Palopegteriparatide for treating chronic hypoparathyroidism

For Zoom – redacted

Technology appraisal committee A, 12 May 2026

Chair: James Fotheringham

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Company: Ascendis Pharma

Palopegteriparatide for treating chronic hypoparathyroidism

- ✓ **Recap from first appraisal committee meeting**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Chronic hypoparathyroidism (hypoPT) background

Overview and epidemiology

- Chronic hypoPT caused by insufficient parathyroid hormone
  - ↳ 75% **post-surgical** – removal or accidental damage to parathyroid glands
  - ↳ 25% **non-surgical** – autoimmune, genetic, idiopathic
- Parathyroid hormone (+ vitamin D) key regulator of calcium + phosphate homeostasis
- Estimated UK prevalence: 21 per 100,000
- Company-estimated population eligible for palopeg: [redacted]*

Diagnosis and classification

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

Symptoms and complications

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

European Society of Endocrinology guideline 2025

Recommended standard treatment:

- vitamin D
- calcium
- thiazide diuretics an option if hypercalciuria present

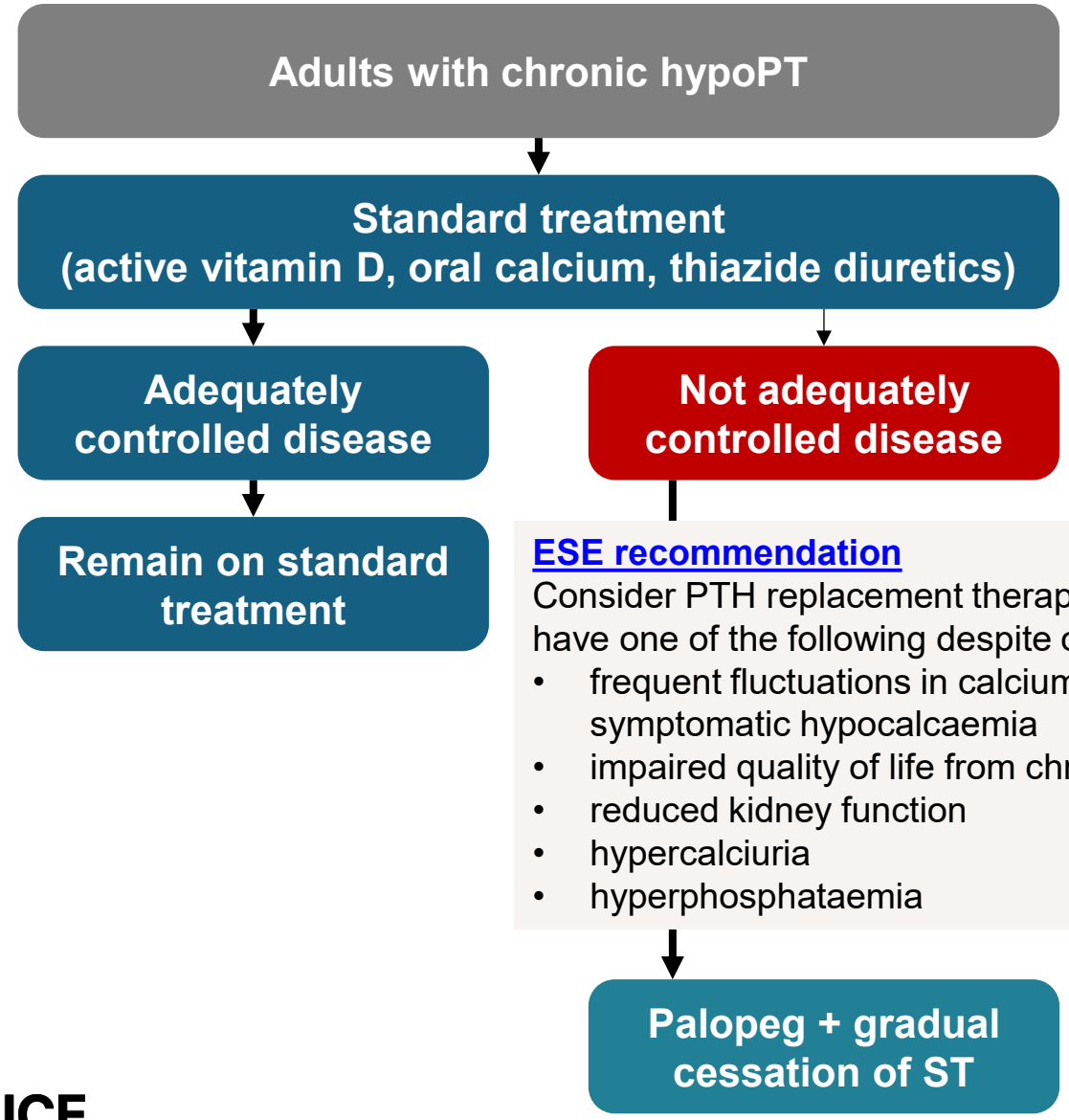
Treatment goals:

- optimise quality of life
- minimise symptoms of hypocalcaemia
- improve long-term prognosis
- maintain calcium levels within the lower part or slightly below the reference range

NICE

*Based on following definition of 'not adequately controlled': requiring a high dose of standard treatment, experiencing severe symptoms and/or high healthcare use, renal impairment or history of renal complications

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

Abbreviations: ST, standard treatment; ESE, European Society for Endocrinology; hypoPT, hypoparathyroidism; NAC, not adequately controlled; PTH, parathyroid hormone; ST, standard treatment

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

Draft guidance recommendation

Palopegteriparatide should not be used to treat chronic hypoPT in adults

Committee considered high level of uncertainty in **clinical evidence** from PaTHway trial, specifically:

- likely differences between trial and NHS population because trial did not need to meet the NAC criteria
- standard treatment in trial suboptimal and likely not as effective as standard treatment in the NHS because doses of calcium and vitamin D were reduced and thiazide diuretics were prohibited
- primary outcome did not allow fair comparison between palopeg and standard treatment – unlikely people on standard treatment (which includes calcium) could meet 'independence from therapeutic doses of calcium' component
- functional unblinding (when people can tell which treatment they are on) may have affected patient-reported outcomes because of greater reductions in calcium and vitamin D doses in palopeg arm

Committee considered high level of uncertainty in **cost effectiveness evidence** from model, specifically:

- model structure with health states defined by treatment used rather than a clinical outcome conceptually weak and biased against standard treatment
- most of modelled benefits on mortality, complications and lower resource use derived from CPRD analysis, which had major limitations
- appropriate cost of treating hypocalcaemia and hypercalcaemia adverse events not clear

Abbreviations: CPRD, Clinical Practice Research Datalink; hypoPT, hypoparathyroidism; NAC, not adequately controlled

Summary of analyses requested by committee at the first appraisal committee meeting

Analyses requested by committee	Completed by company?
Information on standard treatment in NHS from alternative evidence sources	No
Information on standard treatment in NHS from clinical expert opinion	Yes – Delphi panel
Standard-treatment arm in PaTHway adjusted to reflect standard treatment in the NHS	No
Scenario excluding 'independence from therapeutic doses of calcium' from PaTHway primary outcome and health-state definition used for the response-based model	No – company said no impact of scenario
Response-based model with AC/NAC states defined by PaTHway primary outcome	Yes
Utility values in model defined by response to treatment rather than treatment used	Yes – in later update
Evidence for mortality benefit of palopeg	No evidence available
Evidence for impact of palopeg on complications	No evidence available
More robust resource use costs, including a scenario based on resource use in PaTHway	Partially – some scenarios conducted
Additional evidence on rates and cost of hypocalcaemia and hypercalcaemia adverse events	Yes – Delphi panel and updated costs

Abbreviations: AC, adequately controlled; NAC, not adequately controlled

Committee's preferred model assumptions at first appraisal committee meeting

Committee's preferred assumptions	Implemented by company?
Use of palopeg restricted to NAC on standard treatment population as defined in the Second International Workshop 2022 guidelines	Partially – ESE have published updated guidelines, see key issue
Use MMRM approach to analyse utility values from PaTHway	Yes
Assume 100% relative dose intensity, and drug wastage because of changing pens when changing dose	Yes
Do not include administration costs associated with palopeg	Yes

Abbreviations: MMRM, mixed model repeated measures; NAC, not adequately controlled

Equality considerations

In draft guidance:

- Women, trans men and non-binary people registered female at birth may be at higher risk of post-surgical chronic hypoPT because of their greater risk of thyroid disease
- Pregnancy may preclude people from having palopeg
- People with learning disabilities may have impaired access to treatment

Because recommendation does not restrict access to treatment for some people over others, the committee agreed these were not potential equality issues

DG notes that palopeg is administered as a once daily subcutaneous injection – committee heard people unable to self-administer likely already get support taking standard treatment multiple times per day

Issues raised during consultation on draft guidance:

- HypoPT rare so limited specialist expertise; care quality varies regionally, leading to postcode inequality
- Women, trans men and non-binary people registered female at birth face particular disadvantage: hormonal changes during menstruation, perimenopause, and menopause can worsen calcium fluctuations and mental health distress
- Suggestion that access to parathyroid hormone replacement would standardise care and improve safety across all demographic groups

How should any equalities issues be taken into account in the committee's decision making?

Abbreviations: hypoPT, hypoparathyroidism

Remaining key issues

Issue	ICER impact
Effectiveness of standard treatment in NHS vs trial	Unknown
Primary outcome: independence from calcium endpoint	Unknown
Response-based economic model	Large
Resource use and definition of AC/NAC from CPRD	Large
Modelling of adverse events – rates	Large
Modelling of adverse events – costs	Medium

Abbreviations: AC, adequately controlled; CPRD, Clinical Practice Research Datalink; ICER, incremental cost effectiveness ratio; NAC, not adequately controlled

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Consultation comments

- 1 patient impact statement
- Responses from:
  - UK Renal Pharmacy Group
  - Society for Endocrinology
  - Parathyroid UK
- 21 responses submitted on the NICE website

Patient impact

Comments from patients and Parathyroid UK

The worst disease that robs you of your quality of life

- Draft guidance strongly contested – comments describe possibility of palopeg treatment restoring normal life, preventing further organ damage, and reducing healthcare burden
- One respondent able to access palopeg reported symptom resolution within weeks: improved mobility, no more pain or leg cramps, and normal sleep; other reports of transformative impact
- NHS resource use high without this treatment: frequent emergency admissions, ambulance calls, GP visits, blood tests, scans and renal monitoring
- Current guidance underestimates burden of disease, inadequacy of standard care and the physiological necessity of parathyroid hormone
- High burden even in ‘stable’ patients
- Risks leaving patients in an outdated, high-burden care model that perpetuates instability and preventable harm

Note: other stakeholder comments included on relevant slides later in presentation

Comments from professional groups

UK Renal Pharmacy Group and Society for Endocrinology

- Concern that committee may be overestimating the size of any future palopeg-treated cohort: rare condition and only a small, clinically defined subgroup would be eligible
  - multidisciplinary-based pathways could ensure appropriate access
  - significant unmet need for these people, whose condition is not controlled on standard therapy – denied an effective treatment
- Specific patients would benefit further:
  - recurrent hypocalcaemia after parathyroidectomy: need frequent, clinically risky IV calcium in hospital
  - significant kidney disease – thiazide diuretics less effective at low eGFR and often poorly tolerated
  - people who need very high doses of calcium and vitamin D could reduce calcium load; high calcium need increases risk of cardiovascular calcification – additional long-term harms

Note: other stakeholder comments included on relevant slides later in presentation

Abbreviations: eGFR, estimated glomerular filtration rate; IV, intravenous

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ESE and Second International Workshop guidelines

Definition of NAC population

People with chronic hypoPT that is not adequately controlled

Background: No consistent definition of NAC population used in NHS; committee conclusion at first committee meeting: satisfied that criteria suggested by company based on the Second International Workshop 2022 guidelines would be appropriate for determining eligibility for palopeg

Company draft guidance response

- Since first committee meeting, European Society of Endocrinology (ESE) has published a revised guideline on management of chronic hypoPT in adults
- Expected to become standard reference for determining suitability for palopeg – recommends PTH therapy for patients not adequately controlled on optimised standard treatment
- No fundamental change to the criteria for defining patients who are not adequately controlled on standard treatment so revised guidelines are not expected to affect the current evaluation

EAG critique: ESE guideline reasonable definition for palopeg eligibility. Differences from company definition are:

1) **impaired QoL**: ESE – attributable to chronic hypoPT; company SF-36 <40 (any cause)
2) **renal insufficiency**: ESE – reduced kidney function (low eGFR); company also includes 'history of renal insufficiency or kidney stones'

Society for Endocrinology and Parathyroid UK: PTH replacement therapy should be available if hypoPT not adequately controlled despite optimised care – in line with ESE

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Abbreviations: hypoPT, hypoparathyroidism; NAC, not adequately controlled; PTH, parathyroid hormone; QoL, quality of life; ST, standard treatment

Does committee agree that the ESE guideline would be suitable for determining eligibility for palopeg?

Effectiveness of standard treatment in NHS vs trial (1/2)

Background

- Committee concluded PaTHway trial design likely meant standard treatment in trial not as effective as in NHS – thiazide diuretics prohibited, vitamin D reduced; uncertainty about relative effectiveness of palopeg
- Asked company to adjust efficacy data to better reflect standard treatment in the NHS, including benefit of thiazide diuretics, informed by alternative evidence sources and clinical expert opinion

Company draft guidance response

- Expert clinical opinion sought via a formal Delphi panel exercise in response to committee request: provides robust clinical feedback and insight from experts actively treating patients
- PaTHway standard treatment considered to be representative of NHS care; trial restrictions on vitamin D and thiazide diuretics would have had little clinically meaningful impact on outcomes; thiazide diuretics not widely used
- Standard treatment arm not adjusted given the clinical input received and lack of evidence to inform any adjustment

EAG critique

- New evidence is based on clinical expert opinion – does not address fundamental concerns with PaTHway

Thiazide diuretics

- EAG's clinical adviser considered that many genuinely NAC patients would be offered thiazide diuretics
- In PaTHway, 13% with prior thiazide diuretic use – figure should be interpreted cautiously because average baseline calcium and active vitamin D doses suggest some in trial would likely be considered AC

Abbreviations: AC, adequately controlled; EAG, external assessment group; ICER, incremental cost effectiveness ratio; NAC, not adequately controlled

Effectiveness of standard treatment in NHS vs trial (2/2)

EAG critique (cont'd)

Reduced vitamin D and calcium doses

- Still concerned that reduced doses mandated by trial protocol (both arms had to reduce vitamin D by one-third to one-half at start of trial; calcium dose could vary but aim was to reduce therapeutic calcium to meet primary outcome) meant ST arm did not reflect NHS care
- Serum calcium levels worsened in ST arm during trial (down by 0.39 mg/dl at week 26); EMA had similar concerns (EPAR: '*standard care in the trial was potentially sub-optimal*')
- Patients enrolled into PaTHway had to have normal or near-normal serum calcium levels; but at week 26 only 48% in ST arm had normal levels of serum calcium; given that CS notes '*even mild deviations … can significantly impair neuromuscular and neurological function*', potential bias in favour of palopeg

Company: week 26 results for ST arm reflect expected clinical variability of hypoPT, not a trial limitation

Professional and patient groups

- Role of thiazide diuretics over emphasised – rarely effective in practice, often poorly tolerated, and carry electrolyte risks; recent NHS survey showed only ~6% of NHS patients with hypoPT use them routinely
- Standard treatment (calcium plus active vitamin D) can normalise serum calcium but is workaround, not true replacement; does not restore normal renal, skeletal, neurological physiology

Abbreviations: AC, adequately controlled; CS, company submission; EMA, European Medicines Agency; EPAR, European public assessment report; hypoPT, hypoparathyroidism; NAC, not adequately controlled; ST, standard treatment

Do the comments received change committee's conclusion at first committee meeting that standard treatment in PaTHway was suboptimal?

Primary outcome: independence from calcium endpoint

Background

- Committee concluded that trial primary outcome did not capture aspects of treatment important to patients
- Primary outcome was a composite, including independence from therapeutic doses of calcium
- Committee agreed that people on standard-treatment unlikely to be able to meet this part – asked company to provide analysis of clinical-effectiveness results from PaTHway excluding it

Company draft guidance response: excluding independence from calcium (and independence from both calcium and vitamin D) did not alter proportion meeting primary endpoint; no impact on cost effectiveness in response-based model

EAG critique

- EAG has not seen the results of company's analysis - limited evidence to support response
- Only outcome relevant to the standard treatment arm is serum calcium in normal range (80.3% palopeg, 47.6% standard treatment at 26 weeks in PaTHway)
- Independence from calcium and vitamin D surrogate outcome – does not demonstrate actual clinical benefit

Parathyroid UK: Calcium stability + independence from vit D/calcium is a major clinical milestone: translates into outcomes that patients identify as top priorities: fewer tablets and emergency visits and better quality of life

Does the information supplied reduce the uncertainty around whether the primary outcome can be used to assess the effectiveness of palopeg compared with standard care? What conclusions can be drawn about the comparative efficacy of palopeg?

Large ICER impact

Response-based economic model (1/2)

Background

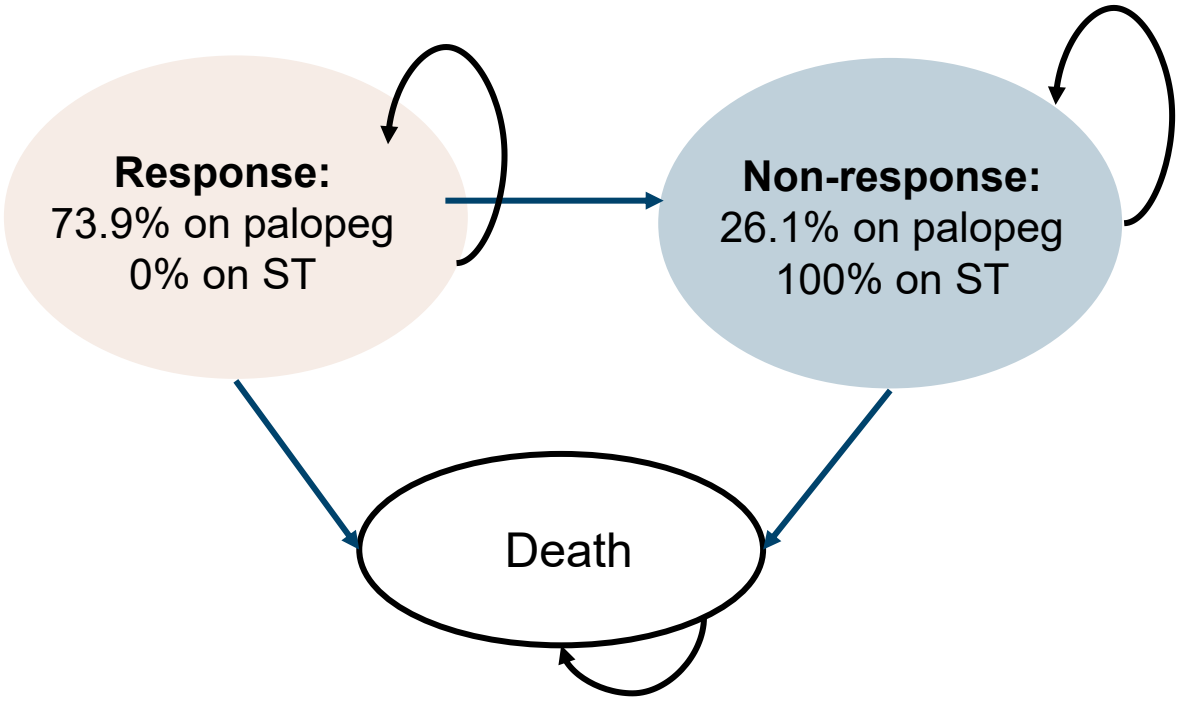
- Company's original model assumed everyone on palopeg was AC and everyone on standard treatment NAC; not possible to achieve AC if on standard treatment
- Committee requested response-based model using the primary outcome of PaTHway and utility values based on revised health states and MMRM approach

Company response

- Provided response-based model using primary endpoint to inform health states and utilities
- 1 person (4.8%) on ST met primary endpoint but was not included as a responder: argued that not biologically plausible to model a response in chronic NAC patients on ST - supported by Delphi Panel
- Response on ST likely due to recovery of residual parathyroid gland function (may occur after down titration of ST)
- Assumed 0 responders in ST arm and removed 4.8% from responders in palopeg arm

Updated model submitted 29 April and has not been fully critiqued by EAG

Updated company response-based model



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Abbreviations: AC, adequately controlled; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MMRM, mixed model repeated measures; NAC, not adequately controlled; ST, standard treatment

Large ICER impact

Response-based economic model (2/2)

EAG comments that still apply to the latest company model

- Company's response-based model does not reflect PaTHway trial: 1 out of 21 patients on standard treatment met primary endpoint, but company disregarded the observed evidence based on Delphi panel; EAG considers this inappropriate
- EAG's clinical advice suggests some people can reduce or stop standard treatment over time, supporting the trial evidence that response can happen with standard treatment
- People are classed as responders or non-responders at model start; does not reflect clinical practice, in which response would be assessed after 6 months – implies treatment benefits instant in responders
- Limited discussion of appropriateness and acceptability of the 6-month assessment period in trial
- EAG base case allows for response in the standard treatment arm
- Concern remains that PaTHway's design and composite endpoint do not allow a fair comparison of the interventions, even using response-based data in the model

Parathyroid UK: only minority have stable control on standard therapy; spontaneous recovery is not typical

Does the company's/EAG's response-based model reduce uncertainty in the modelling? Are they suitable for decision making?

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio

Resource use and definition of AC/NAC from CPRD (1/3)

Background

- Company used analysis of CPRD to inform model inputs, inc healthcare resource use and complications
- In absence of direct clinical measures in the CPRD, control of hypoPT (AC and NAC) was inferred from outpatient and inpatient visits and verified by clinical advice
- Committee considered CPRD generally reasonable source of resource use costs but definitions of NAC/AC based on resource use problematic – did not reflect patient experience, not supported by empirical evidence
- Requested more robust model inputs including a scenario using resource-use costs informed by PaTHway

Company draft guidance response

- Delphi panel supported using healthcare usage from CPRD as a clinically valid way to differentiate AC/NAC
- Revised (1) definition of NAC and (2) health state resource use costs to limit to disease-specific costs in line with NICE reference case (previously all-cause costs)
- Suggests updated analysis conservative because:
  - hypoPT-specific costing likely underestimates total burden as affects several organs
  - AC costs may be overestimated because some high-cost hypoPT cases now fall into the AC group
  - scenarios included all-cause costs and removal of hypoPT-related inpatient costs for AC patients (reflecting low expected complications with palopeg)
- Clinical experts said post-surgical/non-surgical status does not meaningfully affect resource use, once time since diagnosis is accounted for
- Resource-use estimates from PaTHway not considered appropriate as not representative of NHS

Abbreviations: AC, adequately controlled; CPRD, Clinical Practice Research Datalink; EAG, external assessment group; hypoPT, hypoparathyroidism; ICER, incremental cost-effectiveness ratio; NAC, not adequately controlled

Large ICER impact

Resource use and definition of AC/NAC from CPRD (2/3)

Society for Endocrinology

- Concerned that emergency and acute presentations related to hypo- and hypercalcaemia on standard therapy are under-recognised – HES coding does not reliably identify these presentations but expert clinicians observe these events occurring frequently in practice
- ~39% to 48% of UK patients with chronic hypoPT had at least 1 emergency department visit in past year
- ~16% had an unplanned hospital admission within 12 months
- Frequent emergency presentations and admissions for dyscalcaemia suggest current health economic models likely understate the true burden of standard care

Parathyroid UK: 2017 survey (n=230) found 45% of people required unplanned hospital visits to A&E, 38% needed intravenous calcium infusions, 22% admitted for an average of 3 days or more

Abbreviations: AC, adequately controlled; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; hypoPT, hypoparathyroidism; IP, inpatient; NAC, not adequately controlled; OP, outpatient

Company updated definition of AC/NAC used for CPRD analysis

Health state	Original	Updated (informed by Delphi panel)
AC	≤5 outpatient visits and <1 inpatient visit per patient per year	All patients without complications who do not meet definition of NAC
NAC	>5 outpatient visits and ≥1 inpatient visit per patient per year	≥1 inpatient visit per patient per year, with hypoPT as the primary or secondary diagnosis

CPRD population	Mean IP visits/year	Mean OP visits/year
All	[redacted]	[redacted]
NAC	[redacted]	[redacted]

Total annual health state costs per person:
AC (n=[redacted]; NAC (n=[redacted]) [redacted]
→ **Significant resource use cost savings for palopeg**

CPRD database includes inpatient, outpatient, primary care and emergency visits – see CPRD analysis – resource use

Large ICER impact

Resource use and definition of AC/NAC from CPRD (3/3)

EAG critique

- Main concern remains that AC/NAC in CPRD analysis defined by healthcare use, not clinical severity; does not match model health states; circular assumption: high resource use = severe disease = high costs
- Delphi opinion alone is not strong enough evidence for such large implied cost savings
- Revised NAC definition is very narrow, and based on small sample (n=[redacted]); likely captures only most severe patients with highest resource use (previously n=[redacted])
- Concern that high NAC inpatient costs ([redacted] of total costs) may be driven by small number of people – shown by large variation in inpatient costs
- Much lower costs in previous NAC group
- CPRD cohort has [redacted] non-surgical patients vs 15% in PaTHway → costs may not be representative; EAG clinical advice is that most hypoPT is post-surgical
- Cannot check or adjust costs for aetiology because data is not reported – reweighting previously resulted in substantial reduction in costs associated with NAC health state
- Overall: NAC costs are highly uncertain and probably overstated, inflating modelled cost savings
- **EAG base case removes all health state costs (acknowledges conservative)**

Mean inpatient costs PPPY [note results not validated by EAG based on latest company economic model]

- Updated NAC: £[redacted]
- Previous NAC: £[redacted]

Abbreviations: AC, adequately controlled; CPRD, Clinical Practice Research Datalink; EAG, external assessment group; hypoPT, hypoparathyroidism; NAC, not adequately controlled; PPPY, per patient per year

Are company's updated definitions of AC and NAC in the CPRD analysis appropriate?
Are the updated health state costs plausible? Is it plausible to assume no difference in costs?

Large ICER impact

Adverse event modelling – rates

Background: company used any grade of AE from PaTHway to calculate model rates (and costs) of hypocalcaemia and hypercalcaemia treatment-related AEs – argued that trial AEs artificially low because intensive monitoring prevented them worsening; said in NHS lower-grade AEs likely to become more severe and need hospital treatment; committee requested evidence that AE risk higher in clinical practice than in trial

Company draft guidance response

Little published evidence but widely accepted that intensive monitoring in clinical trials reduces risk of acute events and complications; Delphi panel agreed that serious symptomatic hypocalcaemia events could be artificially low in PaTHway; said typical NAC patient has symptomatic hypocalcaemia at least 2 to 3 times a year and that this would usually need hospital admission lasting 3 to 4 days

EAG critique

- Clinical opinion not robust enough to justify company's assumptions that base AE event rates on any-grade events, while associated costs assume hospitalisation
- Does not accept that trial would systematically underestimate incidence of serious AEs, in particular assumption that all grade 1 and 2 events would escalate to needing hospital admission
- Maintains only grade 3 or 4 AEs should be used to calculate AE rates
- Disagrees with company's claim that NAC patients have 2 to 3 symptomatic events each year
- CPRD data show much lower rates: [redacted] patients with ≥1 symptomatic hypocalcaemia inpatient admissions had [redacted] hospitalisations over nearly [redacted] person-years ≈ [redacted] events per person per year, far lower than Delphi panel estimate of multiple events each year

Does the evidence suggest that PaTHway underestimates serious AEs? Is it appropriate to include any grade AEs or only grade 3/4?

Abbreviations: AE, adverse event; CPRD, Clinical Practice Research Datalink; EAG, external assessment group; NAC, not adequately controlled

Medium ICER impact

Adverse event modelling – costs

Background

- Company applied AE costs (including hospitalisation) for hypo and hypercalcaemia regardless of severity
- Committee uncertain about appropriate costs for AEs; requested CPRD-derived costs, up to date Hospitalisation for Heart Failure NHS reference cost, and further consideration/input on resource use

Company draft guidance response

- Used mean cost of a symptomatic hypocalcaemia admission from CPRD in updated base case
- Fluid or Electrolyte Disorders HRG code (KC05) proposed by EAG not appropriate (covers range of conditions many not as complex or resource-intensive as symptomatic hypocalcaemia)

Source	Cost per admission (£)
CPRD* inflated to 2025 prices using ONS CPI **(updated company base case)**	[redacted]
Hospitalisation for heart failure HRG code (company scenario)	2,575
EAG scenario (mean cost per event)	[redacted]

EAG critique

- Agrees CPRD values more relevant; but calculation unclear; if patient-level average used would not match model (requires cost per event); could bias results if frequent users have different costs; unclear if appropriate; EAG scenario using mean cost per event
- Small number of patients used (n=[redacted]; [redacted] events); standard deviation larger than mean = estimate highly uncertain; important because model predicts large cost savings, which depend on these estimates

*Mean cost per admission of symptomatic hypocalcaemia in post-surgical + non-surgical patients without complications; abbreviations: CPI, Consumer Price Index; CPRD, Clinical Practice Research Datalink; HRG, NHS Healthcare Resource Group; ONS Office for National Statistics

Is the company's CPRD cost appropriate?
Is the EAG's alternative CPRD cost preferred?

Company and EAG base case assumptions

Updated assumptions after consultation

Assumption	Company	EAG
Basis for determining health states and health state utilities	Response – does not allow response on standard treatment MMRM for utilities	Response – allows response on standard treatment MMRM for utilities
Health state costs	Included based on patterns of healthcare use from CPRD	Removed
Trial AEs used to model treatment-related AEs	All grades	Only grade 3 and 4
Complication rate	Assumed lower risk of complication for palopeg based on resource use analysis from CPRD	Assumes no impact of palopeg on complication rates
Source of AE costs	CPRD: mean cost for a symptomatic hypocalcaemia inpatient admission	Same – but scenario with cost per event calculated by dividing total costs by number of events
Mortality hazard ratio	2.89 for both model arms from 2022 company sponsored CPRD-based study	Same

Abbreviations: AE, adverse event; CPRD, Clinical Practice Research Datalink; EAG, external assessment group; MMRM, mixed model repeated measures; ST, standard treatment

Company updated base case (deterministic)

Technology	Total costs	Total QALYs	Incremental QALYs	Incremental costs	ICER
Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£28,862
Standard treatment	[redacted]	[redacted]	-	-	-

Results based on updated response-based model submitted 29 April and has not been fully critiqued by EAG

Company scenarios using former treatment-based model (for illustration only)

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

EAG scenarios

Calculated using former treatment-based model – for illustration only, ICERs to be updated after ACM2

Scenario	Technology	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER
Company base case	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£20,031
	Standard treatment	[redacted]	[redacted]	-	-	
1 Response-based model (EAG base case)*	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£40,178
	Standard treatment	[redacted]	[redacted]	-	-	
2 Remove health state maintenance costs (EAG base case)	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£128,850
	Standard treatment	[redacted]	[redacted]	-	-	
3 Use grade 3/4 AEs (EAG base case)	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£82,852
	Standard treatment	[redacted]	[redacted]	-	-	
4 AE costs – alternative calculation	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£26,802
	Standard treatment	[redacted]	[redacted]	-	-	
5 Exclude complications (EAG base case)	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£21,321
	Standard treatment	[redacted]	[redacted]	-	-	

*EAG's base case using the response-based model allows for response in the standard care arm

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Abbreviations: AE, adverse event; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MMRM, mixed model repeated measures; QALYs, quality-adjusted life years

EAG updated base case (deterministic)

EAG base case (including EAG scenarios 1, 2, 3 and 5)

Technology	Total costs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£304,487
Standard treatment	[redacted]	[redacted]	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

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Uncaptured benefits

Company

- Cognitive improvements with palopeg not captured in QALY calculation – EQ-5D does not measure cognitive functions (memory, attention, executive function)
- In hypoPT cognitive impairment ('brain fog') common and clinically significant

Patient and professional groups

- Psychological and emotional burden not captured by EQ-5D – depression, cognitive fog, social withdrawal, anxiety, feeling of being unsafe because symptoms appear suddenly and unpredictably
- Hidden burden of acute presentations to emergency care settings relating to hyper and hypo-calcaemia associated with standard care – HES coding does not seem to reliably capture but aware this is frequent
- High pill burden with hypoPT – fewer tablets means reduced self-adjustment and trial-and-error dosing, less time spent managing disease

Are there any uncaptured benefits of palopeg?

NICE

Abbreviations: EQ-5D EuroQol 5 Dimensions; HES, Hospital Episode Statistics; hypoPT, hypoparathyroidism; QALY, quality-adjusted life year

Palopegteriparatide for treating chronic hypoparathyroidism

- ❑ Recap from first appraisal committee meeting
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Remaining key issues

Issue	ICER impact
Effectiveness of standard treatment in NHS vs trial	Unknown
Primary outcome: independence from calcium endpoint	Unknown
Response-based economic model	Large
Resource use and definition of AC/NAC from CPRD	Large
Modelling of adverse events – rates	Large
Modelling of adverse events – costs	Medium

Abbreviations: AC, adequately controlled; EAG, external assessment group; ICER, incremental cost effectiveness ratio; NAC, not adequately controlled

Committee questions

Category	Key questions
Equality considerations	How should any equalities issues be taken into account in the committee's decision making?
Population	Does committee agree that the ESE guideline would be suitable for determining eligibility for palopeg?
Standard treatment	Do the comments received change committee's conclusion at the first committee meeting that standard treatment in PaTHway was suboptimal?
Primary outcome	Does the information supplied reduce the uncertainty around whether the primary outcome can be used to assess the effectiveness of palopeg compared with standard care? What conclusions can be drawn about the comparative efficacy of palopeg?
Model	Does the company's/EAG's response-based model reduce uncertainty in the modelling? Are they suitable for decision making?
Definition of AC/NAC	Are company's updated definitions of AC and NAC in the CPRD analysis appropriate?
Resource use	Are the updated health state costs plausible? Is it plausible to assume no difference in costs?
AEs	Does the evidence suggest that PaTHway underestimates serious AEs? Is it appropriate to include any grade AEs or only grade 3/4? Is the company's CPRD cost appropriate for modelling AE costs? Is EAG's alternative CPRD cost preferred?
Complications	Does the evidence support modelling a lower risk of complications with palopeg?
Uncaptured benefits	Are there any uncaptured benefits of palopeg?

Abbreviations: AC, adequately controlled; AE, adverse event; CPRD, Clinical Practice Research Datalink; ESE, European Society of Endocrinology; NAC, not adequately controlled

Palopegteriparatide for treating chronic hypoparathyroidism

Supplementary appendix

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Decision problem population

Second International Workshop guidelines 2022:

Palopeg should be considered for patients who are ***NAC on standard treatment***

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 ≥2,000 mg daily

European Society of Endocrinology (ESE) 2025:

Consider PTH therapy in patients with 1 of the following despite optimised standard treatment:

- Frequent fluctuations in calcium levels, or symptomatic hypocalcaemia
- Impaired quality of life attributable to chronic hypoPT
- Reduced kidney function (eGFR < 60 mL/min per 1.73m²)
- Hypercalciuria
- Hyperphosphataemia

Treatment pathway
Definition of NAC population

Abbreviations: eGFR, estimated glomerular filtration rate; HypoPT, hypoparathyroidism; NAC, not adequately controlled; PTH, parathyroid hormone; SF-36, 36-Item Short Form Survey

Delphi panel methodology

At ACM1 committee requested additional data sources for model inputs including robust, transparent clinical expert opinion

Company commissioned a structured Delphi panel to:

- validate definitions, identification methods, resource intensity associated with NAC patients
- ensure the economic model accurately reflects NHS clinical practice

From an initial pool of 13 potential participants, 9 successfully completed the Delphi process

Participants were clinical experts with extensive experience in the specialist management of chronic hypoPT with most (6 out of 9) overseeing the direct care of more than 70 chronic hypoPT patients

Delphi process incorporated multiple safeguards to ensure rigour and minimise bias, including:

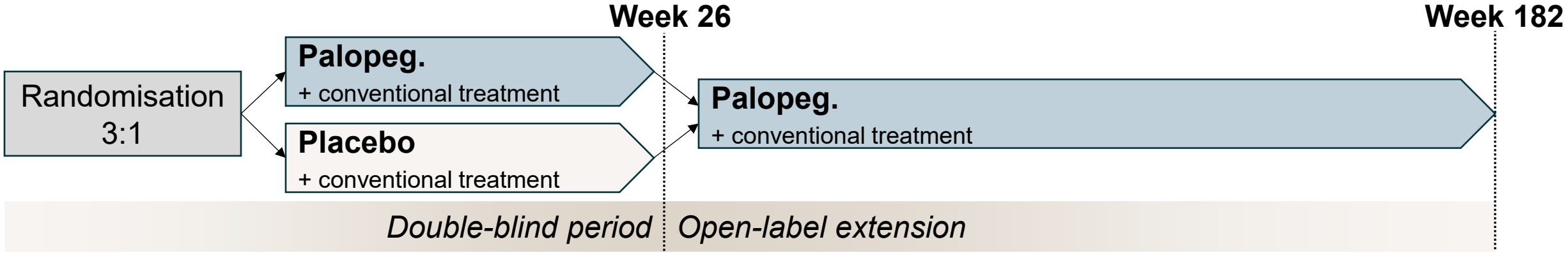
- predefined eligibility criteria
- anonymised responses
- 2 iterative rounds
- controlled feedback
- predefined consensus measures

Effectiveness of standard treatment in NHS vs trial

Abbreviations: ACM, appraisal committee meeting; hypoPT, hypoparathyroidism; NAC, not adequately controlled

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.

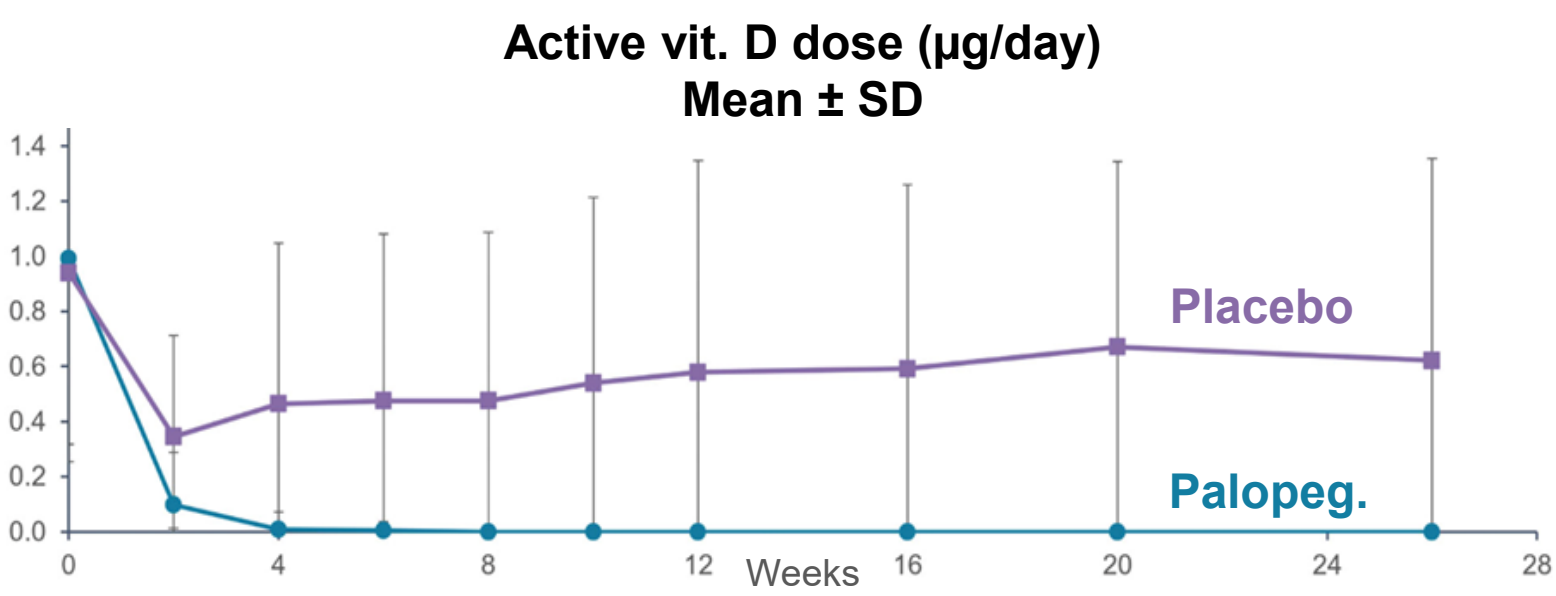
NAC, not adequately controlled; SF-36, 36-item short form survey

Standard treatment in PaTHway

EAG: clinical benefit of standard treatment 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 (13% did this) due to potential confounding of urinary calcium



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 ST used will not have been as comprehensive and effective as the ST available in the NHS – so clinical benefit for ST and costs in the model will be underestimated

Draft guidance recommendation
Effectiveness of standard treatment in NHS vs trial

ST, standard treatment; ICER, incremental cost-effectiveness ratio; NAC, not adequately controlled; SD, standard deviation

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 standard treatment is not a plausible goal for standard treatment
- 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 ST	81% (63/78)	
Week 52, Independence from ST	95% (74/78)	
Week 104, independence from ST	97% (74/76)	

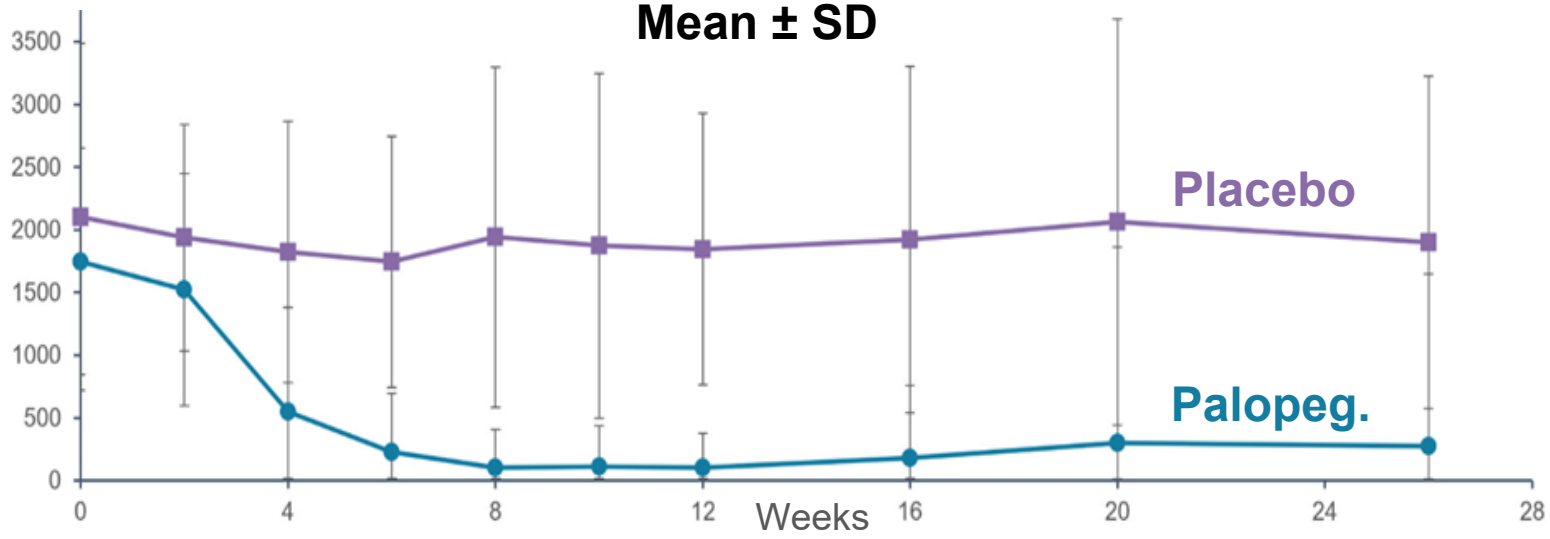
Uncertainty in patient-reported outcomes

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

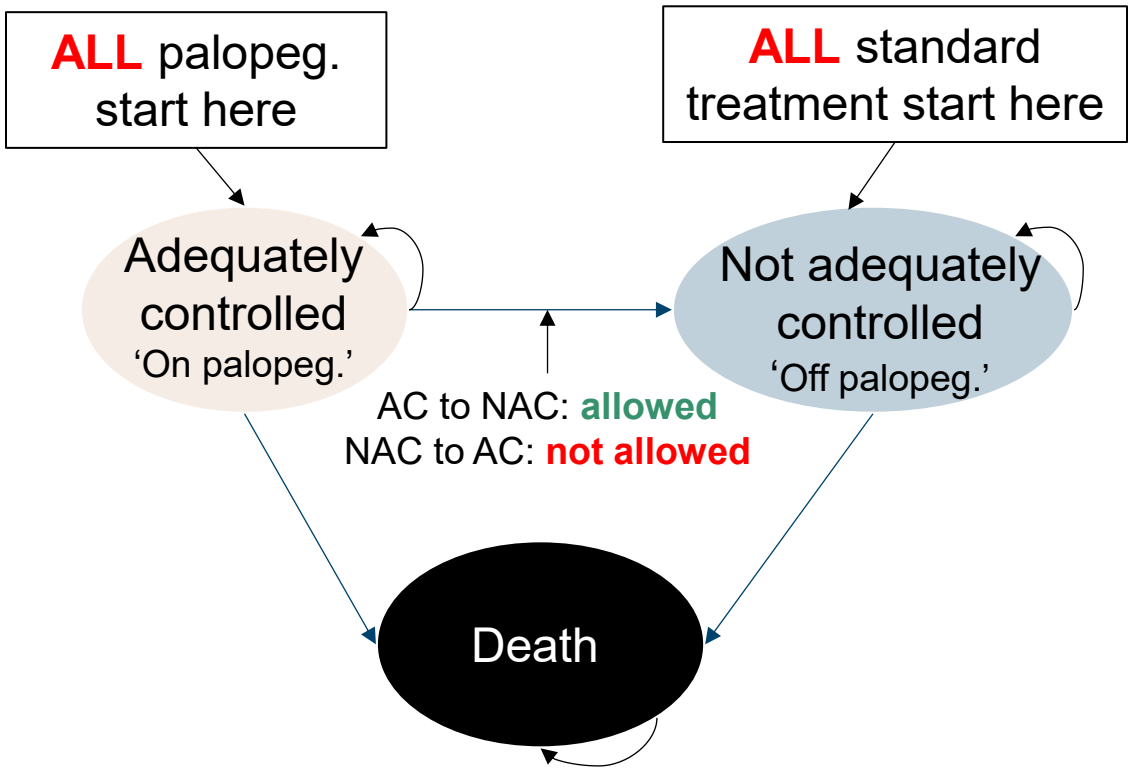
EQ-5D	Palopeg. (n=61)	Placebo (n=21)
Baseline Mean (SD)	0.708 (0.186)	0.661 (0.238)
Baseline Median (Min, Max)	0.736 (0.09, 1.00)	0.710 (0.08, 1.00)
Mean change from baseline (SD)	0.085 (0.148)	-0.006 (0.220)
Median change from baseline (Min, Max)	0.047 (-0.21, 0.62)	0.000 (-0.51, 0.31)

Draft guidance recommendation

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

Company's original model

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

Draft guidance recommendation
Response-based economic model

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

CPRD analysis – resource use

CPRD Aurum database covers participating primary care practices in the UK (~19 million patients); links with HES and death registration data from ONS

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

Categories of cost included from the CPRD dataset in updated analysis:

- inpatient admissions coded to a composite of complications associated with chronic hypoPT
- outpatient visits coded to relevant specialities
- all-cause emergency care attendances
- primary care visits coded to a composite of complications associated with chronic hypoPT

Draft guidance recommendation
Resource use and definition of AC/NAC

Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; hypoPT, hypoparathyroidism; ONS, Office for National Statistics

Small ICER impact

Complications modelling

Background

- Company modelled lower risk of complications (e.g. renal and cardiovascular disease) for palopeg; no evidence on this from PaTHway so based on analysis of resource use in CPRD
- Committee requested evidence to justify surrogate relationship, and scenario analyses using literature estimates if possible
- Also asked for updated CPRD-based estimates using AC/NAC definitions aligned to clinically relevant control of the condition rather than treatment allocation

Company draft guidance response

- No alternative evidence to update complication risks identified
- CPRD data could not be aligned to response-based states so original complication rates were retained
- CPRD complication risks informed by standard treatment so model may underestimate palopeg benefits

EAG critique

- Underlying issues not addressed; no new evidence to support modelled impact on complication rates
- Company analysis relies on unsubstantiated surrogate relationships and strong assumption that resource use is proxy for complication rates
- Retains base case assumption of complication rate of zero for both health states

Company and EAG base case assumptions

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

Does the evidence support modelling a lower risk of complications with palopeg?

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]

Complications modelling

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

Company scenarios, calculated using former treatment-based model – for illustration only

	Technology	Total costs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Original base-case (treatment- based model)	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£20,031
	Standard treatment	[redacted]	[redacted]	-	-	-
Alternative health state costs based on all-cause costs	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£5,025
	Standard treatment	[redacted]	[redacted]	-	-	-
Alternative health state costs based on removal of inpatient costs from AC health state	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£13,970
	Standard treatment	[redacted]	[redacted]	-	-	
Revised adverse event costs based on cardiac HRG code	Palopeg	[redacted]	[redacted]	[redacted]	[redacted]	£30,311
	Standard treatment	[redacted]	[redacted]	-	-	-

Company updated base case results

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years