoping consultation, consultees highlighted the following equality considerations:

- Post-surgical HypoPT more common in women than men as women are more likely to have thyroidectomies because of increased risk of thyroid disease
- People with a learning disability, communication difficulty or a language barrier may have impaired access to treatment
- Pregnancy may prevent patients from accessing treatment

EAG:

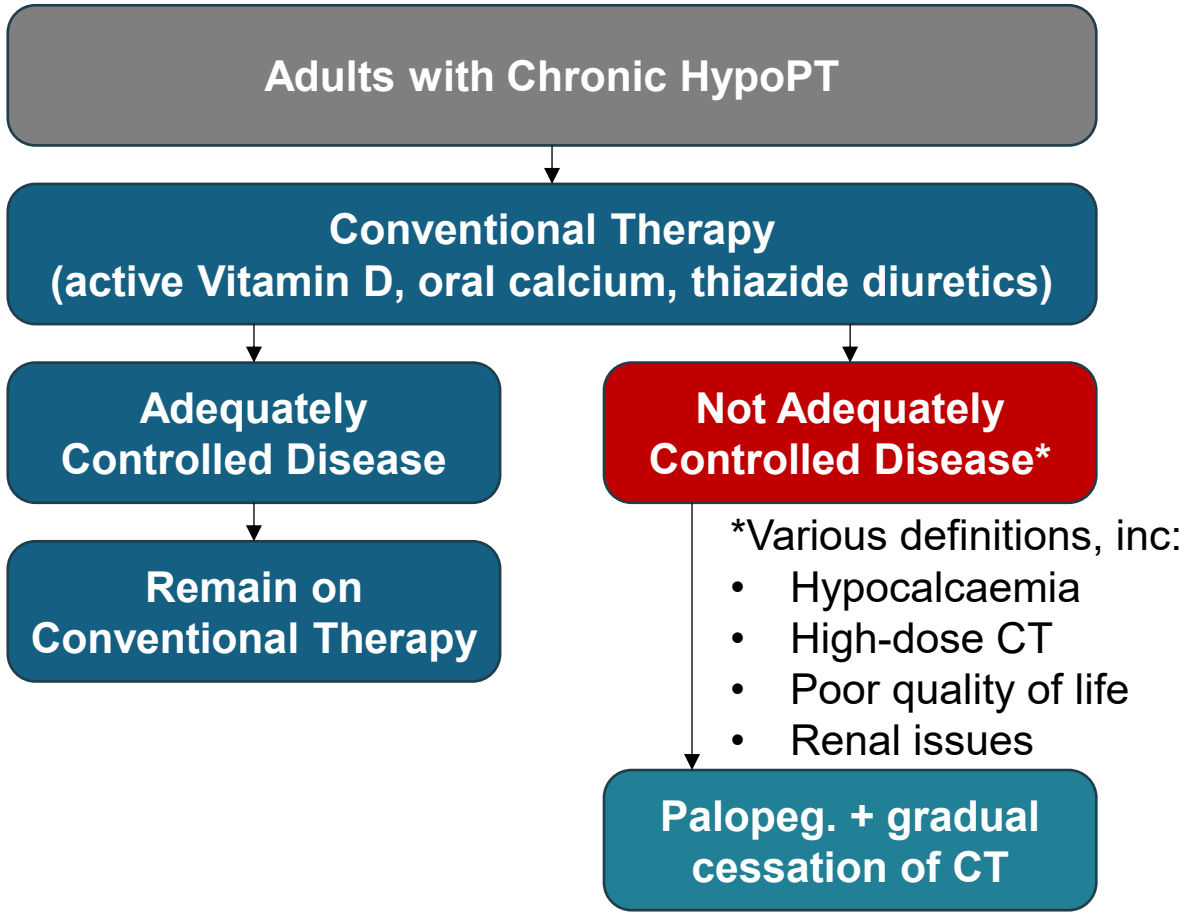
- Some patients may require help administering palopeg.
- Providing support would necessitate daily visits
  ↳ If this level of provision cannot be supported, it may raise important equity concerns, as it could exclude more vulnerable patients who would otherwise be eligible for treatment

Key issues

Issues	ICER impact
Decision problem issues	
Uncertain definition of the “Not Adequately Controlled” population	Unknown
Clinical effectiveness issues	
Primary outcome in PaTHway does not permit a fair comparison with conventional therapy	Unknown
Use of sub-optimal conventional therapy in the PaTHway trial	Unknown
Uncertainty in the patient-reported quality of life outcomes in PaTHway trial	Unknown
Cost-effectiveness issues	
Model structure	Unknown
Lack of direct evidence for complication and mortality benefits	Small
Non–reference case approach to healthcare resource use	Large
Modelling of healthcare resource use	Large
Modelling of adverse event rates and costs	Large
Analysis of utility values	Small
Drug wastage assumptions	Medium
Self-administration of palopeg.	Medium

NICE ICER, incremental cost-effectiveness ratio.

Treatment pathway



Palopeg. marketing authorisation:

'Indicated for the treatment of adults with chronic HypoPT'

Company submission population:

*'Adults with chronic HypoPT who are **not adequately controlled using conventional therapy**'*

Company rationale for optimisation:

- NAC subpopulation shows biggest clinical benefit and drives cost-effectiveness
- NAC subpopulation confirmed and validated by UK clinical experts

Clinical experts:

- What criteria would be used in the NHS to select people for palopeg.?
- What proportion of people in the NHS with chronic HypoPT would be eligible for palopeg.?
- Given some views on how calcium supplementation is bad for patients, would you want to use palopeg. in people who are adequately controlled with conventional therapy?

CT, conventional therapy; HypoPT, hypoparathyroidism; NAC, not adequately controlled.

Unknown ICER impact

Key issue: Decision problem population

EAG: 'Not adequately controlled' population is not well-defined, may be small minority of patients

Company's chosen definition at clarification – 'Second international workshop guidelines 2022' criteria:

Palopeg. should be considered for patients who are ***NAC on CT***

NAC considered to be any of:

- Symptomatic hypocalcaemia (per medical history)
- Hyperphosphataemia (>1.45 mmol/L)
- Renal insufficiency (<60 mL/min, renal stone, etc.)
- Hypercalciuria
- Poor quality of life (SF-36 <40)
- High dose of calcium ≥2000 mg daily

EAG:

- Agree with optimising the population to NAC, but uncertainties remain
- Various definitions of NAC population available in clinical practice + provided in the submission (appendix), unclear which would be used
- Clinical advice – patients can have well controlled HypoPT while meeting any one of the criteria opposite
- Size of eligible palopeg. population unclear – EAG clinical advice suggests only small % are NAC on conventional therapy

- Which set of criteria are most appropriate for defining the decision problem population?
- What proportion of people with chronic HypoPT would be eligible for palopeg. based on these criteria?

NICE

HypoPT, hypoparathyroidism; ICER, incremental cost-effectiveness ratio; NAC, not adequately controlled; SF-36, 36-item short form survey.

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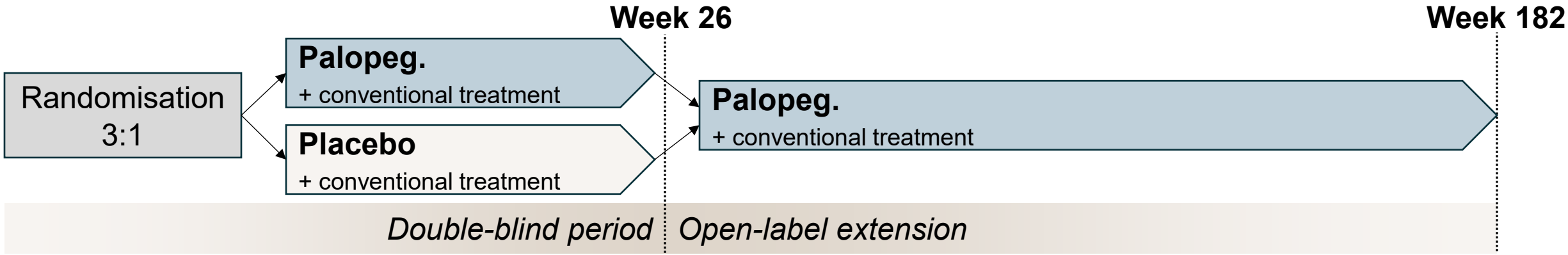
NICE National Institute for Health and Care Excellence

Key clinical trial – PaTHway – population

Design: Randomised, double-blind, placebo-controlled trial to week 26, followed by 156-week open-label extension



Key inclusion criteria:

- Adults with chronic (≥26 weeks) HypoPT – **did not need to be NAC**
- Had conventional treatment for ≥12 weeks, on stable dose for ≥5 weeks

Company: [redacted]% in trial met NAC definition*:

Criteria	Freq. n=82
Symptomatic hypocalcaemia	[redacted]
Hyperphosphataemia	[redacted]
Renal insufficiency	[redacted]
Hypercalciuria	[redacted]
Poor quality of life (SF-36)	[redacted]
High dose of calcium	[redacted]
Met any of the above	[redacted]

*'Second international workshop' criteria

EAG:

- Clinical advice – baseline calcium + vit. D doses in PaTHway mean that some people appear to be adequately controlled
- Reiterate issues with NAC criteria
- Consider trial population does not well represent NHS population that would have palopeg.

Does the population of PaTHway represent the population that would have palopeg. in the NHS?

NAC, not adequately controlled; SF-36, 36-item short form survey.

Unknown ICER impact

Key issue – PaTHway – primary outcome

More people met primary endpoint with palopeg. than placebo

Primary outcome: multi-component at week 26 – **all** of:

- Albumin adjusted serum calcium within normal range
- Independence from therapeutic doses of calcium (≤600 mg/day)
- Independence from active vitamin D
- No increase in trial drug within 4 weeks of week 26

EAG: Primary outcome of PaTHway does not permit a fair comparison between arms

- Independence from conventional therapy is not a plausible goal for conventional therapy
- Physical function and renal function are more relevant, but limitations with collection of these

	Palopeg. (N=61)	Placebo (N=21)
Met primary endpoint at Week 26, n (%) [95% CI]	**48 (78.7%)** [66.3 to 88.1] p<0.0001	**1 (4.8%)** [0.1 to 23.8]
Calcium within normal range	49 (80.3%)	10 (47.6%)
Independence from active vit. 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%)
Long-term outcomes, % (n/N)	**Palopeg.**	
Week 52, normal calcium + independence from CT	81% (63/78)	
Week 52, Independence from CT	95% (74/78)	
Week 104, independence from CT	97% (74/76)	

- Can the primary outcome from PaTHway be used to assess the comparative efficacy of palopeg.?
- What conclusions can be drawn about the comparative efficacy of palopeg.?

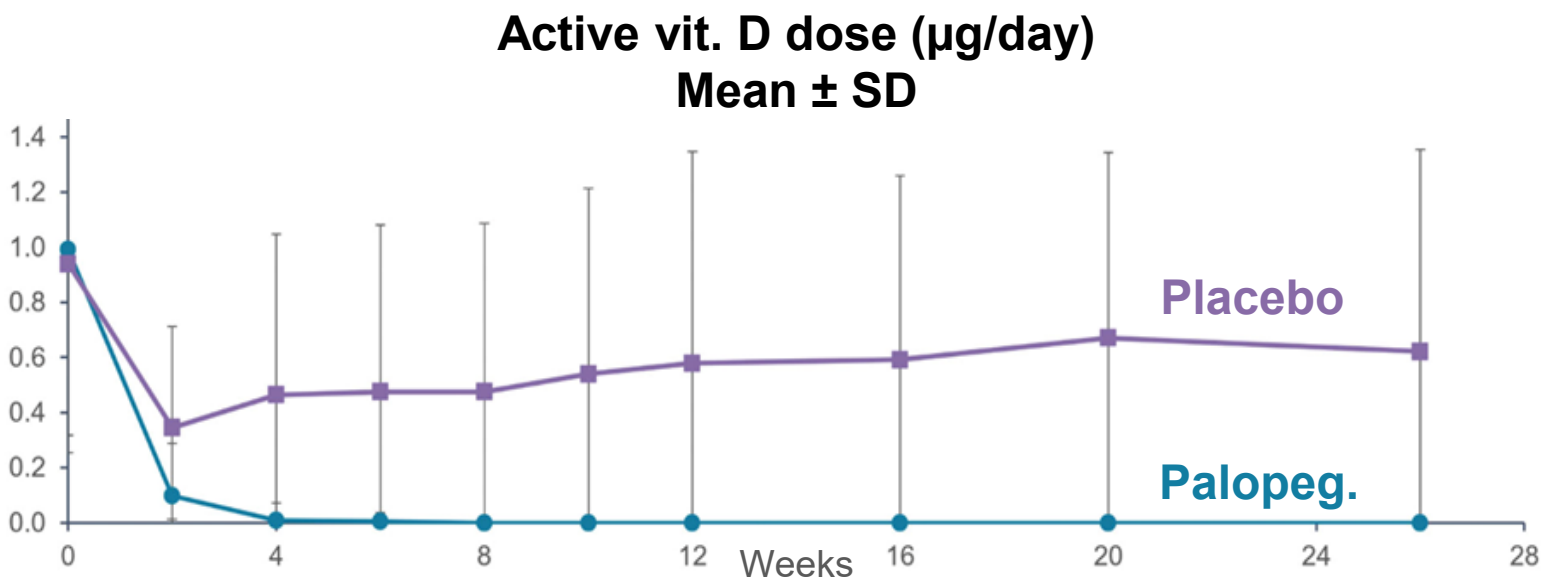
Unknown ICER impact

Key issue: Conventional therapy in PaTHway

EAG: clinical benefit of conventional therapy may be underestimated compared to NHS

Background

- Per protocol, all participants reduced active vitamin D dose by 33% to 50% at the start of the blinded treatment period (subsequent dose changes followed a titration algorithm)
- Thiazide diuretics had to be discontinued in trial run-in due to confounding of urinary calcium
- 13% had any history of thiazide*



EAG: Clinical advice – up to half of NAC patients would be offered thiazide diuretics in NHS

- Large mandatory reduction in vitamin D and the prohibition of thiazide diuretics in the trial means that the CT used will not have been as comprehensive and effective as the CT available in the NHS – so clinical benefit for CT and costs in the model will be underestimated

- What proportion of patients in the NHS use thiazide diuretics? What are your views on the effectiveness of thiazide? Would its use in the NHS mean conventional therapy would work better?
- Given that there was a protocol to reduce CT in PaTHway, was CT in PaTHway suboptimal? If so, how does this affect conclusions about the comparative efficacy of palopeg.?

*Captures any history of thiazide, not just people who discontinued in the run-in.

Unknown ICER impact

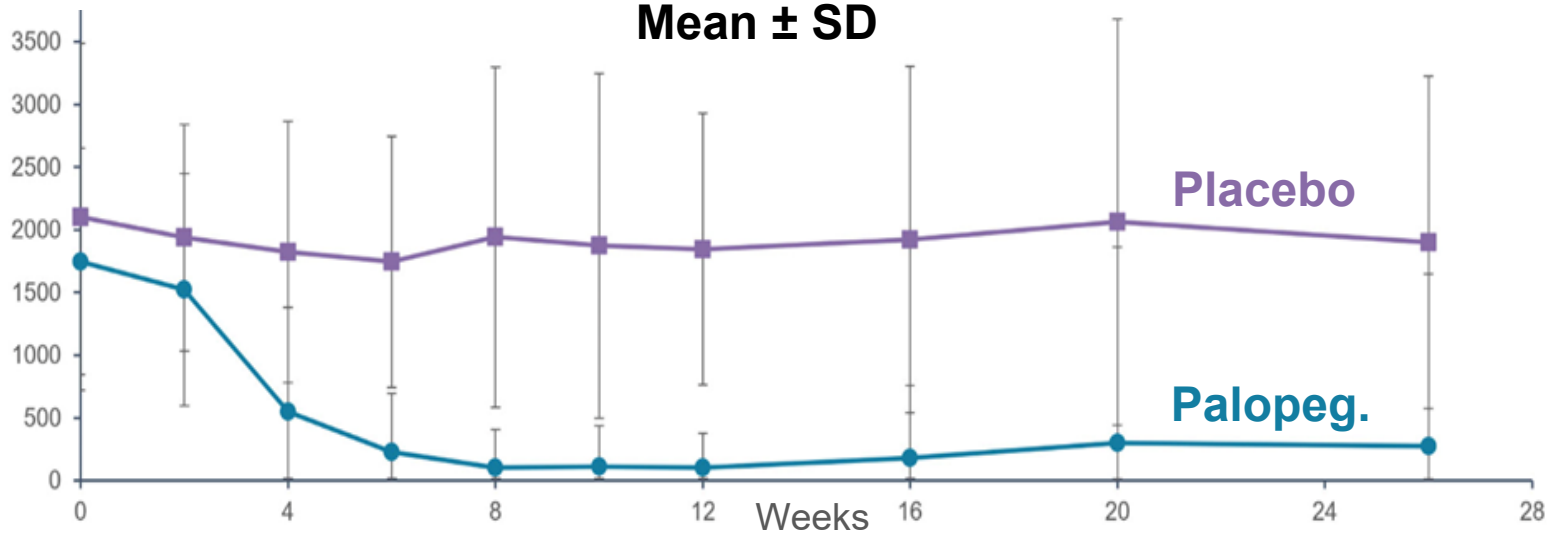
Key issue: Uncertainty in patient-reported outcomes

EAG: 'Functional unblinding' may have biased patient-reported outcomes

EAG

- Calcium monitored every 2 to 4 weeks during blinded period – titrated using algorithm
- Large differences in vit. D and calcium use between arms
- Likely some 'functional unblinding' – where patients know which treatment they are on – leading to larger differences than expected in patient-reported outcomes – also mentioned in EMA assessment

PaTHway calcium dose (mg/day)
Mean ± SD



PaTHway EQ-5D results

EQ-5D	Palopeg. (n=61)	Placebo (n=21)
Baseline Mean (SD)	[redacted]	[redacted]
Baseline Median (Min, Max)	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Median change from baseline (Min, Max)	[redacted]	[redacted]

To what extent is functional unblinding likely to have biased patient-reported outcomes?

EMA, European Medicines Agency; EQ-5D, EuroQol 5-dimension; ICER, incremental cost-effectiveness ratio; SD, standard deviation.

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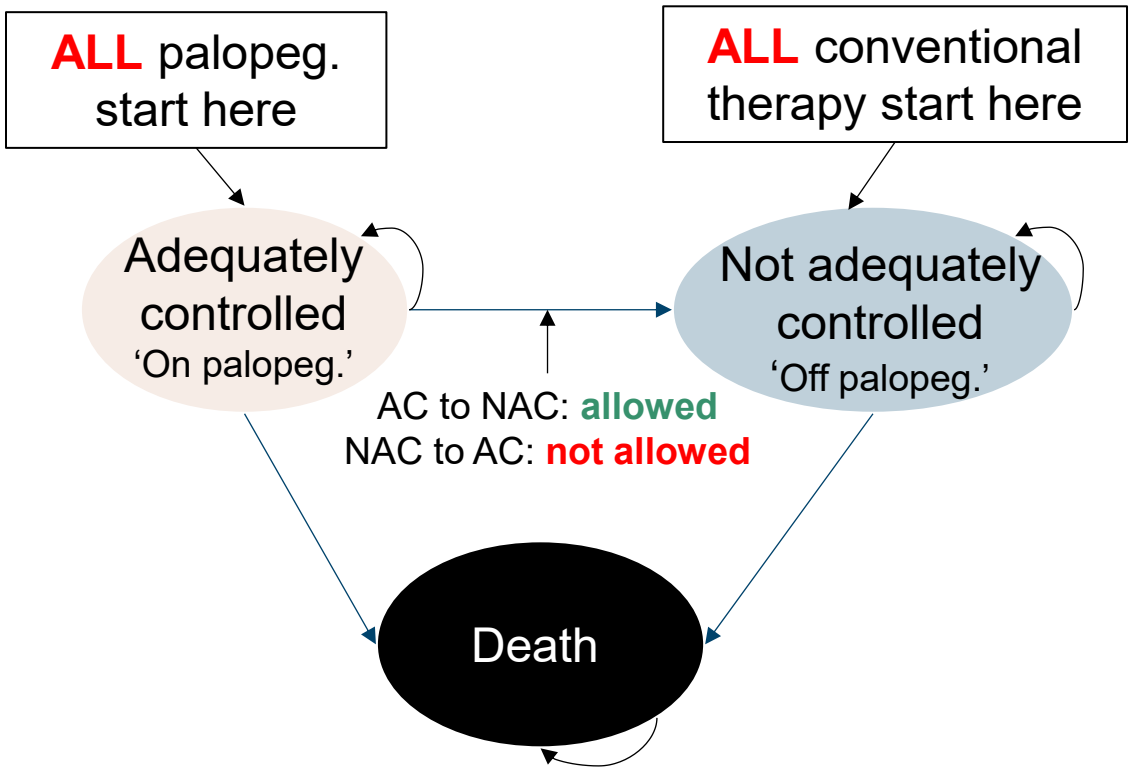
Company's model overview

3-state on/off treatment model



- Linked event-based sub-model captures long-term complications
- Hypo- and hypercalcaemia modelled separately

Palopeg. affects *costs* by:

- Increasing drug acquisition costs
- Reducing AE rates and associated costs
- Reducing healthcare resource use

Palopeg. affects *QALYs* by:

- Improved health-related quality of life
- Reduced complication rates
- Improved survival

Assumptions that *most* affect the ICER:

- AE rates modelled
- Source of AE costs
- Inclusion of health state costs
- How health states costs are estimated and the mix of surgical and non-surgical patients

AC, adequately controlled; AE, adverse event; ICER, incremental cost-effectiveness ratio; NAC, not adequately controlled; QALY, quality-adjusted life year.

Unknown ICER impact

Key issue: Model structure

EAG: Model structure valid for decision making but suggests alternative approach

EAG

- Health states defined by treatment received rather than a clinical endpoint – conceptually weak foundation
- Outcomes not linked to primary outcome or other clinical outcomes in trial – instead treatment effect based on differences in health-related quality of life (EQ-5D) between palopeg and CT arms of PaTHway
- Suggests alternative: response-based model based on PaTHway primary outcome – but rejected by company

- Model assumes **all** palopeg. patients are AC and **all** CT patients are NAC
- Assumption may not be appropriate:
  - ↳ Not clear if all CT patients are clearly NAC
  - ↳ Normal calcium at 26 weeks in PaTHway:
    - Palopeg. = 80%
    - CT = 48%

  Suggests some palopeg. patients are *not* AC, and some CT patients are *not* NAC

  - ↳ Some CT patients may become adequately controlled over time, but model does not permit this
    - One person in CT arm of PaTHway (5%) met primary outcome

Company: On/off model better reflects real-world; response-based model would underestimate benefits

- Assumption that all CT patients are NAC reflects model's target population and aligns with clinical input
- Spontaneous recovery on CT is rare, typically limited to acute cases + not representative of chronic NAC

- Is the model structure suitable for decision-making?
- Would a response-based model be more suitable?

AC, adequately controlled; CT, conventional therapy; ICER, incremental cost-effectiveness ratio; EQ-5D, EuroQol 5-dimensions; NAC, not adequately controlled.

Key issue: Company's CPRD analysis (1/3)

Company uses CPRD analysis to generate key model inputs

Company

- Real-world CPRD analysis used to inform several model inputs
- As CPRD lacks direct clinical measures such as serum calcium levels or medication dosing, disease control was inferred from patterns of NHS activity (below) and verified by clinical input
- The following definitions were applied to people with chronic HypoPT in CPRD to differentiate AC from NAC:

AC: ≤5 outpatient visits and <1 inpatient admissions per patient per year

NAC: >5 outpatient visits and ≥1 inpatient admission per patient per year

- This was to produce key inputs for the model:

Mortality	Complications	Health state costs
AC hazard ratio = [redacted] NAC hazard ratio = [redacted] (vs. general population) **Survival benefit for palopeg.**	See appendix for summary of complications risks **Lower risk of all complications with palopeg.**	AC = [redacted]/cycle NAC = [redacted]/cycle **Significant resource use cost-savings for palopeg.**

Are the company's definitions for differentiating between AC and NAC in the CPRD appropriate?

AC, adequately controlled; CPRD, Clinical Practice Research Datalink; CT, conventional therapy; HypoPT, hypoparathyroidism; NAC, not adequately controlled.

Small ICER impact

Key issue: CPRD analysis – complications + mortality (2/3)

EAG assume no benefit of palopeg on survival or risk of complications

Company

Mortality

AC hazard ratio = [redacted]
NAC hazard ratio = [redacted]
(vs. general population)

Survival benefit for palopeg.

Appendix – effect of mortality assumptions on life expectancy

Complications

See appendix for summary of complications risks

Lower risk of all complications with palopeg.

EAG

- Company cites biological plausibility as justification for benefits
- EAG accepts biological rationale + agrees that improved disease control may lead to downstream benefits – **but no empirical evidence** provided to quantify these effects
- Surrogate relationships between resource use and mortality + complications require strong justification
- Excess mortality calculated from CPRD appears substantially overstated and inconsistent with values reported in literature

Preferred assumption: no benefit of palopeg. on mortality or risk of complications

↳ Equalise mortality by applying published HR of 2.89 to both arms
↳ Set risk of complications to zero for both health states

Clinical advice: Long-term, palopeg. may reduce complications, particularly renal

- Are the inputs for mortality and rate of complications generated by the CPRD analysis appropriate?
- Are these inputs plausible?
- In the absence of direct evidence, is biological plausibility sufficient to infer these benefits to mortality and complications for palopeg.?

Large ICER impact

Key issue: CPRD analysis – resource use (3/3)

EAG remove all health state costs

Company

Health state costs

AC = [redacted]/cycle (28 days)
NAC = [redacted]/cycle (28 days)

Significant resource use cost-savings for palopeg.

- Are the health state costs estimated by the CPRD analysis plausible?
- Should differential health state costs be included in the model using the company's CPRD analysis?
  - ↳ If yes, should the costs be reweighted to align with the proportion of post-surgical patients in PaTHway?

EAG

- Major concerns about approach to modelling health state costs
- Cost saving predicted by model not supported by compelling empirical evidence, and is major driver of cost effectiveness
- Health state costs derived through circular reasoning – resource use used to stratify AC/NAC, then this stratification used to infer relationship between resource use and disease severity
- CPRD data will also capture resource use unrelated to chronic HypoPT – not aligned with NICE reference case
- Furthermore, aetiology of CPRD cohort is mostly non-surgical (77%), whereas in real-world most are post-surgical in line with PaTHway (85%) – important distinction for health state costs
  - EAG presents a scenario that reweights the health state costs to align with the aetiology mix in PaTHway

Preferred assumption: removes health state costs for both arms due to absence of evidence to inform these

AC, adequately controlled; CPRD, Clinical Practice Research Datalink; HypoPT, hypoparathyroidism; ICER, incremental cost-effectiveness ratio; NAC, not adequately controlled.

Large ICER impact

Key issue: Modelling of adverse events

Company and EAG disagree on what grade of AEs should be modelled and how to cost them

Company

- Hypercalcaemia + hypocalcaemia modelled as AEs
- AE rate calculated from PaTHway, using **any grade** AEs
  - ↳ Any grade AEs are a better estimate of frequency of calcium abnormalities, even if they do not reach grade 3/4 severity
  - ↳ Reduced monitoring in real-world versus trial – with reduced monitoring, more likely to experience hyper- and hypocalcaemia
- Cost used – NHS cost for hospitalisation for heart failure
- Provide scenario after EAG report with cost from CPRD analysis

EAG

- Use **only** AEs that led to urgent care visits and/or hospitalisation (grade 3/4) – order of magnitude lower than company AE rate
- Company argument suggests that all grade 1/2 AEs will become grade 3/4 and incur hospitalisation costs – implausible
- Company use OLE data for palopeg. but not CT – inappropriate
- No real-world data presented to support the high frequency of AEs
- Cost used – assumes non-elective short stay

Company

Rate per model cycle	Palopeg.	CT
Hypercalcaemia	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]

Cost	Source
£3,315	**Base case:** 2010/11 NHS ref. costs for hospitalisation for heart failure (2025 inflated)
[redacted]	Scenario: CPRD analysis – inpatient admission for hypocalcaemia *Submitted after EAG report*

EAG

Rate per model cycle	Palopeg.	CT
Hypercalcaemia	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]

Cost	Source
£564	NHS ref. costs for Fluid or Electrolyte Disorders, assuming non-elective short admission

- How is significant hypocalcaemia managed in the NHS? Day case or short-stay? Length of admission?
- Is it appropriate to include any grade AEs or only grade 3/4? Which AE cost is more appropriate?

Small ICER impact

Key issue: Analysis of utility values

Company prefer ANCOVA to estimate utility values; EAG prefer MMRM

Background

- EQ-5D-5L data collected in PaTHway at baseline, and week 10, 20, 26
- Analysis of utility from PaTHway used to inform health state utility value in model

Company – prefer analysis of covariance (ANCOVA)

- ANCOVA compares baseline to week 26, **excludes** data collected at interim visits

↳ Important as treatment effect not fully realised for all patients at interim visits

↳ Including interim visits may introduce bias

EAG – prefer mixed model for repeated measures (MMRM)

- MMRM uses all available data, **including** data collected at interim visits (at weeks 10 and 20)

↳ Increases power and less prone to attrition bias

↳ PaTHway data show increase in EQ-5D by week 10 in line with values at week 26 (see appendix)

Health state utility values

Health state in model	ANCOVA (Company preferred)	MMRM (EAG preferred)
Adequately controlled	[redacted]	[redacted]
Not adequately controlled	[redacted]	[redacted]

Which analysis model does the committee think is more suitable – ANCOVA or MMRM?

ANCOVA, analysis of covariance; EQ-5D, EuroQol 5-dimension; ICER, incremental cost-effectiveness ratio; MMRM, mixed model for repeated measures.

Medium ICER impact

Key issue: Drug wastage

EAG prefer to include drug wastage when patients move between pens

Background
- Palopeg. is administered using prefilled multiuse pens, 3 pens available
- Starting dose typically 18 µg, can be titrated in 3 µg increments
- If dose exceeds 30 µg, must use combination of 2 pens

Palopeg. pens:
↳ Low-dose: 6, 9, 12 µg
↳ Mid-dose: 15, 18, 21 µg
↳ High-dose: 24, 27, 30 µg

Company
- Does not include wastage
- Applies relative dose intensity to palopeg. acquisition costs, using adherence rate from PaTHway ([redacted])

EAG: company assumptions underestimate palopeg. acquisition costs
- Wastage likely to occur when dose is up- or down-titrated to a different pen – which happened throughout PaTHway and long-term extension
- Does not think RDI should be applied: pens must be used within 14 days, so implausible that dose reductions or skipped doses would lead to lower costs

Preferred assumption: apply half a pack wastage when patients move between pens based on reported data on dose adjustments from PaTHway; set RDI to 100%

Clinical advice: Wastage could occur during initial period where dose is titrated

- Does wastage need to be included in the model? Is the EAG's approach to wastage appropriate?
- Should palopeg. acquisition costs be adjusted by RDI?

ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity.

Medium
ICER impact

Key issue: Self-administration of palopeg.

EAG apply admin cost to account for people who cannot self-administer palopeg.

Background

- Palopeg. is administered as a once-daily subcutaneous injection
- Company assumes that patients will be able to self-administer palopeg.

EAG

- Clinical advice – some patients will not be able to self-administer, e.g. older people, people with disabilities
- Past appraisals of self-administered subcutaneous treatments assumed admin costs for 10% of people (EAG cite 3 appraisals of monoclonal antibodies for migraine)

Preferred assumption: 10% of patients on palopeg. incur admin costs equal to daily nurse visit

↳ However, unclear whether NHS could provide this level of support

- What proportion of people would require daily assistance with administering palopeg.?
- Is it feasible that the NHS could provide this level of support?
  - If not, what equality implications could this have for this appraisal? (see slide 6)

NICE ICER, incremental cost-effectiveness ratio.

Summary of key company and EAG base case assumptions

Assumption	Company base case	EAG base case
Complication rates	Included – differential rates for palopeg. and CT (see appendix)	Excluded – complication rates set to 0
Mortality	Different risk for palopeg. and CT based on CPRD analysis: (vs. general population) AC hazard ratio = [redacted] NAC hazard ratio = [redacted]	Same risk applied for both treatments, based on literature: (vs. general population) AC hazard ratio = 2.89 NAC hazard ratio = 2.89
Health state costs	• AC = [redacted]/cycle • NAC = [redacted]/cycle	Removed from model
AE rates and costs	• AE rates based on any grade AE • AE cost based on hospitalisation for heart failure reference cost	• AE rates based on AEs that required urgent care and/or hospitalisation • AE cost based on short stay admission for fluid or electrolyte disorder
Utility analysis method	ANCOVA	MMRM
Drug wastage	• RDI as per trial ([redacted]) • No wastage	• No RDI adjustment • Include wastage due to changing pens
Admin costs	Excluded	Include admin costs for 10% patients
Conventional therapy treatment costs	As PaTHway (with mandatory reduction in vit. D and calcium)	As PaTHway baseline (i.e. assuming no reduction in vit. D and calcium)

Company base case results

After clarification

Deterministic incremental base case results

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
CT	[redacted]	[redacted]	[redacted]	-	-	-	
Palopeg.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,895

Probabilistic incremental base case results

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
CT	[redacted]	[redacted]	[redacted]	-	-	-	
Palopeg.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,217

NICE CT, conventional therapy; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

EAG base case results

In AE rates addendum

Deterministic incremental base case results

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
CT	[redacted]	[redacted]	[redacted]	-	-	-	
Palopeg.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£226,468

Probabilistic incremental base case results

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
CT	[redacted]	[redacted]	[redacted]	-	-	-	
Palopeg.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£227,450

NICE CT, conventional therapy; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Changes from company to EAG base case

No.	Scenario	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
	Company base case (deterministic)	[redacted]	[redacted]	**£19,895**
	EAG-corrected company base case	[redacted]	[redacted]	£17,578
1	Utility values analysis using MMRM	[redacted]	[redacted]	£19,915
2	Exclude complication rates	[redacted]	[redacted]	£18,287
3b	Use survival HR from literature (2.89 for both arms)	[redacted]	[redacted]	£15,486
4	Use AE rate that results in hospitalisation	[redacted]	[redacted]	£68,131
5	Alternative AE cost code	[redacted]	[redacted]	£56,252
6a	Set RDI to 100%	[redacted]	[redacted]	£22,686
6b	Include wastage based on trial dose band changes	[redacted]	[redacted]	£17,880
7	Set CT dosing costs to reflect PaTHway baseline	[redacted]	[redacted]	£15,445
8	eMIT costs for alfacalcidol instead of BNF	[redacted]	[redacted]	£18,166
9a	Remove health state costs	[redacted]	[redacted]	£88,738
10	Admin costs for 10% patients	[redacted]	[redacted]	£25,765
	EAG base case (deterministic) (1–10)	[redacted]	[redacted]	**£226,468**

Additional scenarios around EAG-corrected company base case

No.	Scenario	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
	Company base case (deterministic)	[redacted]	[redacted]	**£19,895**
	EAG-corrected company base case	[redacted]	[redacted]	**£17,578**
3a	No survival benefit (HR=[redacted] both arms)	[redacted]	[redacted]	£15,155
6c	Extrapolate wastage from last period over the model time horizon	[redacted]	[redacted]	£18,115
9b	Reweigh PS/NS health state maintenance costs to PaTHway trial	[redacted]	[redacted]	£30,109
9c	Alternative company weighting of PS/NS health state maintenance costs	[redacted]	[redacted]	£28,956
11	Company revised AE cost ([redacted])	[redacted]	[redacted]	£24,075

NICE AE, adverse event; ICER, incremental cost-effectiveness ratio; NS, not surgical; PS, post-surgical; QALY, quality-adjusted life-year.

Palopegteriparatide for treating chronic hypoparathyroidism

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Issues	ICER impact
Decision problem issues	
Uncertain definition of the “Not Adequately Controlled” population	Unknown
Clinical effectiveness issues	
Primary outcome in PaTHway does not permit a fair comparison with conventional therapy	Unknown
Use of sub-optimal conventional therapy in the PaTHway trial	Unknown
Uncertainty in the patient-reported quality of life outcomes in PaTHway trial	Unknown
Cost-effectiveness issues	
Model structure	Unknown
Lack of direct evidence for complication and mortality benefits	Small
Non–reference case approach to healthcare resource use	Large
Modelling of healthcare resource use	Large
Modelling of adverse event rates and costs	Large
Analysis of utility values	Small
Drug wastage assumptions	Medium
Self-administration of palopeg	Medium

NICE ICER, incremental cost-effectiveness ratio.

Decision-making slides (1/3)

Category	Key questions
Treatment pathway	Clinical experts: • What criteria would be used in the NHS to select people for palopeg.? • What proportion of people in the NHS with chronic HypoPT would be eligible for palopeg.? • Given some views on how calcium supplementation is bad for patients, would you want to use palopeg. in people who are adequately controlled with conventional therapy?
Population	• Which set of criteria are most appropriate for defining the decision problem population? • What proportion of people with chronic HypoPT would be eligible for palopeg. based on these criteria?
PaTHway trial	• Does the population of PaTHway represent the population that would have palopeg. in the NHS? • Can the primary outcome from PaTHway be used to assess the comparative efficacy of palopeg.? • What conclusions can be drawn about the comparative efficacy of palopeg.? • What proportion of patients in the NHS use thiazide diuretics? What are your views on the effectiveness of thiazide? Would use in the NHS mean conventional therapy would work better? • Given that there was a protocol to reduce CT in PaTHway, was CT in PaTHway suboptimal? If so, how does this affect conclusions about the comparative efficacy of palopeg.?

NICE HypoPT, hypoparathyroidism.

Decision-making slides (2/3)

Category	Key questions
PaTHway	To what extent is functional unblinding likely to have biased patient-reported outcomes?
Model structure	• Is the model structure suitable for decision-making? • Would a response-based model be more suitable?
CPRD analysis	• Are the company's definitions for differentiating between AC and NAC in the CPRD appropriate? • Are the inputs for mortality and rate of complications generated by the CPRD analysis appropriate? ↳ Are these inputs plausible? • In the absence of direct evidence, is biological plausibility sufficient to infer these benefits to mortality and complications for palopeg.? • Are the health state costs estimated by the CPRD analysis plausible? • Should differential health state costs be included in the model using the company's CPRD analysis? ↳ If yes, should the costs be reweighted to align with the proportion of post-surgical patients in PaTHway?
Adverse events	• How is significant hypocalcaemia managed in the NHS? Day case or short-stay? Length of admission? • Is it appropriate to include any grade AEs or only grade 3/4? Which cost is more appropriate?

AC, adequately controlled; AE, adverse event; CPRD, Clinical Practice Research Datalink; HypoPT, hypoparathyroidism; NAC, not adequately controlled.

Decision-making slides (3/3)

Category	Key questions
Utility values	• Which analysis model does the committee think is more suitable – analysis of covariance (ANCOVA) or mixed model for repeated measures (MMRM)?
Drug wastage	• Does wastage need to be included in the model? Is the EAG's approach to wastage appropriate? • Should palopeg. acquisition costs be adjusted by RDI?
Admin costs	• What proportion of people would require daily assistance with administering palopeg.? • Is it feasible that the NHS could provide this level of support? ○ If not, what equality implications could this have for this appraisal?
Other factors	• Are there any equality considerations that need to be accounted for? • Are there any benefits of palopeg. that are not captured in the QALY calculations? • Is there any uncertainty in the modelling that needs to be accounted for?
ICER threshold	What is the committee's preferred ICER threshold?
Preferred ICER	What is the committee's preferred ICER?

NICE

ANCOVA, analysis of covariance; ICER, incremental cost-effectiveness ratio; MMRM, mixed model for repeated measures; QALY, quality-adjusted life-year RDI, relative dose intensity.

Supplementary appendix

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Patient perspectives

Submissions from Parathyroid UK

- Living with HypoPT is a lifelong challenge due to the constant need to maintain calcium homeostasis and prevent a life-threatening crisis
- Despite treatment with conventional therapy, most patients continue to experience frequent symptoms, poor symptom control and a subsequent compromised QoL.
- 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.
- Current treatment is inadequate and causes long and short-term complications. Patients are dissatisfied with their treatment regime.

"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."

"Exhausting and unpredictable - you have to consider calcium every day and in absolutely everything you do."

NICE HypoPT, hypoparathyroidism; QoL, quality of life.

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Target population definitions

"UK expert" definition + Chen (2019) ('consolidated definition' in company submission and addendum)	**"Second International Workshop" (2022)** (used in clarification response)	**European expert consensus (PARAT 2022)**	**Oral presentation of updated ESE guidelines, Joint Congress ESPE and ESE conference, May 2025**

Not adequately controlled defined as ANY of:
• High-dose conventional therapy:
  ○ Active vitamin D:
  ▪ Calcitriol ≥ 1.0 mcg/day
  ▪ Alfacalcidol ≥ 2.0 mcg/day
  ○ Calcium ≥ 2000 mg/day
• 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 <40)
• Documented renal insufficiency
• History of kidney stones (nephrolithiasis)
• eGFR < 60 mL/min/1.73m²
	Consider PTH replacement therapy in patients who are not adequately controlled on conventional therapy. Inadequate control is considered to be ANY of:
	• Symptomatic hypocalcaemia (per medical history)
	• Hyperphosphataemia (>1.45 mmol/L)
	• Renal insufficiency (<60 mL/min, renal stone, etc. as per criteria)
	• Hypercalciuria
	• Poor quality of life (SF-36 < 40)
	• High dose of calcium ≥2000 mg daily
		Consider PTH replacement in patients with:
		• Inadequate control of serum calcium levels;
		• Dose of elemental calcium exceeds 2.5 g per day or large amounts of active vitamin D analogues are needed
		• Hypercalciuria, kidney stones, nephrocalcinosis or impaired renal function;
		• Hyperphosphatemia and/or increased phosphocalcic product;
		• Disorders of the gastrointestinal tract associated with malabsorption;
		• Significantly reduced quality of life
			Consider 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 attributable to chronic HypoPT
			• Reduced kidney function (eGFR < 60 mL/min/1.73 m²)
			• Hypercalciuria
			• Hyperphosphatemia

CT, conventional therapy; eGFR, Estimated Glomerular Filtration Rate; ESE, European Society of Endocrinology; ESPE, European Society for Paediatric Endocrinology; HypoPT, hypoparathyroidism; PTH, parathyroid hormone; SF-36, 36-item short form survey.

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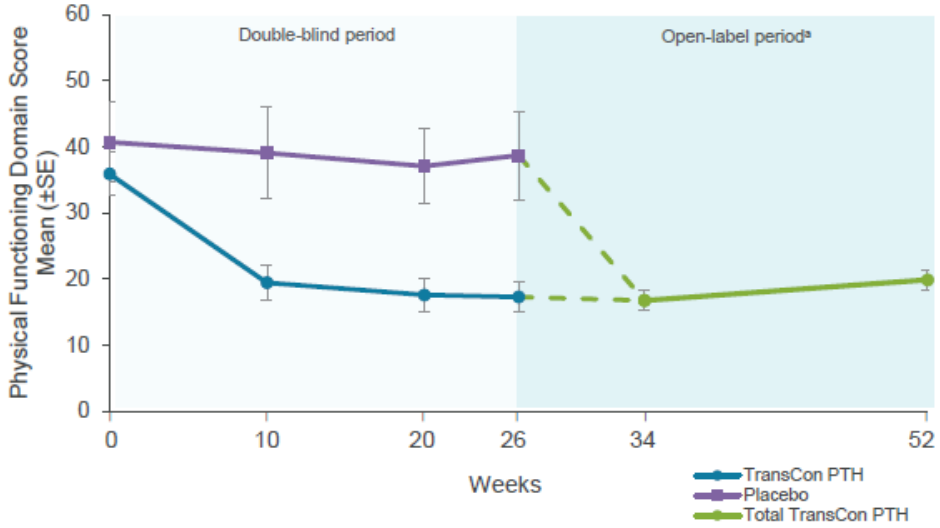
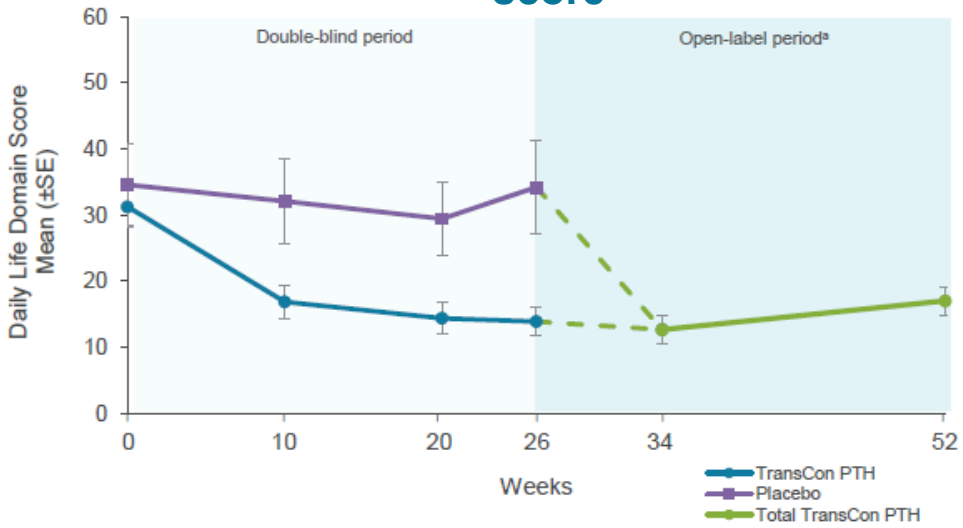
PaTHway outcomes – physical function

Physical functioning was captured as a secondary outcome by the disease-specific HPES and the generic SF-36

HPES-Impact Physical Functioning Domain score

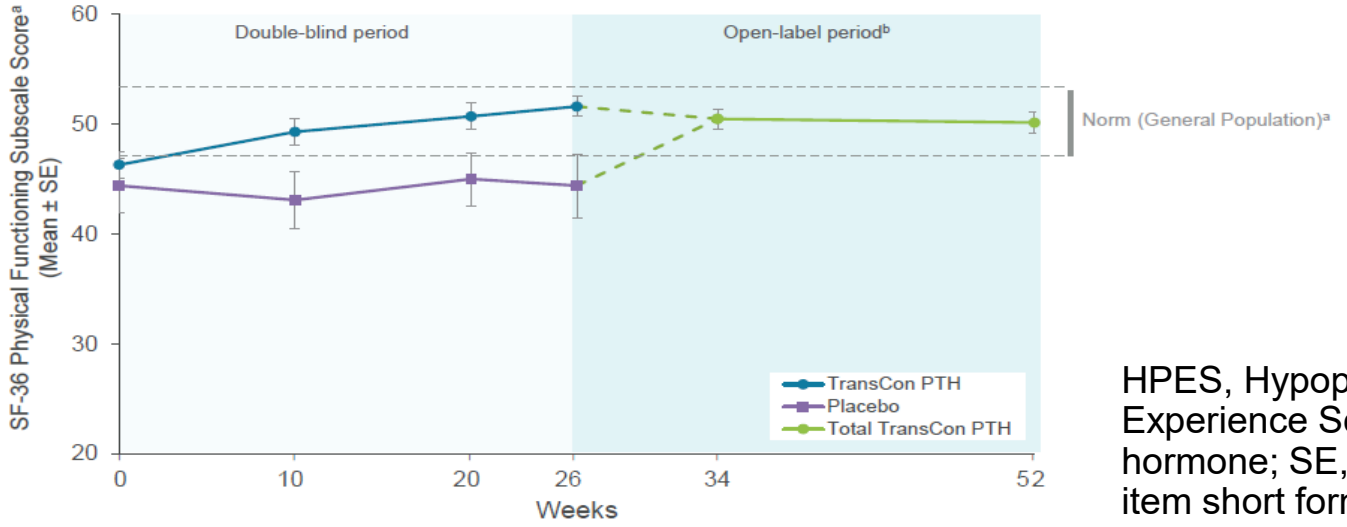


HPES-Impact Daily Life Domain score



Lower scores indicate better physical functioning

SF-36 physical functioning



Higher scores indicate better physical functioning

HPES, Hypoparathyroidism Patient Experience Scale; PTH, parathyroid hormone; SE, standard error; SF-36, 36-item short form survey.

NICE

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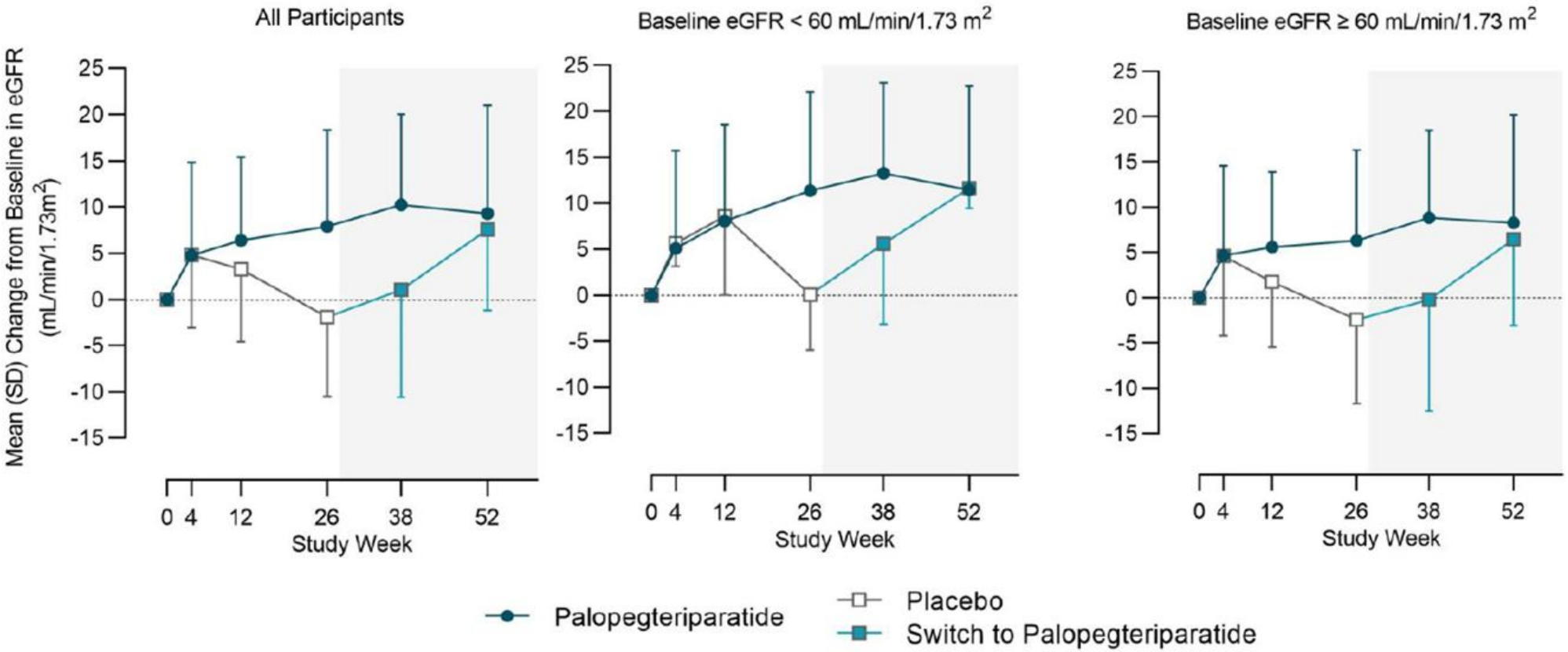
PaTHway outcomes – renal function

Renal function was captured as a post-hoc analysis



Higher eGFR indicates better renal function

NICE eGFR, Estimated Glomerular Filtration Rate; SD, standard deviation.

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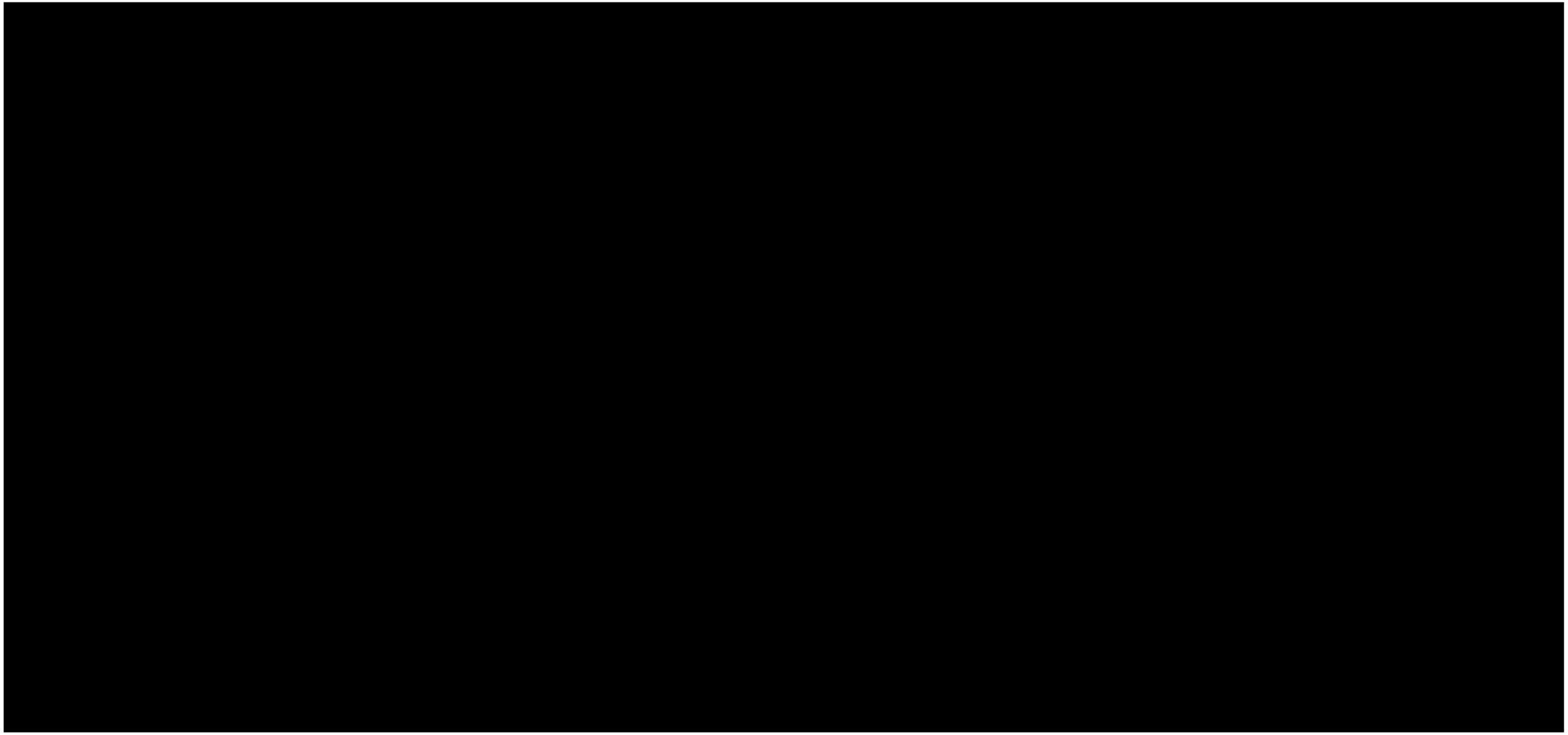
PaTHway titration algorithm



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PaTHway – change in EQ-5D over time

Visit	Palopegteriparatide arm			CT arm		
	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]
Week 10	61	55	[redacted]	19	16	[redacted]
Week 20	60	54	[redacted]	19	17	[redacted]
Week 26	60	59	[redacted]	19	19	[redacted]
Week 34	60	54	[redacted]	18	17	[redacted]
Week 52	59	57	[redacted]	18	18	[redacted]
Week 78	59	53	[redacted]	18	17	[redacted]
Week 104	58	56	[redacted]	18	18	[redacted]
Week 130	58	52	[redacted]	18	15	[redacted]
Week 156	54	54	[redacted]	17	17	[redacted]

Placebo patients switch to palopeg.

Mean EQ-5D in PaTHway

[redacted]

NICE CT, conventional therapy; EQ-5D, EuroQol 5-dimension; OLE, open-label extension; RCT, randomised controlled trial.

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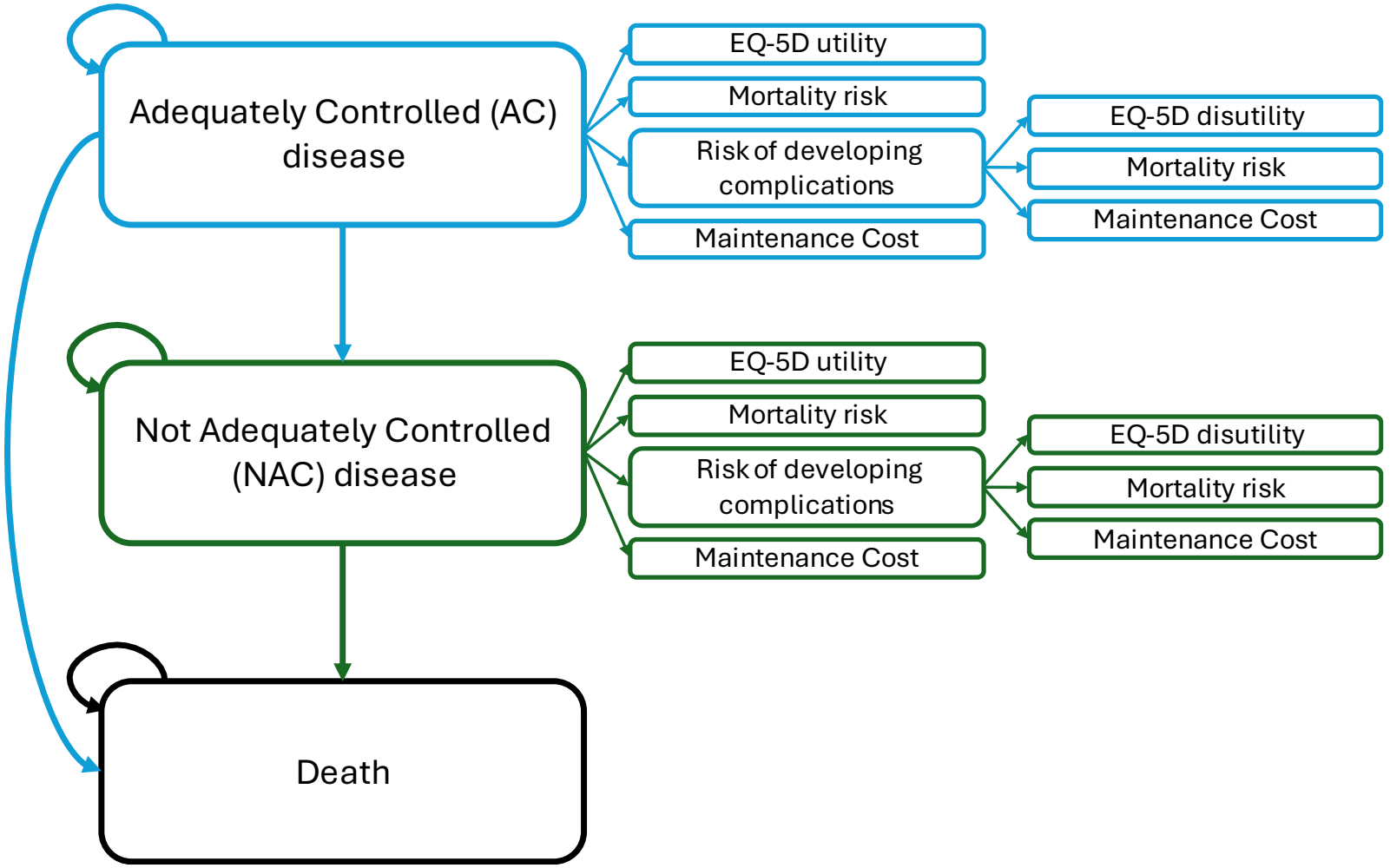
Model structure and linked sub-model



NICE EQ-5D, EuroQol 5-dimension.

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EAG: response-based model alternative

- 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
- Viable alternative would be to use the primary outcome as a measure of treatment response and define health states accordingly – although additional evidence supporting the validity of the primary outcome and its suitability for use in clinical practice would be useful
- 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.

NICE

CT, conventional therapy; EQ-5D, EuroQol 5-dimension; HypoPT, hypoparathyroidism; OLE, open-label extension; RCT, randomised controlled trial.

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Company's CPRD analysis

A retrospective, observational, real-world matched cohort study to investigate the epidemiology, direct healthcare economic burden and clinical burden of complications among patients with chronic HypoPT

Data source description	CPRD Aurum database: • Covers participating primary care practices in the UK (~19 million live patients) • Links with Hospital Episode Statistics, Death Registration data from ONS	
Patients included in analysis set	• Chronic HypoPT, total: [redacted] ↳ Post-surgical: [redacted] ↳ Non-surgical: [redacted] • Adequately controlled, total: [redacted] • Not adequately controlled, total: [redacted]	• Matched controls, total: [redacted] ↳ Post-surgical: [redacted] ↳ Non-surgical: [redacted] • Adequately controlled, total: [redacted] • Not adequately controlled, total: [redacted]

Source: Ascendis Pharma (2025). Retrospective analysis of healthcare resource utilization and cost associated with chronic hypoparathyroidism in England. (CPRD study). Version 8. Data on File.

NICE CPRD, Clinical Practice Research Datalink; HypoPT, hypoparathyroidism; ONS, Office for National Statistics.

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CPRD analysis – complications hazard ratios

Complication	AC vs General population	NAC vs General population
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]

NICE AC, adequately controlled; CPRD, Clinical Practice Research Datalink; NAC, not adequately controlled

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Company arguments for plausibility of benefits

- The modelled long-term benefits of palopeg. – reduced complications, increased life expectancy, and decreased healthcare resource use – are supported by mechanistic, clinical, and methodological reasoning
- (i) Biological rationale:
  - ↳ Palopeg. is a replacement therapy targeting the pathophysiology of HypoPT rather than 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
  - ↳ This addresses mechanisms responsible for long-term complications. So, reductions in complications, and improved survival and reduced healthcare resource use, are biologically plausible and expected.
- (ii) Supporting evidence for surrogate-outcome relationships:
  - ↳ Primary endpoint in PaTHway is surrogate of stable mineral balance and reduced treatment burden
  - ↳ Achievement of this endpoint is associated with reduced 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. The link between sustained biochemical control and reduced complication risk is further supported by expert consensus (Brandi 2016 [guideline]; Khan 2022 [PaTHway study])

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Mortality hazard ratios from literature

Study	Data source	Comparison	Mortality HR
CPRD analysis in company submission	CPRD (UK)	People with chronic HypoPT compared to matched controls Chronic HypoPT stratified into AC and NAC based on healthcare resource utilisation	AC = [redacted] NAC = [redacted]
Reddy et al. 2025 Sponsored by company	CPRD (UK)	People with **post-surgical** chronic hypoparathyroidism compared to matched controls	2.89
Vadiveloo et al. 2018	Primary care database (Scotland)	People with chronic HypoPT compared to matched controls	2.15

AC, adequately controlled; CPRD, Clinical Practice Research Datalink; HR, hazard ratio; HypoPT, hypoparathyroidism; NAC, not adequately controlled

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Effect of mortality assumptions on life expectancy

Model starting age: [redacted] years

If mortality hazard ratio = 1 vs. general population (i.e. no excess mortality due to chronic HypoPT):

- Median age of death: [redacted] years

If mortality hazard ratio = 2.89 vs. general population (EAG preferred, sourced from literature)

- Median age of death: [redacted] years

If mortality hazard ratio for AC = [redacted]; NAC = [redacted] (Company preferred, calculated from CPRD)

- Median age of death for palopeg. = [redacted] years
- Median age of death for CT = [redacted] years

NICE AC, adequately controlled; CPRD, Clinical Practice Research Datalink; NAC, not adequately controlled