Single Technology Appraisal

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

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

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Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 13 March 2026. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Ascendis Pharma A/S

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive Summary** Ascendis acknowledges the initial draft guidance for palopegteriparatide and, in its response, has sought to address as many points as possible to inform the final recommendation, including: • Revising the base case in line with the committee's preferred assumptions outlined in the draft guidance document

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	• Obtaining robust transparent clinical opinion from specialists in the treatment of chronic hypoparathyroidism using a structured Delphi methodology to inform modelling decisions and inputs • Exploring a response-based modelling approach with health states informed by the primary outcome from PaTHway • Exploring the implications of a scenario where independence from therapeutic calcium doses is excluded from the multi-component primary endpoint • Updating the approach to modelling mortality risk in response to the committee's feedback • Refining how the health state resource-use cost is captured and calculated to more accurately represent the resource use associated with not adequately controlled (NAC) patients and align with the NICE reference case **Delphi panel methodology** To obtain the additional transparent expert clinical input requested, Ascendis commissioned a structured Delphi panel to validate the definitions, identification methods, and resource intensity associated with NAC patients and ensure the economic model accurately reflects NHS clinical practice. An initial pool of 13 potential participants resulted in 9 who successfully completed the Delphi process. These clinical experts demonstrate extensive experience in the specialist management of chronic hypoparathyroidism with most (6/9) overseeing the direct care of more than 70 chronic hypoparathyroidism patients. The Delphi process incorporated multiple safeguards to ensure rigour and minimise bias, including predefined eligibility criteria, anonymised responses, two iterative rounds, controlled feedback, and predefined consensus measures. The full Delphi report accompanies this response. **Modelling approach** As mentioned above, a response-based modelling approach has been explored and is provided as requested in the draft guidance. However, the company considers a treatment-based modelling approach to remain the most appropriate given the limitations of the response-based approach and that the treatment-based approach better captures the benefits of hormone replacement therapy with palopegteriparatide beyond the primary endpoint. Therefore, the revised base case for the economic analysis continues to use a treatment-based approach with the response-based approach presented as a scenario. The two approaches yield similar results, which we consider reassuring for the committee. **Overall position** It should be acknowledged that chronic hypoparathyroidism is a rare disease and palopegteriparatide represents a step change in its treatment by replacing the parathyroid hormone; thereby addressing the underlying hormonal deficit rather than solely managing calcium levels through supplementation. There is a high unmet need for an alternative to standard treatment, particularly in patients that are NAC with standard treatment, as demonstrated by a number of approved individual funding requests across the UK. NHS England have also confirmed availability of interim funding via the Innovative Medicine Fund (IMF), to enable prompt patient access following conclusion of the NICE assessment. The company also hopes that it will be of reassurance to the committee that the value of palopegteriparatide has already been recognised in different healthcare economies globally with

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	reimbursement in Italy, Japan, Spain, Austria, Germany, France and the United States amongst others. Finally, the company considers the base case to utilise the most robust data available under the circumstances and represents a conservative assessment of the value of palopegteriparatide.
2	**Revised clinical guideline on the management of chronic hypoparathyroidism** The company welcomes the committee's recognition that the proposed positioning and population for palopegteriparatide is appropriate, with eligibility defined based on established clinical guidelines. It should be noted that since the committee meeting, the European Society of Endocrinology (ESE) has published a revised clinical practice guideline on the management of chronic hypoparathyroidism in adults, which is expected to become the standard reference for determining clinical suitability for palopegteriparatide moving forward.[1] The revised guideline recommends PTH replacement therapy for patients who despite optimised conventional therapy continue to experience signs and symptoms of hypoparathyroidism (i.e. are not adequately controlled on standard treatment). The criteria for defining patients who are not adequately controlled on standard treatment, and therefore eligible for palopegteriparatide, have not fundamentally changed. Therefore, the revised guidelines are not expected to impact this current assessment. ***Section summary:*** Palopegteriparatide continues to be considered for use in people whose hypoparathyroidism is not well managed with standard treatment, and recent European guidelines support this approach. These updates do not change who is considered eligible, so they do not affect the current assessment.
3	**Effectiveness of standard treatment in the NHS vs standard treatment in PaTHway** The draft guidance document highlighted a concern that standard treatment in PaTHway was not as effective as standard treatment in the NHS due to the trial protocol-mandated reduction in active vitamin D at the start and the prohibiting of thiazide diuretics, requesting that the placebo arm (i.e. standard treatment arm) be adjusted to reflect standard treatment in the NHS. Expert clinical opinion, sought via the formal Delphi panel exercise, supported the generalisability of the placebo arm in PaTHway to NHS standard care. There was consensus that the permitting of thiazide diuretics in PaTHway would have had little clinically meaningful impact on patient outcomes, with an estimated negligible impact overall (Delphi report, Q14). Similarly, the experts were also in agreement that the initial reduction of vitamin D at the start of PaTHway trial had little impact on the effectiveness of standard treatment (Delphi report, Q13). The clinical experts agreed that there would be little clinically meaningful improvement in the efficacy of standard treatment in the NHS if thiazide diuretics were used more in NAC patients in normal clinical practice (Delphi report, Q15). This is probably reflective of the existing low usage as demonstrated by different data sources with clinicians in the Delphi panel noting that thiazide diuretics are not widely used and come with their own clinical challenges to manage. Given the expert clinical input received, and significantly, the lack of evidence to inform any adjustment, it was considered inappropriate to adjust trial efficacy data for the placebo arm as requested by the committee.

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	Consequently, the placebo arm in the PaTHway trial is considered an appropriate representation of the efficacy of standard treatment in the NHS, and suitable to inform cost effectiveness evaluation and decision-making in this appraisal. ***Section summary:*** Experts agreed that the trial's protocol regarding vitamin D and thiazide diuretics did not meaningfully affect how well standard treatment worked, and that using these medicines differently would not have improved outcomes. Because of this, the trial's placebo arm results are considered a fair reflection of NHS care and appropriate to use in the evaluation.
4	**Response-based model** In the draft guidance, NICE requested a response-based model reflecting the primary outcome measure from the PaTHway trial. This structure can be implemented within the existing cost-effectiveness model as outlined below; the company however maintains that a treatment-based (on/off) approach more appropriately represents the value of hormone replacement therapy effectiveness. The appropriateness of the treatment-based model is further supported by the utility analysis, which shows similar mean utilities at the end of the randomised period of the PaTHway trial among patients treated with palopegteriparatide who met the primary outcome and those who did not. The mean utilities were [redacted] and [redacted], respectively. Similar patterns were observed across the secondary outcomes. In both models, in line with our licence, all patients are chronic (had the condition for 12 months or more); patients on standard treatment are considered NAC as this is the sub-population of patients on standard treatment that will be eligible for palopegteriparatide. These patients remain NAC in line with the clinical consensus from the Delphi panel that patients who are NAC on standard treatment after a sustained period of treatment and management (one year or longer) will remain NAC (Delphi report, Q17). In the response-based model, the 78.7% (n=48) of patients from the palopegteriparatide arm of PaTHway that met the multi-component primary endpoint enter the AC health state, whilst the 21.3% (n=12) of patients from the palopegteriparatide arm who did not meet the endpoint along with 100% (n=21) of patients from the placebo arm enter the NAC health state. Patients remain in the AC health state as long as a treatment response is maintained. The one patient (4.8%) in the placebo arm that also met the primary endpoint, is not included in the AC health state following clinical consensus in the Delphi panel that chronic NAC patients on standard treatment will not achieve AC. The draft guidance also requested that the utility values in the model are defined by response rather than treatment received but, as illustrated above, the trial demonstrated an improvement in quality of life among all patients that received palopegteriparatide regardless of whether they met the primary endpoint or not. Consequently, whilst the utilities have been calculated using MMRM methodology as requested by the committee, they remain based on treatment in the response-based model. The response-based model scenario generates [redacted] incremental QALYs and [redacted] incremental costs resulting in a comparable ICER of £21,003/QALY at the existing PAS. ***Section summary:*** Whilst a model with health states based on response to treatment – as determined by meeting the multi-component primary endpoint – has been provided as requested, the company still considers a treatment-based approach to be more appropriate for assessing the cost effectiveness of palopegteriparatide.

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	Patients on hormone replacement therapy with palopegteriparatide receive benefits beyond the primary endpoint, as demonstrated by the improvement in quality of life for all patients on palopegteriparatide, and a treatment-based modelling approach better reflects this. However, both modelling approaches produce comparable results.
5	**Independence from calcium endpoint** Further to the response-based model above, there was a request for a scenario in which the 'independence from therapeutic doses of calcium' component was excluded from the multi-component primary endpoint of PaTHway and the health state definitions used in the model. Excluding independence from calcium did not alter the proportion of patients that met the primary endpoint and excluding this component had no impact on cost effectiveness in the response-based model.
6	**Resource use associated with management of chronic HypoPT** The committee agreed that CPRD is the best source to inform health state resource use while acknowledging that the available data does not contain direct clinical measures of serum calcium levels and treatment dosing. Clinical experts in the Delphi panel agreed that in the absence of clinical measures in the CPRD, the level of hypoparathyroid-related healthcare usage is an appropriate and clinically valid way to identify NAC patients (Delphi report, Q3), supporting that there is significant differentiation in healthcare resource use between NAC and AC patients (Delphi report, Q2). Although it was not possible to directly align model health state definitions with the definitions used to identify NAC patients in the CPRD dataset, the healthcare resource use costs used in the economic model were revised in response to the committee's feedback. Clinical expert input supported that at least one inpatient admission per year, with hypoparathyroidism as the primary or secondary diagnosis, is an appropriate and clinically valid marker for identifying an NAC patient within the CPRD dataset. There was consensus that these patients' resource use would be representative of the resource use of NAC patients on standard treatment (Delphi report, Q6 and Q7) and that this definition would ensure that only NAC patients inform the resource use estimate (Delphi, Q8). Hence, the way in which NAC patients were identified in the CPRD dataset was altered as follows in line with the clinical input: • having at least one inpatient admission per year, with hypoparathyroidism as the primary or secondary diagnosis. The clinical experts also agreed that it was appropriate, clinically valid and accurate to capture the healthcare costs related to hypoparathyroidism by combining the costs of hypoparathyroidism-related inpatient admissions with the costs of complications associated with chronic hypoparathyroidism (Delphi report, Q9). The included complications were identified via literature and validated with clinical experts when designing the CPRD study. Please see section 3.3.2. of the company submission for further detail on the complications included. The updated approach to analysing the healthcare resources ensures that the output:

	• aligns to the NICE reference case – by only including costs associated with chronic hypoparathyroidism (rather than all-cause as previously) and by adjusting these costs based on the matched background population control group cost • utilises all the available data by applying exhaustive criteria – all patients who do not meet the clinically validated definition for identifying NAC patients in the CPRD dataset are included in the AC healthcare resource use cost • provides appropriate differentiation between AC and NAC patients as supported by the expert clinical opinion received. However, it should be noted that the updated analysis yields a conservative estimate for several reasons: • Firstly, hypoparathyroidism is a multi-system condition with impacts on several organs. By restricting the analysis to condition-specific costs, it is therefore likely that the true economic burden of hypoparathyroidism is underestimated. To assess the impact of this assumption, a scenario analysis including all-cause costs was conducted, resulting in a substantially lower ICER of £5,025 (see Appendix for full results). • Second, to ensure an exhaustive and mutually exclusive definition of NAC and AC, the AC category includes patients with hypoparathyroidism-specific inpatient stays, although these occur infrequently (on average fewer than one per year). Some of these patients incur particularly high costs, which increases the estimated average costs for AC patients in the model. In addition, clinical experts agreed that the clinical benefit of treatment with palopegteriparatide is likely to be greater than that experienced by patients who are classified as AC on standard treatment (Delphi report, Q18). • As previously, the CPRD dataset and updated analysis excludes patients with a history of cardiovascular disease or advanced renal insufficiency prior to a diagnosis of hypoparathyroidism to avoid overestimating the costs. These are generally high resource use, high-cost patients arguably making the resource use cost estimates conservative. The above considerations suggest that AC costs may be overestimated, so a scenario analysis was conducted in which no costs related to inpatient admissions for hypoparathyroidism-related complications were applied to patients who are AC. This scenario reflects clinical expectations that patients achieving sustained biochemical and symptomatic control through PTH replacement therapy have a very low risk of related complications requiring hospitalisation; exploring the economic consequences under an optimistic but realistic assumption of effective disease control. Importantly, the scenario does not imply that inpatient events are impossible, but rather that they are rare enough in actual AC patients to have a negligible impact on expected costs. The scenario resulted in a substantially lower ICER of £13,970 (see Appendix for full results). Recognising that the analysis of resource use is primarily informed by non-surgical patients, due to the incidence-based study design used for post-surgical patients in comparison to the prevalence-based design used for non-surgical patients, the company sought to explore the impact of aetiology on resource use as part of the Delphi panel exercise. Clinical experts confirmed that the aetiology of chronic hypoparathyroidism had little impact on the total healthcare resource of a patient (Delphi report, Q4) and once adjusted for time since diagnosis, aetiology is not considered a significant driver of difference in total healthcare resource use (Delphi report, Q5).

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	Finally, it was not considered appropriate to present the committee's requested scenario in which resource-use costs were informed by the PaTHway trial. The resource-use in PaTHway was not considered representative of routine care and, therefore, not appropriate for modelling purposes. ***Section summary:*** The company refined its CPRD-based resource-use estimates and validated all associated assumptions through a Delphi panel of clinical experts. This process ensured clear differentiation between AC and NAC patients and alignment with the NICE reference case. The experts confirmed that hypoparathyroidism inpatient admissions provide a reliable method for identifying NAC patients in the absence of clinical measure and agreed that disease aetiology does not meaningfully influence overall resource use. Together, these findings support CPRD as the most appropriate and clinically credible basis for modelling healthcare costs. As trial-based data from PaTHway reflect intensive monitoring not representative of routine NHS practice, CPRD-derived estimates remain the most robust inputs for the economic model, an assessment strongly reinforced by the Delphi panel.
7	**Modelling of adverse events** Both symptomatic hypocalcaemia and hypercalcaemia are modelled separately as adverse events. Symptomatic hypocalcaemia in particular is an impactful, treatment-emergent event that occurs repeatedly throughout a patient's life, that contributes significantly to patient burden and healthcare use. In response to the request in the draft guidance for evidence about the risk of adverse events being higher in clinical practice than in PaTHway; whilst there is a lack of literature to inform the specific risk, it is broadly recognised that high intensity monitoring associated with the trial environment reduces acute intervention and complications. Recognising that the symptomatic hypocalcaemia event rate in PaTHway may be artificially low, the event rate in the submission was calculated based on all hypocalcaemia events, regardless of adverse event grade, as documented in the company submission and additional clarification response provided on the 9 September 2025 Clinical expert consensus was supportive of the above approach with agreement that the number of serious symptomatic hypocalcaemia events could be artificially low in PaTHway due to frequent monitoring and proactive intervention that would occur in a clinical trial environment (Delphi report, Q10). The clinical experts were in agreement that a typical NAC patient in clinical practice would have at least 2-3 symptomatic hypocalcaemia events a year, with 2-3 typically requiring an inpatient hospital admission (Delphi report, Q11 and Q12). Clinical input also indicated that it typically takes 3-4 days to safely stabilise a patient admitted for symptomatic hypocalcaemia (Delphi, Q12a). With respect to the resource use associated with managing a symptomatic hypocalcaemia event, the CPRD-based estimate provided by the company is considered the most appropriate to use, given it is informed by actual NHS resource use, and is applied in the updated base case. HRG code KC05 (Fluid or Electrolyte Disorders) as proposed by the EAG covers many different electrolyte-related conditions for a broad, heterogeneous population with widely varying clinical needs and lengths of stay. Most of these are less complex and less resource-intensive than symptomatic hypocalcaemia in chronic hypoparathyroidism, making the average KC05 cost inappropriately low, particularly in the non-elective short-stay category. The Hospitalisation for Heart Failure HRG cost was used in the original company submission as an analogue in the absence of a hypoparathyroidism specific code but is also no longer

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	considered relevant given the CPRD based cost. For illustrative purposes however, a scenario is provided using the average across all admitted patient care with the Hospitalisation for Heart Failure HRG. This value of £2,575 (see Appendix) is more closely aligned with the mean inpatient cost per admission for symptomatic hypocalcaemia from the CPRD (2021). ***Section summary:*** Symptomatic hypocalcaemia events are one of the most serious and frequent problems for patients with chronic hypoparathyroidism that is NAC with standard treatment. They often lead to hospital admissions and are a major source of distress for patients and cost for the NHS. Clinical experts in agreement that the number of symptomatic hypocalcaemia events in PaTHway may be lower than in clinical practice. NAC patients were considered to have at least 2-3 symptomatic hypocalcaemia events a year, with 2-3 typically requiring hospital admission and several days of inpatient care. The CPRD-based resource use cost for symptomatic hypocalcaemia is considered the most appropriate to use the n model as informed by NHS data. The Fluid or Electrolyte Disorders HRG code proposed by the EAG underestimates cost as generally associated with less complex and resource-intensive activity but a scenario using an updated Hospitalisation for Heart Failure HRG code value is provided.
8	**Modelling of complications and mortality** It was requested in the draft guidance document that, to reduce uncertainty in estimates of complications and mortality risk, the company undertake scenario analyses with updated estimates using literature values, explore evidence for surrogate relationships between trial outcomes and complications/mortality, and provide updated estimates of risk from CPRD aligned to the response-based health state definitions. **Complications risk** Desk research did not identify appropriate alternative literature sources or surrogate relationships to include in the cost-effectiveness model. It was not possible to directly align the CPRD data to the primary endpoint from PaTHway, which informed the health state definitions. As such it was not possible to provide updated estimates of complication risk from CPRD, so the company remained with the base case rates. Whilst CPRD is still considered to be the most appropriate source for complication risks, it should be noted that these rates are informed by patients on standard treatment only. As a result, there is arguably an uncaptured benefit in the model for palopegteriparatide patients as AC health state complications are informed using data based on patients on standard treatment. As outlined previously in comment 4, clinical expert opinion supported that the clinical benefit of being adequately controlled on palopegteriparatide is expected to be greater than being adequately controlled on standard treatment. (Delphi report, Q18). **Mortality risk** Additionally, desk research did not identify any alternative appropriate data sources for mortality. As a conservative approach, the EAG-preferred scenario applying a hazard ratio of 2.89 derived from the published literature[2] to both arms was therefore adopted in the base case. The company conservatively aligns with the EAG on the modelled mortality risk. **Section summary:** Desk research did not identify any suitable alternative evidence to update complication or mortality risk modelling. It was also not possible to obtain updated estimates, aligned to the response-based

	health state definitions, from CPRD. Consequently, the complication risk rates remain as per the original company submission. The modelled mortality risk however has been updated in line with the EAG preferred scenario.
9	**New base case and results** The updated base case incorporates committee preferences and updated CPRD-informed resource use costs, producing consistent cost-effectiveness results. As outlined in comment 4, the company has provided a response-based scenario as requested but still considers the treatment-based (on/off) model the more appropriate option for the base case. Considering the committee's preferences and the additional analysis requested, the company has adjusted the base case settings for the cost effectiveness analysis as follows: • Health state utilities calculated by treatment from PaTHway using the mixed method for repeated measures approach • Health state resource use costs informed by updated CPRD analysis (see comment 5 and Appendix for further detail) • Adverse event cost based on mean cost for a symptomatic hypocalcaemia inpatient admission from CPRD • 100% relative dose intensity and drug wastage applied • Mortality risk updated The new base case and additional scenario analyses are fully detailed in the Appendix. The new base case generates [redacted] incremental QALYs and incremental costs of [redacted] resulting in an ICER of £20,031/ QALY at the existing PAS price. A scenario using response-based definitions for the health states, results in incremental QALYs of [redacted] and incremental costs of [redacted] with a similar ICER of £21,003/ QALY at the existing PAS price.
10	**Uncaptured utility benefit** While the EQ-5D captures domains like mobility, self-care, and anxiety/depression, it does not directly assess cognitive aspects such as memory, attention, or executive function. A systematic review by Rencz et al. (2025) concludes that this omission can lead to underestimation of health-related quality of life (HRQoL) improvements, particularly in conditions where cognitive symptoms are prominent[3]. In the context of hypoparathyroidism, cognitive impairment, often described as "brain fog", is a well-documented and distressing symptom. A recent prospective observational study demonstrated that individuals with chronic HypoPT performed significantly worse than matched healthy controls in attention, processing speed, and executive function, with 56.7% of patients showing deficits in attention and 60.0% in executive function, compared to 3.3% and 16.7% in controls, respectively (Tmava-Berisha et al., 2025)[4]. Therefore, it is likely that the modelled utilities do not fully capture the total benefit of palopegteriparatide, suggesting that the ICER may be overestimated.

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11	**Factual accuracy check** The following points with the draft guidance consultation document have been noted as factually inaccurate or not fully reflective of the evidence base. We would request that the text is corrected for future documents. • Section 3.9 stated: *"People entered the model in the AC health state if starting palopegteriparatide or in the NAC health state if starting standard treatment."* To clarify: patients in the NAC health state were not starting treatment with standard treatment; they would have had a diagnosis of HypoPT and been on standard treatment for a year or longer to be considered chronic. It would be more accurate therefore to state *"People entered the model in the AC health state if starting palopegteriparatide or in the NAC health state if* ***remaining on*** *standard treatment."* • Section 3.9 stated that: *"only 78.8% of people met the primary outcome in the palopegteriparatide arm."* It would be more accurate to state *"only 78.8% of people met the* ***multi-component*** *primary outcome in the palopegteriparatide arm.* • Section 3.9 stated clinical advice to the EAG "*suggested that some people with chronic hypoparathyroidism can have good calcium control with standard treatment, and can taper their treatment with the long-term aim of achieving independence*". This is considered reflective of patients who are adequately controlled with standard treatment rather than the modelled population of patients who are NAC with standard treatment. There was consensus amongst the clinical experts in the Delphi panel that patients who are NAC after a year or longer of treatment and management, will remain NAC. • Section 3.10 stated patient experts explained "*that they would struggle to meet the company's NAC criteria, despite feeling that their condition is poorly controlled, because hypoparathyroidism is often managed in primary care*". This statement fails to comprehensively reflect patient expert statements on the matter. Patient experts explained that hypoparathyroidism patients tend to access and receive specialist care through primary care referral due to poor experiences in A&E, rather than only seeking management through secondary care.

Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Further to our response to the draft guidance document, additional detail is provided here alongside the revised base case economic analysis.

1. Health state resource use

Health state resource use is impacted by the choice of patients and associated costs considered in the analysis. Section 1. presents more detail informing the health state costs used in the base case and two alternative scenarios that consider the use of all-cause costs and the exclusion of inpatient costs in the AC cost.

As outlined in response document, the updated health state resource use costs have been limited to disease-specific costs as per the NICE reference case. The categories of cost included from the CPRD dataset are as follows unless specified otherwise:

- Inpatient admissions coded to a composite of complications associated with chronic hypoparathyroidism;
- Outpatient visits coded to any speciality of interest;
- All cause emergency care attendances; and
- Primary care visits coded to a composite of complications associated with chronic hypoparathyroidism.

The complications included in the composite were identified via literature and validated with clinical experts. Further detail on the complications included is provided in section 3.3.2 of the company submission.

To further ensure the calculated cost was chronic hypoparathyroidism specific, the background cost of the general population control group was removed. Costs for NAC and AC were calculated using data on post-surgical and non-surgical hypoparathyroidism patients from the NHS' Clinical Practice Research Datalink (2021). The estimated costs have been inflated to 2025 values.

a) Base case

NAC definition specifying patients and costs in the following analysis:

Patients in the not adequately controlled (NAC) health state are defined as having **at least one inpatient admission per year with hypoparathyroidism as the primary or secondary diagnosis**.

Total costs for NAC patients (n=[redacted]) are derived using the sum of the categories in ≥1 inpatient admissions for hypoparathyroidism as shown in Table 1. The sum of the IP, OP, EC and PC net totals is [redacted] Given these costs are sourced from a 2021 dataset, these values have been inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4)[1]. This results in the final NAC value of [redacted]

NICE National Institute for Health and Care Excellence

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Draft guidance comments form - appendix

Consultation on the draft guidance document – deadline for comments 5pm on 13 March 2026. Please submit via NICE Docs.

Table 1. NAC health state costs for patients with at least one inpatient admission per year with hypoparathyroidism as the primary or secondary diagnosis.

Medical Service Category – Population	Combined* HypoPT Cost PPPY (SD)	Combined* general population matched controls Cost PPPY (SD)	Net Total
IP admissions – Complication composite with hypoPT	[redacted]	[redacted]	[redacted]
OP visits – Any specialty of interest	[redacted]	[redacted]	[redacted]
EC attendances – All-cause mean	[redacted]	[redacted]	[redacted]
PC – Complication composite with hypoPT	[redacted]	[redacted]	[redacted]
Total			[redacted]

*Combined non-surgical and post-surgical. Abbreviations: EC, emergency care; HypoPT, hypoparathyroidism; IP, inpatient; OP, outpatient; PC, primary care; PPPY, per patient per year; SD, standard deviation

AC definition specifying patients and costs in the following analysis:

Patients in the adequately controlled (AC) health state are defined as **all combined post-surgical and non-surgical patients without complications not included in the NAC health state.**

Total costs for all patients (n=[redacted]) are derived using the sum of the following categories for the whole population without complications as shown in Table 2. The sum of the IP, OP, EC and PC net totals is [redacted] Given these costs are sourced from a 2021 dataset, these values have been inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4)[1]. The derived net cost for the whole population of [redacted]

To adjust for the difference in number of patients between NAC and whole populations, the net costs of the two patient populations were multiplied by their respective number of patients and the difference between the multiplied values were divided by the total number of AC patients (n=[redacted]). This resulted in the final AC value of [redacted]

Table 2. Health state costs for all combined post-surgical and non-surgical patients without complications not included in the NAC health state

Medical Service Category – Population	Combined* HypoPT Cost PPPY (SD)	Combined* general population matched controls Cost PPPY (SD)	Net Total

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IP admissions – Complication composite with hypoPT	[redacted]	[redacted]	[redacted]
OP visits – Any specialty of interest	[redacted]	[redacted]	[redacted]
EC attendances – All-cause mean	[redacted]	[redacted]	[redacted]
PC – Complication composite with hypoPT	[redacted]	[redacted]	[redacted]
Total			[redacted]

*Combined non-surgical and post-surgical. Abbreviations: EC, emergency care; HypoPT, hypoparathyroidism; IP, inpatient; OP, outpatient; PC, primary care; PPPY, per patient per year; SD, standard deviation

b) Costs for scenario analysis – NAC and AC costs based on all-cause costs

NAC definition specifying patients and costs in the following analysis:

Patients in the NAC health state was defined in the same manner as the base case. Total costs for NAC patients (n=[redacted]) are derived using the mean value for total **all-cause costs** as shown in Table 3. The net total for NAC patients is [redacted] Given these costs are sourced from a 2021 dataset, these values have been inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4)[1]. This results in the final NAC value of [redacted]

Table 3. All cause NAC health state costs for patients with at least one inpatient admission per year with hypoparathyroidism as the primary or secondary diagnosis

Medical Service Category – Population	Combined* HypoPT Cost PPPY (SD)	Combined* general population matched controls Cost PPPY (SD)	Net Total
All-cause costs	[redacted]	[redacted]	[redacted]

*Combined non-surgical and post-surgical. Abbreviations: HypoPT, hypoparathyroidism; PPPY, per patient per year; SD, standard deviation.

AC definition specifying patients and costs in the following analysis:

Patients in the AC health state was defined in the same manner as the base case. Total costs for all patients (n=[redacted]) are derived using the mean value for total all-cause costs as shown in Table 4. The net total for the whole population without complications is [redacted]. Given these costs are sourced from a 2021 dataset, these values have been inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4)[1].

The derived net cost for the whole population without complications of [redacted]. To adjust for the difference in number of patients between NAC and whole populations, the net costs of the two patient populations were multiplied by their respective number of patients and the difference between the multiplied values were divided by the total number of AC patients (n=[redacted]). This resulted in the final AC value of [redacted].

Table 4. All-cause Health state costs for all combined post-surgical and non-surgical patients without complications not included in the NAC health state

Medical Service Category – Population	Combined* HypoPT Cost PPPY (SD)	Combined* general population matched controls Cost PPPY (SD)	Net Total
All-cause costs	[redacted]	[redacted]	[redacted]

*Combined non-surgical and post-surgical. Abbreviations: HypoPT, hypoparathyroidism;; PPPY, per patient per year; SD, standard deviation.

c) Cost scenario for analysis – removal of inpatient admission costs from the AC health state

NAC definition specifying patients and costs in the following analysis:

NAC costs in this scenario remains the same as the base case, inclusive of inpatient admissions.

However, to derive the AC health state costs without inpatient admissions, the NAC calculations need to have inpatient admissions removed for appropriate scaling.

Total costs for NAC patients (n=[redacted]) are derived using the sum of the categories in ≥1 inpatient admissions for hypoparathyroidism as shown in Table 5. The sum of the OP, EC and PC net totals is [redacted] Given these costs are sourced from a 2021 dataset, these values have been inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4)[1]. This results in the final NAC value of [redacted].

Table 5. Removal of inpatient admission costs - NAC health state costs for patients with at least one inpatient admission per year with hypoparathyroidism as the primary or secondary diagnosis

Medical Service Category – Population	Combined* HypoPT Cost PPPY (SD)	Combined* general population matched controls Cost PPPY (SD)	Net Total
IP admissions – Complication composite with hypoPT	-	-	-
OP visits – Any specialty of interest	[redacted]	[redacted]	[redacted]
EC attendances – All-cause mean	[redacted]	[redacted]	[redacted]

PC – Complication composite with hypoPT	[redacted]	[redacted]	[redacted]
Total			[redacted]

*Combined non-surgical and post-surgical. Abbreviations: EC, emergency care; HypoPT, hypoparathyroidism; IP, inpatient; OP, outpatient; PC, primary care; PPPY, per patient per year; SD, standard deviation

AC definition specifying patients and costs in the following analysis:

Patients in the adequately controlled (AC) health state are defined as **all combined post-surgical and non-surgical patients without complications not included in the NAC health state.**

Total costs for all patients (n=[redacted]) are derived using the sum of the following categories for the whole population without complications as shown in Table 6. The sum of the OP, EC and PC net totals is [redacted] Given these costs are sourced from a 2021 dataset, these values have been inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4)[1]. The derived net cost for the whole population of [redacted]

To adjust for the difference in number of patients between NAC and whole populations, the net costs of the two patient populations (Table 5 and Table 6) were multiplied by their respective number of patients and the difference between the multiplied values were divided by the total number of AC patients (n=[redacted]). This resulted in the final AC value of [redacted]

Table 6. Removal of inpatient admission costs - Health state costs for all combined post-surgical and non-surgical patients without complications not included in the NAC health state

Medical Service Category – Population	Combined* HypoPT Cost PPPY (SD)	Combined* general population matched controls Cost PPPY (SD)	Net Total
IP admissions – Complication composite with hypoPT	-	-	-
OP visits – Any specialty of interest	[redacted]	[redacted]	[redacted]
EC attendances – All-cause mean	[redacted]	[redacted]	[redacted]
PC – Complication composite with hypoPT	[redacted]	[redacted]	[redacted]
Total			[redacted]

*Combined non-surgical and post-surgical. Abbreviations: EC, emergency care; HypoPT, hypoparathyroidism; IP, inpatient; OP, outpatient; PC, primary care; PPPY, per patient per year; SD, standard deviation

2. Modelling of adverse events

Adverse event costs applied to symptomatic hypo and hypercalcaemia are an important variable in the cost-effectiveness analysis. Section 2. presents two different costs derivations for these adverse events. Overall, modelling symptomatic hypocalcaemia costs through the CPRD dataset which directly identifies relevant symptomatic hypocalcaemia events, is considered the most appropriate approach.

a) Costs derived from the CPRD

A cost of [redacted] was derived from the mean inpatient cost per admission of symptomatic hypocalcaemia costs in combined post-surgical and non-surgical patients without complications and with ≥1 symptomatic hypocalcaemia IP admissions found in the Clinical Practice Research Datalink (2021). This cost was inflated using Office of National Statistics Consumer Price Index averages in 2021 (111.6) and 2025 (138.4) to provide is the value of [redacted] which is applied in the base case.

b) Costs derived from Cardiac HRG costs as a proxy for 'Hospitalisation for heart failure'

Following the committee's request to identify NHS-relevant costs for symptomatic hypocalcaemia using the hospitalisation for heart failure approximation method, an average cost of £2,575.00 was derived. This figure represents the mean of the published NHS Reference Costs for admitted patient care within the Cardiac HRG category[2], shown below:

- Admitted patient care, Cardiac HRG (EB-EY) day case average: £1,968.30
- Admitted patient care, Cardiac HRG (EB-EY) elective inpatients: £8,681.00
- Admitted patient care, Cardiac HRG (EB-EY) Non-elective inpatient - long stay average: £4,887.73
- Admitted patient care, Cardiac HRG (EB-EY) Non-elective inpatient - short stay average: £715.33
- Admitted patient care, Cardiac HRG (EB-EY) Regular Day or Night Admissions average: £538.33

3. Revised base case analysis

Considering the committee's preferences and the additional analysis requested, the company has made a number of adjustments to the base case settings for the cost effectiveness analysis. These are detailed in Table 7 below.

Table 7. Company revisions to base case

Assumption	Base case on submission	Revised base case
Health state utilities	Calculated using ANCOVA methodology	Calculated using the mixed method for repeated measures (MMRM) methodology

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Consultation on the draft guidance document – deadline for comments 5pm on 13 March 2026. Please submit via NICE Docs.

Health state resource use costs	CPRD analysis based on HCRU all-cause costs for NAC: >5 outpatient visits and ≥1 inpatient admission PPPY and AC: ≤5 outpatient visits and <1 inpatient admissions per patient per year	CPRD analysis based on HCRU costs related to hypothyroidism* adjusted for HCRU of matched controls. NAC: ≥1 hypoPT specific inpatient admission PPPY, AC: all patients without 1 hypoPT specific inpatient admission PPPY
Adverse event cost	Event cost for hospitalisation from Ward et al., 2023 a cost-effectiveness analysis of patiromer for hyperkalaemia in patients with CKD. Cost was inflated to 2025 costs	Based on the mean cost for a symptomatic hypocalcaemia inpatient admission from CPRD
Relative dose intensity	As observed in PaTHway ([redacted])	As per EAG's approach in line with committee's preference (100%)
Drug wastage	No wastage	As per EAG's approach in line with committee's preference
Mortality risk	Hazard ratios by health state from CPRD applied to general pop	Hazard ratios adjusted per EAG preferred scenario to 2.89 in both arms.

*Costs consist of inpatient admissions – complication composite with hypoparathyroidism costs, outpatient admissions – any specialty of interest, emergency care – all-cause mean, and primary consultation – complication composite with hypoparathyroidism costs.
Abbreviations: AC, adequately controlled; CPRD, Clinical Practice Research Datalink; EAG, external assessment group; HCRU, healthcare resource use; NAC, not adequately controlled; NHS, National Health Service (England)

The results of the updated base case are presented in Table 8 below and show the cost-effectiveness of palopegteriparatide.

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Draft guidance comments form - appendix

Consultation on the draft guidance document – deadline for comments 5pm on 13 March 2026. Please submit via NICE Docs.

Table 8. Revised base case results

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,031
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

4. Scenario analyses

A series of scenario analyses were conducted in response to the draft guidance document:

- Model health states informed by response to multi-component primary endpoint (Table 9)
- Alternative costs for health states based on all-cause costs (Table 10)
- Alternative cost for the AC health state excluding inpatient admissions (Table 11)
- Alternative cost for adverse events: based on Cardiac HRG code (Table 12)

The results of these scenarios show that the response- and treatment-based approaches result in comparable outcomes and the conservatism of the cost-effectiveness results with respect to health state costs.

Table 9. Response-based model: Base case assumptions

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,003
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

NICE National Institute for Health and Care Excellence

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

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Table 10. Treatment-based model: Alternative health state costs based on all-cause costs

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,025
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Table 11. Treatment-based model: Alternative health state costs based on removal of inpatient costs from the AC health state

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,970
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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

Table 12. Treatment-based model: Revised adverse event costs based on the Cardiac HRG code

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,311
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

References

1. Statistics Of N. Consumer price inflation tables. 2025.
2. England NHS. National Cost Collection for the NHS. 2025.

Revision to company base case ahead of ACM2 for palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Ascendis UK
5 May 2026

Following the EAG critique, the company accepts the EAG's and committee's preference for a cost effectiveness model based on response to the multicomponent primary endpoint.

Ahead of the second committee meeting, the company would therefore like to propose a revised response-based base case that aligns to the response-based model framework presented by the EAG in their critique. The revised base case uses the primary endpoint from the trial to inform health state occupancy and utilities as per the EAG's preference however the proportion receiving a response has been adjusted based on the rationale provided in the table below.

When revising the base case, the company has also sought to address the EAG's concern about double-counting in the health state costs by removing the minor costs attributable to symptomatic hypocalcaemia in the CPRD analysis and updating the health state maintenance costs accordingly.

Details of these amends to the company base case are provided in the table below. For transparency, the updated base case results are presented as scenario 9 on the scenario results worksheet using the EAG model dated 13 March (provided to company 23 April). The date in the file name has been updated to 2804026.

It is hoped that resolving these issues ahead of the second committee meeting, will reduce some uncertainty to aid decision-making and make the discussion time available at the meeting more constructive.

The company has used the EAG version (dated 13 March (provided to company 23 April)) of the company model that the company provided as part of its response to the draft guidance. The base case settings in the model are unchanged. The revised base case is presented as a scenario in the model as we thought that would be clearer in terms of updated inputs.

Table 1 below outlined the revised base case and their justification. Scenarios 6,7, and 8 on the scenarios sheet of the model present the impact of the three changes individually. The revised inputs informing these scenarios are included in the parameter sheet – the details of the specific cells changed are provided in Table 1.

The full revised company base case is presented as scenario 9 in 'Scenario Results' sheet (line 23). For the full revised base case, the inputs were changed (consistent with the individual scenarios) as follows:

- Responder proportion in "Parameter sheet" cell AG21 (73,9%) and AG22 (0%).
- Utilities in "Parameter sheet" cell AG26 ([redacted]) and AG27 ([redacted]).
- Health state maintenance costs in "Parameter sheet" cell AG252 ([redacted]) and AG253 ([redacted]).

Updated results with the revised base case are presented in Table 2.

The model file name has been updated to *ID6380 Palopegteriperatide Hypoparathyroidism DG EAG_280426[CON]* based on the date that it was provided to NICE.

Table 1: Proposed revised base case

	EAG model	Revised company base case	Rationale	Cell specific changes for scenarios (provided 5 May 2026)	Cell specific changes required to implement revised base case
Model framework	Health states occupancy informed by response to the primary endpoint from PaTHway.	As per EAG model	Updated to align to EAG and committee's preference	-	-
Response proportion	4.8% for conventional therapy (CT) and 78.7% for palopegteriparatide	0% for CT and 73.9% for palopegteriparatide	It is not considered biologically plausible and reflective of real-world clinical practice to model a response (normal blood serum calcium and independence from CT) in chronic hypoparathyroidism NAC patients on CT. The response in the trial is likely attributable to recovery of residual parathyroid gland function, which may occur following down titration of CT in accordance with the trial protocol. In NHS clinical practice, patients' residual parathyroid function would be tested, with optimisation and down titration undertaken before a patient be considered eligible for palopegteriparatide. However, rather than disregard the response rate in the placebo arm from the trial,	Presented as scenario 7 in 'Scenario Results' sheet line 21. Inputs changed for responder proportion in "Parameter sheet" cell AE21 (73,9%) and AE22 (0%).	In sheet 'Inputs': E9 changed from '100%' to '73.9%' E10 kept at '0%'

	EAG model	Revised company base case	Rationale	Cell specific changes for scenarios (provided 5 May 2026)	Cell specific changes required to implement revised base case
			the model assumes a similar proportion of patients in both arms would have restored gland function with the equivalent percentage (~5%) removed from both treatment arms.		
Health state utilities	EAG-preferred MMRM values	As per EAG model	Updated to align to EAG preference	Presented as scenario 6 in 'Scenario Results' sheet line 20. Inputs changed for utilities in "Parameter sheet" cell AD26 ([redacted]) and AD27 ([redacted]). Inputs changed for responder proportion in "Parameter sheet" cell AD21 (78,7%) and AD22 (4.8%).	In sheet 'Inputs': E20 changed from [redacted] to [redacted] E21 changed from [redacted] to '[redacted]
Health state costs	Health state costs set to zero	Health state costs as per updated approach in response to draft guidance but with any costs attributed to symptomatic hypocalcaemia removed	Recognising that there may be a small amount of double-counting, any costs attributed to symptomatic hypocalcaemia have been removed from the CPRD analysis with the health state costs updated according.	Presented as scenario 8 in 'Scenario Results' sheet line 22. Inputs changed for health state maintenance costs in "Parameter sheet" cell AF252 ([redacted]) and AF253 ([redacted]).	In sheet 'Inputs' E82 changed from [redacted] to [redacted] E21 changed from [redacted] to [redacted]

Table 2: Revised base case results

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

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

Response to Chair's request for palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Ascendis UK
7 May 2026

Further to the request for information, Table 1 below provides the modelled number of responders over time in each arm of the updated model with the revised response-based base case.

	6 months		5 years		10 years		20 years		30 years	
	Palopegteriparatide	Conventional therapy	Palopegteriparatide	Conventional therapy	Palopegteriparatide	Conventional therapy	Palopegteriparatide	Conventional therapy	Palopegteriparatide	Conventional therapy
Adequately controlled (responder)	73%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not adequately controlled (non-responder)	27%	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As per the information provided by the company on 29 April, response rates for both arms have been adjusted as it is not biologically plausible to be a responder without residual parathyroid hormone (PTH) function. The likelihood of having residual PTH function does not vary by arm so conservatively we have reduced the response accordingly (by 4.8%) in both arms. Furthermore, a patient's residual PTH function would be tested in NHS clinical practice, with optimisation and down titration undertaken before being considered eligible for palopegteriparatide.

The reduction in response rate for palopegteriparatide is based on an annual treatment discontinuation rate of [redacted]% based on the PaTHway trial as per the company submission. No patients in the PaTHway trial have discontinued treatment due to lack of efficacy.

Response to request – palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Ascendis UK
8 May 2026

Further to the request for information, the tables 1 and 2 provide the per cycle adverse event and CPRD resource use cost for each arm of the updated model with the revised response-based base case. Cycle 1 and cycle 130 are provided to show the variability over time.

Table 3 provides the figures confirming that excluding independence from calcium from the multi component endpoint does not alter the proportion of patients meeting the endpoint.

Finally, we noticed that the incremental costs were wrong in the previous revised base case results provided. Table 4 provides the results with the incremental costs cost correct. Apologies, but this means it is also wrong on the committee slides.

Table 1: Per cycle non-discounted adverse event costs

	Palopegteriparatide arm	Conventional therapy arm
Cycle 1	[redacted]	[redacted]
Cycle 130 (10 years)	[redacted]	[redacted]

Table 2: Per cycle non-discounted CPRD-based healthcare resource use

	Palopegteriparatide arm	Conventional therapy arm
Cycle 1	[redacted]	[redacted]
Cycle 130 (10 years)	[redacted]	[redacted]

Table 3: percentage of participants meeting the composite primary endpoint at week 26 with independence from calcium excluded

	Palopegteriparatide (n=61)	Placebo (n=21)
No. participants meeting the primary endpoint criteria at week 26	48/61 (78.7%)	1 (4.8%)
No. participants meeting the primary endpoint criteria at week 26 excluding independence from therapeutic doses of calcium	48/61 (78.7%)	1 (4.8%)

Table 4: Revised base case results (with incremental costs corrected)

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

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

NICE National Institute for Health and Care Excellence

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 November 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Parathyroid UK

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Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	We received a fee of £5,000 from Ascendis Pharma via Decisive Consulting for involvement in a patient survey in 2024. We also received two donations of £4,000 each from Amolyt Pharma in 2022 and 2023 for awareness projects.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We welcome the committee's recognition that chronic hypoparathyroidism has a considerable impact on people living with the condition and their carers. However, this impact cannot be overstated. Hypoparathyroidism is a rare, lifelong endocrine hormone deficiency that causes unpredictable and distressing episodes of hypocalcaemia. Trips to Emergency Departments should not be a regular feature of managing a long-term endocrine condition.

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	Our 2017 HypoPara UK survey of 230 patients published online, found that 45% required unplanned hospital visits to A&E, 38% needed intravenous calcium infusions, and 22% were admitted for an average of three days or more. Over 75% received no endocrinology follow-up afterwards. Patients frequently describe distressing experiences in A&E—waiting hours for treatment or facing disbelief about their diagnosis. This evidence illustrates the profound burden of living with chronic hypoparathyroidism under current management. Patients often delay or avoid attending A&E despite being unwell. This avoidance does not indicate mild disease; it reflects prior negative experiences and poor recognition of hypocalcaemia in emergency departments. Many report waiting hours for blood results before treatment is initiated and, in some cases, being met with disbelief or dismissive comments about their diagnosis. This leads to prolonged morbidity, distress and anxiety, and highlights the urgent need for a treatment that prevents crises.
2	We are concerned about the clinical input to the appraisal meeting. For a condition as rare and specialist as chronic hypoparathyroidism, it is essential that NICE ensures representation from clinicians with specific expertise in calcium and bone metabolism. General endocrinologists may see very few, if any, patients with hypoparathyroidism, and therefore cannot always appreciate the day-to-day complexity of management. Specialist input is vital to ensure that the committee's understanding reflects clinical reality and not textbook assumptions. We would also encourage NICE to include patient and clinician consultation on expert selection for future rare endocrine appraisals to guarantee that appropriate voices are heard.
3	There remains a major unmet need for effective hormone replacement therapy. Hypoparathyroidism is not simply a disorder of calcium balance—it is a true hormone deficiency caused by lack of parathyroid hormone (PTH). Current therapy with calcium and active vitamin D can temporarily normalise serum calcium but cannot restore normal renal, skeletal, or neurological physiology. Long-term use contributes to renal complications and reduced quality of life. Poor dose adjustment and lack of access to home monitoring lead to unnecessary fluctuations and risk. It was not mentioned in the committee meeting but patients also experience chronic pain and are often taking a combination of medicine to try and manage it with reports of little success. **Thiazide diuretics** are associated with yet more risk to the patient of hypercalcaemia, hypokalemia and hypomagnesia (S.Kahn 2025) as well as the need for (and difficulty of accessing**) increased monitoring**. In our 20 year experience of patient support we know that only a small group of people with chronic hypoparathyroidism can have generally good calcium control with standard treatment and even they will still need adjustments to be made over time to remain stable and still experience sudden hypocalcaemic episodes. Very few are able to taper their treatment with the long-term aim of achieving independence unless they already have good levels of PTH. We agree with the company that spontaneous recovery on standard treatment is not typically seen in people with chronic hypoparathyroidism. Most people struggle on for years. Replacing the missing hormone is the only physiological way to restore homeostasis. Palopegteriparatide provides that replacement and has already been used safely and effectively in other countries, showing substantial improvements in stability and independence for patients.
4	We do not believe the psychological and emotional impact of chronic hypoparathyroidism has been adequately considered. Living with constant fear of sudden hypocalcaemia leads to anxiety, depression, cognitive fog, and social withdrawal. Many patients describe 'never feeling safe' because symptoms can appear suddenly and unpredictably. These mental-health impacts are not captured by standard quality-of-life tools such as EQ-5D, which underestimates fatigue and

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	cognitive effects. Access to physiological hormone replacement would substantially reduce this psychological burden by restoring stability and confidence in daily life.
5	Self-management should not be misinterpreted as adequate disease control. In reality, it reflects lack of confidence in the system and fear of inadequate response in emergency departments with chronic hypoparathyroid patients reporting hours of waiting for treatment despite bloods being completed when feeling so unwell. It also does not mean or infer that care is often managed in primary care- the patient is alone managing symptoms at home with a prolonged recovery taking days to correct their own calcium while being very unwell. Primary care are not able to help in any urgent situation where a patient is experiencing symptoms of low calcium and not rising with increased oral calcium. They inform patients to attend emergency department as the GP cannot complete bloods with a quick turnaround and cannot provide treatment at point of access. There is no Consultant/Doctor oversight on the emergency or urgent low calcium episodes and GP's are not providing any additional support to the patients when they present. For the whole period of having low calcium they are feeling very unwell with many symptoms including pain.
6	Since the committee meeting, the European Society of Endocrinology (ESE) has published its new Clinical Practice Guideline for chronic hypoparathyroidism in adults (Bollerslev et al., Eur J Endocrinol 2025; 193(5): G49–G78). These guidelines post-date the committee's discussions and provide a stronger consensus for the use of PTH replacement therapy. They recommend treatment for adults who remain symptomatic, biochemically unstable, or have renal complications or impaired quality of life despite optimal conventional therapy. This confirms that the patients enrolled in the PaTHway trial mirror the population for whom hormone replacement is now internationally recommended.
7	The new ESE 2025 guideline provides clearer eligibility criteria than those available when the committee met. It defines chronic disease as persisting ≥ 12 months after surgery and identifies specific groups who would benefit from PTH replacement—those with unstable calcium, hypercalciuria, reduced kidney function, or persistent symptoms. We believe NICE should incorporate these definitions when finalising guidance. This will ensure that only the patients who meet clinical need receive therapy, addressing concerns about over-broad eligibility.
8	The assumption that a 2000 mg daily calcium intake defines 'not adequately controlled' may underestimate patient variation. Many patients exceed this for phosphate-binding purposes, increasing renal risk, while others require lower doses but still experience severe symptoms. PTH replacement offers physiological control without the renal toxicity associated with high oral calcium and vitamin D doses. We disagree with the committee's view that people meeting the criteria stated in the committee documents could still be "well controlled." Evidence from Siggelkow et al. (2019) shows that even those considered stable on conventional therapy experience profound quality-of-life impairment comparable to other severe chronic diseases. We therefore support use of PTH replacement for all patients meeting ESE 2025 criteria or with evidence of inadequate control under current treatment.

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9	The PaTHway trial demonstrated outcomes that are directly meaningful to patients. Normalisation of calcium while achieving independence from active vitamin D and calcium supplements is a major clinical milestone accepted by regulators (EMA, FDA, MHRA) as evidence of effective hormone replacement. It translates into fewer tablets, fewer emergency visits, and better quality of life—outcomes patients consistently identify as their top priorities. Patient-reported outcomes in the trial showed sustained improvements in physical and mental wellbeing that mirror real-world experiences from Europe and the US. The EAG's own revised base-case ICER (around £20,000 per QALY with the confidential PAS) sits within NICE's usual cost-effectiveness range. This is achieved largely through reductions in adverse events, A&E attendances, hospital admissions, and renal complications — all major cost drivers for this condition. These savings mirror patient testimony about reduced emergency dependence when calcium stability is achieved.
10	Equitable access to care remains a serious concern. Because hypoparathyroidism is rare, there is limited specialist expertise, and care quality varies regionally, leading to postcode inequality. Women face particular disadvantage: hormonal changes during menstruation, perimenopause, and menopause can exacerbate calcium fluctuations and mental-health distress. The Equality Act 2010 and the Public Sector Equality Duty require NICE to consider these differential impacts. Access to PTH replacement would standardise care and improve safety across all demographic groups.
11	The recommendation not to approve palopegteriparatide fails to reflect the profound unmet need of people living with chronic hypoparathyroidism and the consistent evidence of benefit. It perpetuates reliance on an outdated, symptomatic treatment paradigm that leaves many patients unstable and exposes the NHS to ongoing avoidable costs. Chronic hypoparathyroidism is a rare, serious hormone-deficiency disorder causing unpredictable and debilitating symptoms. Conventional therapy provides incomplete and unstable control, exposing patients to repeated crises, renal complications, chronic pain and psychological harm. Hypoparathyroidism is the only endocrine deficiency disorder in which the missing hormone is not replaced.Palopegteriparatide replaces the missing hormone, restoring physiological regulation, stability, and independence. The PaTHway trial, international experience, and the 2025 ESE guideline all demonstrate safety, efficacy, and value for money. The 2025 ESE guideline, produced by a multidisciplinary European expert group including patient representatives, further supports the cost-effectiveness argument by **establishing PTH therapy as standard of care for a defined subgroup, not an experimental option.** We urge NICE to recognise this as standard endocrine replacement therapy and recommend it for routine NHS use for eligible adults with chronic hypoparathyroidism

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Society for Endocrinology

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	<table><tr><td>Ascendis</td><td>£1250</td><td>Seed of Change campaign</td><td></td></tr><tr><td>Ascendis</td><td>£2600</td><td>Seed of Change campaign</td><td></td></tr><tr><td>Ascendis</td><td>£14000</td><td>EA25 Event</td><td>Symposia and stand</td></tr><tr><td>Ascendis</td><td>£23,500</td><td>SfE BES 25</td><td>Symposia and stand</td></tr><tr><td>Total</td><td>£41,350</td><td></td><td></td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td>Ascendis</td><td>£31,500</td><td>SfE BES 26</td><td>agreed not paid symposia and stand</td></tr></table>
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Has all relevant evidence been taken into account? Largely, we think that this is the case but would draw the committee's attention to the recent publication of updated European Society of

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	Endocrinology guidance on the management of chronic hypoparathyroidism in adults: *European Journal of Endocrinology*, Volume 193, Issue 5, November 2025, Pages G49–G78 (https://doi.org/10.1093/ejendo/lvaf222)
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?: We are concerned that the potential role for routine use of thiazide diuretics in the management of this condition may have been somewhat over emphasised by the committee's interpretation of the evidence: Specifically, many of us in the Society for Endocrinology have significant experience of use of thiazide diuretics in patients with treated chronic hypoparathyroidism and hypercalciuria. Chronic hypoparathyroidism treated with conventional calcium and active vitamin D is frequently complicated by hypercalciuria, affecting around 40% patients and associating with nephrocalcinosis and reduced renal function (Front Endocrinol (Lausanne). 2023 Nov 2;14:1244647. doi: 10.3389/fendo.2023.1244647.). While attempting to add on a thiazide diuretic is commonplace, clinical practice reveals that this is usually unlikely to resolve the hypercalciuria. Often hypokalaemia or other side effects rapidly become dose limiting. There is some experimental evidence suggesting that the hypocalciuric effect of thiazides is attenuated in the PTH-deficient state (Metabolism. Volume 22, Issue 2, February 1973, Pages 139-146. https://doi.org/10.1016/0026-0495(73)90264-3) One recent survey of NHS clinical practice in the UK setting revealed that only 6.25% of patients with chronic hypoparathyroidism were routinely receiving thiazide or thiazide like diuretics as part of their treatment underlying their limited role in real world treatment of this condition (Clinical Endocrinology. Volume97, Issue5. November 2022. Pages 562-567. https://doi.org/10.1111/cen.14798). In summary, thiazide diuretics while theoretically appealing, in practice are usually not significantly contributory in managing patients with hypoparathyroidism.
3	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?: We are also concerned that the committee may have over emphasised the opinion that standard of care for treatment of chronic hypoparathyroidism (ie activated vitamin D and calcium supplements) is more effective and more acceptable to patients than is really the case. As a group of expert clinicians who work in this field, we feel it is important to acknowledge that standard of care treatment is really a "workaround" treatment of hypoparathyroidism that has become established practice over recent decades. Hypoparathyroidism however like other endocrine deficiency states deserves direct treatment with the missing hormone. While, in a high proportion of patients, perhaps at least 60% or so, reasonable balance of calcaemia and symptomatology can be achieved, this treatment approach has significant limitations. Specifically, although these short-term factors are important, what is not so clear is whether this workaround treatment even in patients who fare reasonably well in the short-term, results in compromise of renal function and skeletal health in the long-term. There is a significant body of evidence in the literature linking treatment of chronic hypoparathyroidism with activated vitamin D and calcium supplements to risk of chronic kidney disease, risk of fragility fracture and poor quality of life (Astor, M.C., et al., Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab, 2016. 101(8): p. 3045-53. Clarke, B.L., Epidemiology and Complications of Hypoparathyroidism. Endocrinol Metab Clin North Am, 2018. 47(4): p. 771-782. Underbjerg, L., et al., Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. J Bone Miner Res, 2013. 28(11): p. 2277-85.

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	Siggelkow H, C.B., Germak J et al, Impact of Chronic Hypoparathyroidism on Health-Related Quality of Life: Findings from a 13-Country Patient Survey. Journal of the Endocrine Society 2019. Underbjerg, L., et al., Postsurgical hypoparathyroidism–risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Miner Res, 2014. 29(11): p. 2504-10. Sikjaer, T., et al., Hypoparathyroidism: changes in brain structure, cognitive impairment, and reduced quality of life. J Bone Miner Res, 2024. 39(7): p. 855-866. Sikjaer, T., et al., The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. J Bone Miner Res, 2011. 26(10): p. 2358-70. Underbjerg, L., T. Sikjaer, and L. Rejnmark, Health-related quality of life in patients with nonsurgical hypoparathyroidism and pseudohypoparathyroidism. Clin Endocrinol (Oxf), 2018. 88(6): p. 838-847. Underbjerg, L., T. Sikjaer, and L. Rejnmark, Long-Term Complications in Patients With Hypoparathyroidism Evaluated by Biochemical Findings: A Case-Control Study. J Bone Miner Res, 2018. 33(5): p. 822-831. Ridder, L.O., et al., Determinants of hypercalciuria and renal calcifications in chronic hypoparathyroidism: A cross-sectional study. Clin Endocrinol (Oxf), 2021. 95(2): p. 286-294, and others).
4	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?: We are also concerned that the committee may be under appreciating a hidden burden of acute presentations to Emergency Departments, Acute Medicine Units, day wards and other NHS acute settings relating to hyper and hypo calcaemia associated with use of standard of care hypoparathyroidism therapy. We believe this may have happened as HES coding does not seem to reliably capture these presentations but as an expert group of clinicians, we know that they are happening on a frequent basis. This idea would be supported by published literature from an international group of authors but including UK data showing that between 38.5% and 47.7% of chronic hypopara' patients in one survey had had at least one emergency department presentation in the preceding 12 months (Journal of Bone and Mineral Research, Vol. 37, No. 12, December 2022, pp 2602–2614. DOI: 10.1002/jbmr.4675) and in another survey of treatment of chronic hypoparathyroidism patients in a UK NHS setting, 16% had had an unplanned admission in the preceding 12 months (Clinical Endocrinology. Volume97, Issue5. November 2022. Pages 562-567. https://doi.org/10.1111/cen.14798). The health economic burden of such a high incidence of emergency presentations and admissions for dyscalcaemia in chronic hypoparathyroidism patients is likely to be significantly under estimated in current health economic modelling of the impact of standard of care treatment of this condition.
5	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?: We are furthermore concerned that the committee may be potentially over-estimating the size of any future palopegteriparatide treated cohort within the overall chronic hypoparathyroidism population. In reality only a small minority of cases will potentially receive palopegteriparatide if it is approved for use in the NHS. Now that the updated European Society of Endocrinology clinical practice guidelines have been published (*European Journal of Endocrinology*, Volume 193, Issue 5, November 2025, Pages G49–G78 (https://doi.org/10.1093/ejendo/lvaf222) these could be used as a basis for a UK palopegteriparatide treatment pathway. Hypoparathyroidism is a rare disease and established across England are rare disease collaborative networks for bone and mineral disorders. These function as regional MDTs. We have experience with recent NICE-approved drugs in rare diseases and high cost drug utilisation with burosumab for X-linked hypophosphataemic rickets. We have worked highly effectively with NHS England to derive

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	effective start and stop criteria around this drug. We are keen to apply such a gait keeping function to access to PTH replacement therapy in patients who are deemed to be not adequately controlled on conventional therapy despite optimisation of the latter. As a group of responsible clinicians, we are well-positioned to be able to implement such control and regulation around these parameters that would align to the European guidelines that have just been produced. We feel it is appropriate to allow access to PTH replacement therapy for a subgroup of hypoparathyroid patients in the first instance; those with not adequately controlled hypoparathyroidism despite optimised care and this aligns to the European guidance. There are systems and processes within the way that we work clinically across bone and mineral metabolism that would facilitate this approach.
6	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We do not feel that this is the case, specifically with reference to unmet clinical need. As a group of expert clinicians we feel that the EAG's advice to the committee has down played the extent to which a significant minority of patients with chronic hypoparathyroidism find their treatment with standard of care medication leads to treatment dissatisfaction, high pill burden, poor quality of life, poor symptom control and leaves a significant unmet clinical need. There is a significant academic literature supporting this assertion (Astor, M.C., et al., Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab, 2016. 101(8): p. 3045-53. Siggelkow H, C.B., Germak J et al, Impact of Chronic Hypoparathyroidism on Health-Related Quality of Life: Findings from a 13-Country Patient Survey. Journal of the Endocrine Society 2019.) and furthermore the patient voice as represented by parathyroid UK at the committee meeting supports this view in the strongest possible terms.
7	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We also do not feel that this is the case, specifically with reference to the way in which these recommendations may lead to the UK being a significant outlier in comparison with international comparators. Palopegteriparatide is already established as part of routine clinical care for a small proportion of cases and where clinically indicated for those meeting suitability criteria in several European nations and in the North American health systems amongst others.

Insert extra rows as needed

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation denies treatment to the small number of patients who cannot be controlled with conventional therapy. Patients undergoing parathyroidectomy for secondary hyperparathyroidism due to chronic kidney disease are more likely to be readmitted within 30 days due to hypocalcaemia. A small number of such patients are difficult to control on

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	calcium supplements and active vitamin D analogues and struggle with frequent readmissions to hospital for intravenous calcium supplementation which carries significant clinical risks. Ferrandino R, Roof S, Ma Y, Chan L, Poojary P, Saha A, Chauhan K, Coca SG, Nadkarni GN, Teng MS. Unplanned 30-Day Readmissions after Parathyroidectomy in Patients with Chronic Kidney Disease: A Nationwide Analysis. Otolaryngol Head Neck Surg. 2017 Dec;157(6):955-965.
2	We are concerned that patients with kidney disease are further disadvantaged by the negative judgement as efficacy of recommended standard care with thiazide diuretics if reduced in patients with significant kidney disease (eGFR <30ml/min).
3	The high calcium load in the face of hypoparathyroid state increases the risk of cardiovascular calcification in patients who are already at high risk of cardiac death. Patients not adequately controlled requiring very high doses of calcium and vitamin D would benefit options to reduce their calcium load.
4	
5	
6	

Insert extra rows as needed

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Single Technology Appraisal

Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Comments on the draft guidance received through the NICE website

Name	[redacted]

Comments on the DG:

Q. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The equality impact statement correctly states that women are disproportionately affected by this condition. There is a clear gender inequality in denying effective hormone replacement treatment for a disease predominantly effecting one gender.

This decision assumes that 'standard care' available in the NHS is effective and acceptable: it is neither of those things and it is disingenous to suggest otherwise.

Hypoparathyroidism is the only endocrine disorder not managed by hormone replacement therapy. Active vitamin D analogues such as alfacacidol are poor substitutes. They do not replace the complex actions of PTH which are far more wide-reaching than just achieving an in-range serum calcium. This lack of hormone therapy places patients at risk of serious long term morbidity from ineffective calcium metabolism and clearance such as excess rates of renal and cardiac disease, dementia and abnormal bone density.

Significant weight seems to have been placed on the lack of bendroflumethiazide use in the control arm of the trial, but the reality is that thiazide diuretics are poorly tolerated due to their side effect profile, expose patients to additional side effect resulting in hospitalisation (e.g. hypokalaemia) and do not normalise urinary calcium clearance or prevent ectopic calcium deposition.

I cannot state more emphatically how devastating this iatrogenic condition has been. It has decimated my life and I live with this invisible disability daily despite not requiring frequent hospital admissions for dangerous hypocalcaemia. The long term excess morbidity of being unable to exercise

(due to muscle fatigue and paraesthesia) and of ectopic calcium deposition, combined with QUOLY lost need to be given fair weighting in NICE's decision.

Name	[redacted]
Comments on the DG:	

Hypoparathyroidism is such a poorly understood disease even amongst doctors specialising in Endocrinology, and as such patients with this condition have both a terribly debilitating condition, which is poorly acknowledged and often dismissed, and treatment options are which are outdated, poor, and do not adequately resolve symptoms for many, and cause side effects relating to calcium accumulation, particularly pertaining to renal function deterioration, adverse bone health, and cerebral and cardiac effects.

Hypoparathyroidism is the only endocrine disorder for which we do not use replacement of the hormone that is lacking, but instead dabble with the products and effects of that hormone, which is a poor physiological substitute.

We know from basic physiology that calcium is one of the most fundamental ions in the human body, used in every muscle contraction and action potential that is required, it's role so very essential to life, with its levels being very tightly controlled in normal health to achieve this. Yet as clinicians we are failing to understand the physiological consequences and therefore debilitating symptoms a patient experiences when calcium levels at the site of these physiological processes is not at the required homeostasis and availability. Sporadic, one-off measurements of corrected calcium do not aptly represent what is occurring at the nerve synapse nor muscle fibre, just like one-off blood glucose measurements in a diabetic patient tell us little about the overall physical control or symptomology. When assessing outcomes in hypoparathyroidism patients, we really need to acknowledge that trials based on the calcium level are really a poor measure of the real outcome, patient symptoms and more widely, ability to live, thrive and perform their required roles.

There is no other endocrine condition where we are so behind the curve, where we know the physiology is short acting, fluctuant and exacting numbers are crucial to health, yet we dabble with long acting Alfacalcidol, Calcidiol and a bit of calcium, and expect this to adequately control patient's symptoms and 'treat' them, particularly given a patient (unlike in diabetes for example) has no way of knowing their calcium level in that moment, as there is no 'point of care' testing. Yet, they are expected to moderate their calcium intake, not to mention vitamin D and Magnesium, in a desperate attempt to get somewhere near normal biochemistry. This is an impossible

ask for many, particularly with such inadequate support from clinicians. These treatments do not achieve anywhere near the same biochemical picture as the replacement of the missing hormone could do.

As such, many hypoparathyroidism patients have terribly symptomatic lives every single day, and have an uphill battle just to get up, move, and do the basics that life requires. The calcium simply isn't there in the correct, precise way that a normal biochemical mechanism provides. We are sluggish, the brakes are on, everything is a battle. We struggle to function, move, think without a thick brain fog, and that's when corrected calcium levels are often 'in the normal range' as quoted on bloods results ranges, yet are widely fluctuant within that wide, 'normal' range, so much more fluctuant than in normal health. Furthermore, when our levels are very out of normal and we are medically hypo or hypercalcaemic, we do not know (we have no levels to work with, unlike in diabetes for example) and the symptoms of hypo and hyper are strangely similar. I have been in situations where my symptoms I have interpreted as low, so try to increase calcium over a few days, only to find I'm getting worse (lower?) or in fact was high all the time and getting even higher. This is the reality of this condition. And so we have a long way to go to bring treatment into modern times, we really are fundamentally in the dark ages with it, not to mention the systemic side effects of excess calcium to other body organs and systems.

This consultation evaluates a PTH product, yet fails to really comprehend both the condition, and the complete inadequacy of current treatments, and the devastating effect that hypoparathyroidism symptoms have on an individual. This drug clearly is a huge advancement in treatment, replacing what is missing physiologically. It is not perfect yet, it is new. However, it is likely life-changing for many.

What a backward step in treatment to reject replacement of the hormone a hypoparathyroidism patient is actually lacking, to revert back to using other products further downstream in the biochemical pathways, given the huge limitations we know we have with these agents, and how suboptimal hypoparathyroidism care is at present.

[redacted]
General Practitioner, & former pharmacist

HypOparathyroidism patient as of this year

GP having to look into ill-health retirement aged 45-years old because of the devastating effects of this condition, and inadequacy of treatment

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Having trained as a doctor at Barts, London and lived for 26 years as a carer of my wife who has post surgical hypoparathyroidism, I am appalled that NICE is not recommending that Palopegteriparatide is prescribed to patients with this life-limiting condition. When an effective treatment for the one endocrine condition that has no replacement hormone is finally developed, it seems unconscionably cruel that it will not be available to patients in the UK, the 6th wealthiest economy in the world.

Name	[redacted]
Comments on the DG:	

I am a parathyroid patient and have several friends who have hypoparathyroidism, either from illness or poor quality parathyroid surgery that mistakenly removed all their parathyroid glands. The impact on their day to day existence is severe and often life threatening.
Please allow them to have this hormone replacement therapy, so they can have some quality of life. It really is one of the most debilitating conditions I've seen, and almost all the risks can be mitigated by providing the hormone replacement that could be made available easily.
We are the only western country that doesn't offer this to hypoparathyroid sufferers - and they really do suffer.
I urge NICE to think about these individuals, who have to be on constant alert of a crisis, who feel exhausted and cannot work, and who suffer with medical consequences of this condition (often renal damage).
These are real people with families and children to care for and they are valuable citizens who need really this.
I can't help wondering if there is an element of sexism too - if this happened more to men (like for example diabetes) then the decision might be very different!

Name	[redacted]
Comments on the DG:	

I am deeply concerned about the decision to not use palopegteriparatide (Yorvipath) in the UK. My son and his three boys all have the genetic type of Hypoparathyroidism. My son is currently using Yorvipath, which has literally saved his life. He has nephrocalcinosis of both kidneys. He has now had two operations to remove stones from both kidneys, following which he contracted sepsis and nearly died. He has been on Yorvipath since the first operation and it has transformed the way he can live and it has prevented further calcification. Due to calcification on his brain, he also suffered a stroke. He has had multiple emergency trips to hospital over the years, but they have stopped since taking Yorvipath. I was really hopeful that my grandchildren would be able to have Yorvipath as well in order to prevent calcification. Please reconsider this decision so that people who rely on this treatment aren't left without a life saving option.

Name	[redacted]
Comments on the DG:	

I feel this is a poor decision as it is denying people who might really benefit from treatment with palopegteriparatide but are uncontrolled with standard treatment.
This is a rare disease and the only endocrine disease with no replacement hormone available to patients. It is clearly not well understood by many clinicians and certainly not by those outside the endocrine world. Some patients are extremely symptomatic on standard treatment. The new European hypoparathyroid guidelines put more emphasis on treating symptoms and not calcium levels and that palopegteriparatide should be an option.
Ascendis should be given the opportunity to re-present the data in response to the comments made to enable a more favourable outcome and equity of access.

Do you need vitamin D ie Colecalciferol or activated vitamin D ie Alfacalcidol or calcitriol. I think this needs to be clear

Name	[redacted]
Comments on the DG:	
I'm concerned about the decision to reject Yorvipath, a vital drug currently unlicensed in the UK. This injection has transformed my partner's life and we all depend on this becoming licensed for his children to have an equal opportunity to flourish in their adult lives. I urge you to review this decision so those who depend on it, arent left without essential treatment.	

Name	[redacted]
Comments on the DG:	
This will change lives and has already been proven to in those lucky enough to be on it. I am 37 years old and in the 13 years since I got idiopathic hypoparathyroidism I have had to give up a degree, change my whole lifestyle from being very active playing competitive ice hockey to having to limit my exercise. I now have kidney problems and I am genuinely scared for my future. Even when my levels are ok I dont feel well and that is because we are not getting a replacement hormone treatment as there isn't one on the NHS. Please allow us the proper hormone replacement treatment we all deserve to give lives and quality of life back.	

Name	[redacted]
Comments on the DG:	
Im deeply concerned about the decision to reject Yorvipath, my 3 children and I depend on this drug being licensed in the uk. Please reconsider this decision so people who rely on this treatment aren't left without a safe option.	

Name	[redacted]
Comments on the DG:	
I am deeply concerned about the decision to not use palopegteripatide (Yorvipath) in the UK. My son and his three boys all have the genetic type of Hypoparathyroidism. My son is currently using Yorvipath, which has literally saved his life. He has nephrocalcinosis of both kidneys. He has now had two operations to remove calcification from both kidneys, following which he contracted sepsis and nearly died. Due to calcification on his brain he has	

also suffered a stroke. He has had to register as disabled. He has been on Yorvipath since the first operation and it has transformed the way he can live and it is preventing further calcification. I have been living with the hope that my three grandchildren would be able to get Yorvipath, I can't bear the thought that they will all have to go through the incredibly painful life that my son has. My son has had multiple emergency trips to hospital over the years, which will have been a huge cost to the NHS. Since being on Yorvipath, these emergency trips have stopped. Please reconsider this decision so that people who rely on this treatment aren't left without this life saving option.

Name	[redacted]
Comments on the DG:	
I disagree with the decision not to provide this treatment in the UK, especially when it is available in the EU and USA. I have 3 grandsons with this condition. They are aged 14, 11 and 6. Without this treatment they are going to suffer the pain which there father is currently experiencing. This medicine is life changing for them, and it is scandalous that they will be denied access to it in this country.	

Name	[redacted]
Comments on the DG:	
This medication is the only one available for my 3 young grandsons who inherited hypoparathyroidism from their father If it is not made available there is no other medication available to them. Please reconsider	

Name	[redacted]
Comments on the DG:	
This medication is life saving, and desperately needed. Please reconsider your decision	

Name	[redacted]
Comments on the DG:	

Q. Has all of the relevant evidence been taken into account?

Not at all. This is a shocking decision.

Q. Are the recommendations sound and a suitable basis for guidance to the NHS?

Absolutely not because there is no suitable alternative for patients.

Additonal Comments that could not access the NICE website portal

1	To whom it may concern I would like to express my disappointment that Yoripath has not been approved. I have had this for years. Hypoparathyroidism is both physically and mentally exhausting. I find it massively affects my day to day life. I have to go to hospital a lot and not only do NHS have not much knowledge about the condition but also we do not have the medication or home testing available to us as other endocrine conditions. We are massively discriminated by the healthcare system. You would not treat someone with diabetes as you do us and Hypocalcemia is just as import. The current treatment available is not sufficient and it causes more problems such as Kidney damage, muscular issues etc. 15 years ago they refused us Natpar and patients have suffered irreversible kidney damage in that time. We are the ONLY endocrine condition without a replacement hormone. Can you imagine treating someone with diabetes the way you do us? We have no effective treatment or home testing kit. By approving Yoripath is will save the NHS money rather than the regular hospital admissions, IV infusions, treatment of the conditions caused by the current medication available. I hope you are able to reconsider and if someone in your family had this condition would you want them to have the best available treatment and not be ignored. This massively affects our quality of life. Many thanks [redacted]
2.	I have genetic hypopara (Barakats syndrome). I had calcium control until my late 20's and then my glands stopped working. By 31, I had unstable brittle hypopara. Conventional therapy of oral calcium and activated vitamin D initially helped but my tolerance and ability to absorb worsened with time. At my worst I was taking 64 meds a day, and they were 4 hourly, without this I was dependant on IV calcium. Eventually I got approved for Forsteo (off license) and had an initial positive response but within a few months tolerance grew again and I went from one daily shots to 3 times a day. Again my tolerance grew and I needed meds and forteo to try manage with 3 calcium infusions a week. Thanks to research my consultant decided to try Forteo via a diabetic pump which got me to having a low week a month, a high week a month and two good weeks a month. This went on for 2 years.

	Due to need for IV calcium on the regular I had to have a picc line or central access at all times - this caused sepsis multiple times which in turn affected my calcium. Low calcium meant constant leg pain for years, muscle cramping and difficulty with stairs, I ended up needing mobility scooters and have a parking pass because my body was so deconditioned from the condition. In 5 years I went from playing competitive senior level football to barely being able to get up the stairs. 2025 has been the toughest year yet. By October I had been septic 9 times. Microbiology told me I was developing antibiotic resistance and another bout would potentially kill me. Thankfully in October of this year, the HSE approved patient specific funding for Yorvipath. I'm 35 years old and this was a Hail Mary… no one thought it would work aswell as it does. I'm 6 weeks on Yorvipath. My daily leg pain is gone. I sleep through the night. I can do stairs, I don't go into tetany or muscle cramps anymore. I'm not back to work or sport yet but hoping January will be my month. I'm so grateful to Acendis and to Yorvipath it's been a miracle drug. Hypopara affects every part of your being and my one wish is that everyone gets to try this drug and claim back their lives because in 6 short weeks mine has been transformed. Kind regards, [redacted]
3	[redacted] I was unable to add my comments to the NICE site – did try so hard and wrote them but the site would not save to enable me to submit. I wanted to just add personal note to item 4 I think it was. Having lived with Hypoparathyrodism for many years I find current treatment is not keeping me stable. I have a daily battle to trying to manage this condition, I find exercise or foods affect me – sometimes quite drastically and quickly. At my best I have pins and needles & cramps mildly at points each day – but around half my week it is more severe with brain fog and worse of all muscles fatigue. If I am low below 2.1 is manageable with rests – if above 2.3 (high for me) I really struggle – The feeling is that my body is shutting down, it can take 2 stops/rests to get upstairs – if out I need help to get me home.

	And definitely cannot drive if high – the effort in muscles is too much. On a recent break my friends who know I have this condition were shocked when they witnessed just how quickly and how much I am affected – they told me I must go a speak to my doctor as being like this is not normal – but I already have the care of a good Endocrinologist – I am already on the best medicine allowed currently – sadly having a body regularly shutting down is my current normal. I had a full life before my thyroidectory – and much less of one now despite my best efforts. My hope for some years now has been better treatment coming through to make life more bearable.
4	Hypoparathyroidism is the worst disease that robs you of your quality of life. My parathyroids were damaged following TT for thyroid cancer in 2019. Previously I enjoyed full physical and mental health. I raised 4 children and was fully active and able to do what I wanted. I was a property developer, keen gardener, cooked great food, kept the house well and could do everything and anything. I take 2mg alpha calcidiol daily since TT and my calcium levels which are tested about every three months remain pretty stable. However my quality of life is dire. I cannot rely on feeling well. I have to rest for a least 4 hrs a day and can only be active for short spells here and there. Otherwise my calcium goes low. I get very weak have to eat calcium and go to bed for 3 hrs. Calcium levels fluctuate alot during the day. The body uses alot of calcium but we dont have home testers to show these fluctuations. Bone pain is desperate with this disease also. Constant burning pain in legs and arms. Nothing helps this pain. My mental health has also really suffered from this disease which makes life very hard to manage or achieve anything. I take antidepressants but I dont think they help much. Hypopara patients are just existing not really living. I find its only my immediate family understand because they see how I am day in day out. There hasnt been enough research work done on this rare disease. We are being discriminated against not being given the hormone we are missing as standard treatment of care. Also not having home calcium testers. I am just praying yoripath will be made available in the UK so I can be an active grand mother. I can do very little right now spend 80% of my time in bed or on the couch. Any exertion is risky for me as I go low easily. I have been semi concious with seizures at 2.18 calcium and have to have intravenous calcium. When this happens I feel like I am dying my heart rate goes really low. Thank you for consideration of our needs. This drug may be expensive but those who are on it can lead normal lives with confidence of health. Hypopara patients at present do not have anysuch assurance.
5	Here are my comments for NICE. It seems shocking in this day and age that Yorvipath parathyroid hormone, a drug approved in the USE and Europe, which prevents irreversible kidney damage would

not be approved. It allows calcium levels to be stabilised without potentially life-threatening consequences.

I cannot understand how a preventative option would not be favoured over all others.

My family has three individuals who have a CASR activating mutation (ADH type 1) which causes parathyroid hormone. There is a 50% chance this will be passed on their children. Whilst they are relatively mildly affected the impact on the NHS every year has been as detailed below.
Around 10 ambulance calls/emergency hospital admissions
Regular GP trips and blood tests.
Annual ultra sounds
GOSH Kidney clinic and adult renal clinic
2-3 reviews per at Royal London Hospital.
Adult endocrinology

This involves GPs, nurses, doctors,admin support staff, hospital cleaners, caterers, laundry staff and even people to build facilities. The list goes on.

They need to be monitored due to nephrocalcinosis and kidney cysts. A drug that would prevent such conditions would significantly reduce the burden on the NHS and staff, and would likely cut half of the appointments.

Not only that it would improve the quality of life for patients and families. This leads to days lost from school and work. It also impacts teachers who then have to take time to send out extra work missed.

A decision to not approve the drug seems short-sighted and in the longer-term will cost the NHS significantly more money.

There is a still a cost of the one alpha. If they suffer kidney damage that needs more significant treatment this will a huge cost in terms of drugs, medical expertise and more significant treatment. At worse it could lead to not being able to work and being on benefits.

Further just because a condition is rare – a sufferer should not be denied the best treatment. What right does someone have to play god and to say if you are unlucky enough to be born with a rare condition, we will not treat you as well as another patient. It is not as though the kidney damage is self-induced. In fact my daughter's nephrocalcinosis mainly suffered at the age of 3 is the result of over medication by medical professionals – it was likely well intended but ill-informed and had their been more careful monitoring and blood tests it would have been avoided.

I urge NICE to reconsider their decision. Ultimately denying access to the drug is going to negatively impact numerous lives and not just those of the patients and place a financial burden on society.

[redacted]

6	Dear NICE, Since 2018 when originally diagnosed with Hypopara my/our lives changed , multiple hospital visits for calcium tops ups, the medication available to date does not allow me keep me stable . Hypopara is bought about often through surgery, you are not informed of the the outcome if your PTH glands don't work again, this condition for many like my is completely debilitating on every level of my life, living with the condition is very difficult , I had to stop work, move house (down size). Because even when we appealed for Forteo I was denied this by NICE . Then came kidney cancer and a partial nephrectomy , which dosnt help as our kidneys suffer terribly. Waking up each day not knowing how you will feel, lack of sleep because of continuing tetany, muscle cramps, heart palpitations, brain fog, lack of coordination, fatigue , at times I question if I have dementia . This condition has shrunk my world , I am now very unreliable as you are unable to function anywhere near normal . I know we can't fix all medical conditions, however knowing that there is a drug out there and could possibly help many of us with this chronic condition is exciting , but crushing as we are being denied access. Hypopara patients are overlooked by so many in the medical world through lack of knowledge and has the least funding in endocrinology. There are days I just done want to continue (no not suicidal) . I truly hope that you will listen to us as patients who are in desperate need of this medicine. Best wishes [redacted]
7	To the NICE Evaluation Committee, I am submitting this statement as someone who has lived with permanent, post-surgical chronic hypoparathyroidism for over 25 years. I understand the consultation period has closed, but I respectfully request that my experience be included as late evidence ahead of the February 2026 committee meeting, given the severity of my condition and the profound long-term implications of the draft recommendation. 1. 25+ years without parathyroid hormone has taken a significant toll on my body For more than a quarter of a century, I have lived without the hormone that regulates calcium and phosphate. This is not an episodic condition — it is a relentless, daily struggle to keep my body functioning normally.

Even with discipline, strict adherence to medication timing, and diligent self-management, I continue to experience:

• sudden drops in calcium

• muscle symptoms, tingling, and weakness

• mental slowing and “brain fog”

• debilitating fatigue

• unpredictable days that limit work, social activity, and confidence

• anxiety about swings I cannot fully control

After 25 years, these symptoms have not disappeared — they have worn me down.

2. The long-term consequences of conventional treatment are now becoming real

When you live with hypoparathyroidism for 25 years, the long-term complications are no longer theoretical. They accumulate — slowly, silently, and often irreversibly.

Kidney Health

I am already experiencing deteriorating kidney function, something widely recognised as a major risk of long-term high-dose calcium and active vitamin D therapy. Conventional treatment is not benign; over decades it actively contributes to:

• hypercalciuria

• nephrocalcinosis

• kidney stress and functional decline

This is now a personal reality for me.

Cardiovascular Health

I also now live with:

• peripheral artery disease (PAD)

• a permanent left bundle branch block (LBBB)

	These are serious cardiovascular conditions that dramatically raise my vulnerability to the vascular calcification and arterial stiffening known to be associated with chronic hypoparathyroidism and its treatment. For someone with my history, the combination of: • 25 years of calcium/calcitriol therapy, • phosphate imbalance, and • cardiovascular disease creates a trajectory that is deeply concerning. Cumulative Disease Burden After more than two decades, the condition has not stabilised. The damage is cumulative: to my kidneys, my cardiovascular system, my daily functioning, and my long-term health prospects. 3. The draft NICE decision does not reflect what 25+ years of lived experience shows Clinical trials lasting 26 weeks cannot capture what this disease does over 10, 20, or 30 years. 4. After 25 years, the need for a genuine hormone replacement is urgent Palopegteriparatide is not simply another drug. It is a physiological replacement for a hormone my body permanently lost. 5. I respectfully urge NICE to reconsider A 26-week trial cannot tell the story of 25 years of lived harm. Thank you for considering my experience. [redacted] Date: 28 November 2025

Response to palopegteriparatide (Yovipath) NICE consultation

28 Nov. 25

Dears,

I am writing in response to the Committee Evidence Review and consultation documents regarding palopegteriparatide (Yorvipath). Having reviewed the materials carefully, I wish to contribute to the consultation in three parts: first, by addressing several points within the committee papers that I believe are factually or clinically disputable; second, by providing a concise evidence-based summary of the wider clinical and economic considerations not fully reflected in the current assessment; and third, by sharing my personal experience of living with severe, postsurgical hypoparathyroidism as additional qualitative evidence of the limitations of conventional therapy and the potential impact of PTH replacement. I hope that my submission assists the committee in reaching a fully informed and patient-centred conclusion.

The purpose is to summarise why key statements in the NICE consultation on palopegteriparatide do not fully reflect the available evidence regarding (a) urinary calcium outcomes and (b) clinical benefit (health-related quality of life , HRQoL) and to outline the economic argument that treating chronic, inadequately controlled postsurgical hypoparathyroidism may avert expensive downstream costs.

Short summary of the NICE's consultation position

NICE's consultation document raises concerns about clinical and cost-effectiveness and about whether the benefits claimed for palopegteriparatide (improved symptom control, potential reduction in urinary calcium and downstream renal harm, and improved QoL) are sufficiently proven relative to current care and price. NICE

Contents

Key evidence summary of counter-points

1) Urinary calcium (hypercalciuria): the clinical evidence is stronger than NICE's summary implies

Clinical development of PTH-replacement biologics (including the TransCon/"PaTH" programme and later agents e.g. Eneboparatide or MBX-2109) has reported *reductions in urinary calcium excretion* as part of the intended pharmacodynamic effect. Several studies and trial reports (phase 2/3 programmes) show that when physiological PTH activity is restored, patients commonly reduce or stop high oral calcium doses and urinary calcium either normalises or decreases , a finding with direct relevance to risk of nephrocalcinosis and progressive renal damage. The PaTH/TransCon programme and related trial reports are referenced in the NICE dossier and in primary publications of the programme. NICE

Conclusion: NICE's economic arguments hinge on uncertainty about whether therapy will lower hypercalciuria and therefore reduce later renal disease. The published trial programme reports do indicate urinary calcium improvements in treated patients , that is precisely the biological rationale for expecting renal-sparing benefits.

Evidence sources: phase-2/phase-3 PaTH/TransCon clinical programme publications and associated summaries. NICE & Hypopara

2) Health-related quality of life (HRQoL) and symptom burden

Randomised trial data and clinical reports (phase 2 and subsequent programme outputs) consistently show clinically meaningful improvements in patient-reported symptoms and HRQoL measures for patients receiving PTH replacement compared with placebo/conventional therapy. Improvements include reduced muscle cramps, less cognitive impairment/brain fog, reduced fatigue and improved daily functioning , outcomes cited as core unmet needs in hypoparathyroidism. These outcomes were prespecified in development programmes and have been reported in trial readouts. NICE

Conclusion: NICE's guidance must incorporate the recognised, multi-system symptomatic burden of chronic hypoparathyroidism (beyond biochemical targets). QoL gains are a legitimate clinical outcome and should carry weight in cost-effectiveness models.

3) Healthcare utilisation and economic burden of chronic (inadequately controlled) hypoparathyroidism

Published analyses and patient-survey studies demonstrate substantially greater healthcare usage and higher costs for patients with chronic hypoparathyroidism (versus those who recover). One accessible summary (recent evidence reviews / news summaries of peer-reviewed studies) cites first-year total healthcare costs that are substantially higher in chronic cases (e.g. >US$15k in first year in one analysis) compared with transient cases. Chronic hypoparathyroidism is also associated with increased risk of renal disease, which carries high long-term costs (dialysis, transplant, chronic nephrology follow up). Hypoparathyroidism

Conclusion: A health-economic appraisal limited to drug acquisition versus immediate effectiveness misses the avoidable downstream costs (CKD progression, dialysis, hospital admissions for hypocalcaemic emergencies, mental health services, private therapies patients purchase when NHS does not address symptoms). In many health technology assessments an expensive but highly effective upstream intervention can be cost-neutral or cost-saving when prevented downstream costs are modelled.

4) Patient out-of-pocket and societal costs

Many patients with chronic hypoparathyroidism purchase private symptom management (dermatology, specialist therapies, private travel and weekly sessions), and also suffer loss of earnings and care costs. These out-of-pocket costs cumulatively are substantial and should be considered in a broader societal perspective. Case series and patient surveys highlight this (and NICE consultation respondents brought similar concerns to the consultation). Hypoparathyroidism

Practical economics summary

1. **Downstream savings:** If palopegteriparatide reliably reduces urinary calcium and stabilises calcium homeostasis, it should reduce the incidence/progression of nephrocalcinosis and renal impairment (and therefore costly CKD care, potential dialysis). A single case of dialysis avoidance saves tens of thousands of pounds per year; preventing even a few such events materially offsets drug costs over time. (Please see the published burden-of-illness and renal-cost literature cited in this paper.) Hypoparathyroidism
2. **HRQoL and productivity:** Valuing improved quality of life and restored productivity (reduced disability and carer demands) increases the benefit side of any cost-utility model and can turn borderline ICERs into acceptable ones.
3. **Patient/carer cost reduction:** When patients currently pay privately for expensive symptom control (e.g. specialised dermatology or frequent private visits, weekly travel to private clinics), these recurring costs should be explicitly modelled as savings to patients and society if an effective medically-funded therapy reduces need for these services.
4. **Model recommendation:** NICE should require (a) a targeted economic model that includes long-term renal outcomes and their costs, (b) sensitivity analyses assuming different levels of urinary calcium reduction, and (c) a societal perspective scenario that counts private costs avoided and productivity gains. If the company is willing to provide a patient access or risk-share scheme tied to renal outcomes and HRQoL, that would substantially reduce budget impact risk.

A concise evidence-based summary

1) NICE: 'Uncertainty that treatment reduces urinary calcium / renal risk'

NICE reasoning: they expressed caution about whether the treatment meaningfully reduces hypercalciuria and so lowers renal risk, and noted some uncertainty in the data submitted. NICE

What the trials show: The PaTHway programme reported *reductions* in 24-hour urinary calcium for treated patients (and normalization for many). The peer-reviewed reports show that patients on TransCon PTH/palopegteriparatide could reduce or stop oral calcium and active vitamin D while maintaining normal serum calcium, and that urinary calcium excretion fell in many participants on active PTH therapy (sustained on follow-up). That is direct evidence that the drug can reduce the urinary calcium burden that contributes to nephrocalcinosis / stones. OUP Academic

Conclusion: NICE's caution on this point is understandable (renal outcomes are long-term), but the trial data do directly contradict the assertion that urinary-calcium benefit is unknown , the trials did show reductions in urine calcium at follow-up.

2) NICE: 'Uncertainty about improvements in quality of life and functional outcomes'

NICE reasoning: clinical outcome evidence and patient-reported outcomes were described as limited or of uncertain generalisability. NICE

What the trials show: The PaTHway publications report **clinically meaningful, statistically significant improvements** in disease-specific patient-reported outcome measures (symptom burden and QoL domains) for patients on the active drug versus placebo, alongside biochemical improvements and reduced requirement for supplementary calcium/Vit D. These QoL benefits were a consistent finding in the trial programme reported in peer-reviewed sources. OUP Academic

Conclusion: NICE's note about "uncertainty" is unreasonable: the trial did demonstrate QoL gains. The remaining question is generalisability (size of trial, follow-up length), not absence of benefit.

3) NICE: 'Methodological uncertainties / trial limitations and generalisability'

NICE reasoning: concerns about how representative trial patients are of all people with chronic hypoparathyroidism, duration of follow-up, and whether endpoints used translate into long-term health benefit. NICE

What the trials show: PaTHway is a multi-centre, randomised phase 3 programme with prespecified biochemical and patient-reported endpoints; it demonstrated meaningful biochemical control and symptomatic benefit out to 26 weeks (with extension data at 52 weeks). Those trial design points speak to internal validity. However, NICE is right to flag that **longer-term hard outcomes** (e.g. long-term kidney function, stroke or brain calcification rates) inevitably require longer follow-up or real-world data. The published evidence supports efficacy and short-to-medium term safety/benefit; the open question is very long-term clinical event rates. OUP Academic

Conclusion: the trials are good quality for 26–52 weeks and show real benefit; NICE's request for longer-term data is reasonable as a health-technology assessment issue but does not negate the favourable trial findings.

4) NICE: 'Cost-effectiveness / price and budget impact'

NICE reasoning: Even if clinically effective, the committee cited concerns about whether the drug represents value for money at the proposed price and the budget impact to the NHS. NICE

What the trials show: Trials give clinical-effect estimates (reduced supplement use, improved QoL, lower urinary calcium), which are the inputs for economic models , but they do not by themselves answer the price/value question. Trial data strengthen the clinical-effectiveness inputs (improving the model), but NICE's cost/QALY calculations and affordability judgements remain the principal barrier. OUP Academic

Summary evidence-based points:

1. **Urinary calcium:** the PaTHway programme demonstrated a reduction in 24-hour urinary calcium for many treated patients (and normalization in a large fraction) , directly addressing NICE's stated concern.
2. **Quality of life / symptoms:** the trial reported statistically significant and clinically meaningful improvements in symptoms and QoL measures versus placebo.
3. **Biochemical control and medication reduction:** the trials show patients could reduce/stop oral calcium and active vitamin D while keeping stable serum calcium , an outcome that reduces pill burden and the long-term harm of high oral calcium therapy.
4. **Safety / tolerability:** the clinical programme reported an acceptable safety/tolerability profile through the trial period; remaining uncertainty is about longer-term outcomes (reason for continued surveillance), not absence of benefit.
5. **Policy angle:** NICE's refusal (or non-recommendation) appears to rest mostly on **cost-effectiveness and long-term uncertainty**, not on complete absence of positive clinical data. However, there are multiple argument evidence include (A) the PaTHway trial evidence for urinary calcium and QoL, and (B) modelling / real-world data proposals that show how longer-term uncertainties will be addressed (e.g., managed access, registry data, risk-sharing).

Patient Impact and Real-World Consequences of Current Treatment Limitations

The consultation documents do not sufficiently reflect the lived experience of patients with chronic hypoparathyroidism, especially those with postsurgical disease. I feel it is important to make the following points explicit, not only for myself but for the many patients represented by Parathyroid UK and by clinicians who specialise in this field.

1. Hypoparathyroidism severely disables patients' ability to advocate for themselves

One of the defining features of hypoparathyroidism is impaired cognitive function, memory problems, slowed processing, brain fog, emotional lability, and difficulty expressing symptoms to clinicians. These cognitive limitations are not marginal; they directly impair a patient's ability to articulate their needs, navigate complex services, or participate in consultations where they might otherwise explain what conventional therapy is failing to control.

This should *not* be interpreted as lack of engagement or lack of clinical need. It is a consequence of the disease itself. The overwhelming majority of hypopara patients rely on Parathyroid UK and other advocacy bodies precisely because they cannot always fight their own case without support.

2. The disease destroyed the ability to function, work, and live independently

Before surgery and the subsequent development of permanent hypoparathyroidism, I was a fit, fully functional academic and teacher completing a PhD. I exercised regularly, worked full time, and led a productive and independent life.

Since developing hypopara, I have become completely disabled:

- I suffer debilitating cognitive dysfunction, neuromuscular spasms, tremors, paraesthesia, hypersensitivity, and unrelenting fatigue.
- I have spent years unable to sustain employment or daily self-care.
- Severe skin disease resulting from hypopara (misdiagnosed for years) escalated into painful topical-steroid withdrawal requiring weekly private therapy.
- I suffered fractures, including an open humeral fracture requiring plates and screws , an injury highly unusual at my age but entirely consistent with chronic calcium dysregulation.
- The psychological burden, driven by the condition itself, has resulted in several suicide attempts.

These consequences are exactly what modern PTH replacement therapies are designed to prevent or mitigate.

3. My frequent NHS use is already far more expensive than PTH-replacement therapy

Chronic hypoparathyroidism is not a 'low-cost' condition under conventional therapy. I am an example of this:

- **Frequent blood testing**, sometimes fortnightly.
- Regular endocrine visits.
- Multiple A&E attendances, including a life-threatening hypocalcaemic crash requiring IV calcium.
- Dermatology referrals, phototherapy attempts, high-potency steroids, and misdiagnosis-related complications.
- Visits to orthopaedics, neurology, mental health crisis teams, suicide-prevention services, and chronic-pain services.
- Recurrent kidney complications , kidney stones related to hypercalcaemia, and therefore affected by parathyroid surgery.
- Recurrent long GP appointments due to system-wide symptoms affecting every organ.

This volume of NHS usage , plus the cost of emergency care, specialist referrals, fractures, mental health interventions, and lost productivity , substantially exceeds the annual cost of PTH-replacement, particularly when long-term renal outcomes are factored in.

4. Conventional therapy is *not* the standard of care for long-term control , this is increasingly recognised internationally

The most recent European expert consensus (October 2025) acknowledges that conventional therapy (oral calcium + active vitamin D alone) does **not** restore physiological stability, is associated with poor symptom control, and should not automatically be considered ‘adequate therapy’ in chronic hypopara.

This aligns with the lived reality: high-dose calcium + Alfacalcidol is imprecise, destabilising, and harmful to kidneys long term. It has never been a physiologically equivalent substitute for PTH. It does not prevent cognitive dysfunction, neuromuscular instability, psychiatric symptoms, dermatological flares, or bone complications.

To deny replacement therapy on the assumption that conventional therapy is sufficient is clinically outdated and mismatches modern endocrine understanding.

5. Wider economic and societal considerations

The difference between supporting and denying PTH replacement is not merely biochemical:

- Patients who could be fully functioning citizens become dependent on the welfare system, mental health services, crisis teams, and long-term medical support.
- Families lose earners. Individuals lose careers and independence.
- The economy loses skilled workers , in my case, an experienced educator and researcher.
- Untreated chronic hypopara increases long-term renal, neurological, and skeletal burden , all of which are far costlier than PTH-replacement therapy.

From a societal perspective, the economic argument is overwhelmingly in favour of safe, effective, physiological treatment that restores function and independence.

6. In my case, the NHS caused the condition , and the NHS should treat it adequately

My permanent hypoparathyroidism was caused by NHS surgical management.
I did not have symptoms beforehand.
I was a healthy adult with mild blood abnormalities that did not meet NICE surgical criteria.
After surgery, I was denied timely diagnosis and treatment for years, which worsened the long-term damage.

When a permanent iatrogenic condition is created, morally and clinically, the NHS must fund the treatment that restores some quality of life , particularly when this treatment is now established as safe, effective, and physiologically appropriate.

Moreover, **80% of hypopara cases worldwide are postsurgical**. Making PTH replacement available would also encourage safer surgical practice and more cautious decision-making , reducing future NHS costs and harm.

Conclusion

Chronic hypoparathyroidism is not merely a biochemical abnormality. It is a debilitating, life-altering endocrine failure that conventional therapy does not adequately control. For patients like me, palopegteriparatide is not a 'luxury treatment', it is the only therapy capable of restoring physiological stability, reducing NHS burden, and allowing us to regain meaningful function and dignity.

I urge NICE to consider the economic benefits and real, lived, long-term consequences that current care imposes on patients and on the healthcare system, and the compelling evidence that PTH replacement addresses needs that no other treatment can.

Sources:

- NICE consultation / project documents for palopegteriparatide (Yorvipath) (NICE in-development / consultation pages). NICE
- PaTHway / TransCon PTH clinical programme publications (peer-reviewed trial reports showing biochemical control, urinary calcium reductions and QoL improvements). OUP Academic
- Scottish Medicines / SMC summary and product information for palopegteriparatide (background regulatory/medicines advice context). Scottish Medicines Consortium
- https://www.nice.org.uk/consultations/3108/1/committee-discussion
- PaTH / TransCon clinical programme publications and trial reports (phase-2/phase-3 dataset referenced in NICE documents) , reports include urinary calcium and QoL endpoints. NICE
- Burden-of-illness and healthcare-utilisation reports showing higher costs for chronic hypoparathyroidism vs transient cases (example news/summary of peer-reviewed studies). Hypoparathyroidism

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EAG ADDENDUM

Review of the company's response to consultation on the draft guidance document: Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

Produced by

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None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

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1 OVERVIEW

The External Assessment Group (EAG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the consultation on the draft guidance document (DGD) and to identify any areas of remaining uncertainty. The EAG has conducted high-level checks of the company's accompanying model and has been able to replicate the results presented by the company.

The company's response to the DGD comprises 11 comments. One comment provides an executive summary of the response and is not critiqued directly because the issues raised are addressed in the responses to individual comments. A second comment identifies factual errors in the DGD; these are not addressed by the EAG in this report. A third comment presents revised base-case results, which are discussed in Section 3.1. The remaining eight substantive comments addressed in this report are summarised in Table 1.

Table 1 Summary of the comments

#	**Comment**
1	Revised clinical guideline on the management of chronic hypoparathyroidism (DGD Section 3.2)
2	Effectiveness of standard treatment in the NHS vs standard treatment in PaTHway (DGD Section 3.6)
3	Response-based model (DGD Section 3.9)
4	Independence from calcium endpoint (DGD Section 3.9)
5	Resource-use associated with management of chronic HypoPT (DGD Section 3.15)
6	Modelling of adverse events (DGD Section 3.13)
7	Modelling of complications (DGD Section 3.12) and mortality (DGD Section 3.11)
8	Uncaptured utility benefit

The company submitted a revised base case that adopts four of the five assumptions preferred by the committee (DGD Section 3.21). The remaining preference concerns the appropriate use of palopegteriparatide (hereafter "palopeg") in clinical practice and is not a modelling issue.

The company also supplied further analyses requested by the committee and information requested by the committee to support its decision-making where possible (DGD Section 3.22). Where analyses or information are not provided, it is because the evidence does not exist or because it was considered by the company not to reduce any uncertainty. The company's responses to each of the comments are discussed in Section 2 while Section 3 presents the company's revised base case and the updated EAG base case.

The company's response is structured with reference to the DGD response. A summary table is provided in the Appendix comparing these comments with the key uncertainties identified by the EAG in the EAR and indicating the extent to which the company's response addresses them.

2 DESCRIPTION AND CRITIQUE OF RESPONSE

2.1 Revised clinical guideline on the management of chronic hypoparathyroidism (DGD Section 3.2)

The company stated that the criteria for defining patients who are "Not adequately controlled" (NAC) on conventional therapy (CT) and therefore eligible for parathyroid hormone replacement therapy, such as palopeg have not fundamentally changed in the 2025 revised European Society of Endocrinology (ESE) guideline on the management of chronic hypoparathyroidism in adults.[1]

EAG response

The EAG acknowledges that the ESE guideline represents a reasonable definition of who should be considered for treatment with palopeg, and, by extension, who can be considered as NAC on conventional therapy. i.e. calcium and oral active vitamin D analogues. We note that the population in the original NICE scope was "adults with chronic hypoparathyroidism" and was not restricted to people who are not adequately controlled with conventional therapy. It is also unclear whether the ESE guideline would be adopted in the NHS.

The EAG notes that the criteria defined in the ESE guideline are more specific than those used by the company for defining NAC in their submission, with respect to:

1) Impaired quality of life – the company says this is met by an SF-36 score of less than 40 (a broad criterion), whereas ESE say impaired quality of life should be attributable to chronic hypoparathyroidism (HypoPT). The company's definition of impaired quality of life may include patients whose SF-36 is <40 for reasons other than chronic HypoPT (i.e. due to comorbidities).
2) Renal insufficiency – ESE 2025 refers only to reduced kidney function, defined as being an eGFR < 60 mL/min per 1.73m², whereas the company expands this to also include a history of renal insufficiency or kidney stones.

The EAG therefore considers it likely that if the revised ESE guideline criteria for NAC were applied to the PaTHway cohort, fewer patients would be classed as being NAC. This limits the applicability of the results of PaTHway to the NHS setting.

2.2 Effectiveness of standard treatment in the NHS vs. standard treatment in PaTHway (DGD Section 3.6)

The company considered that the expert clinical opinion, obtained via its Delphi panel exercise, supported the generalisability of the control arm in PaTHway to NHS standard care.

EAG response

The EAG's position on this issue remains unchanged, given that the company's Delphi exercise constitutes the lowest level of evidence (i.e. expert opinion) in evidence-based medicine, and so does not address the fundamental concerns the EAG has with the PaTHway trial, particularly:

1) Use of CT, which does not reflect NHS practice.
2) Functional unblinding, which may have biased patient-reported outcomes such as quality-of-life measures (favouring palopeg).
3) The applicability of PaTHway trial outcomes to the NHS setting, i.e. use of a surrogate primary outcome which does not allow for a fair comparison of conventional therapy with palopeg.

The company's Delphi exercise did not seek to address concerns about 2) or 3) so only issue 1) is discussed below.

The EAG maintains its concern that the reduction in active vitamin D and calcium doses meant that the CT arm of the PaTHway trial did not represent how CT would be used in the NHS and that this could potentially adversely affect serum calcium levels and quality of life. The EAG reiterates that the European Medicines Agency (EMA) had similar concerns about the control arm, with the European Public Assessment Report (EPAR) stating that "standard care in the trial was potentially sub-optimal".[2] Additionally, the EAG would also like to highlight that although one of the PaTHway inclusion criteria was "optimization of supplements prior to randomization to achieve the target serum levels of albumin-adjusted or ionized serum calcium level in the normal range, or just below the normal range", at week 26 in PaTHway only 48% of CT patients had albumin-adjusted serum calcium within the normal range. Given that the CS notes (on p20) that "even mild deviations below the normal calcium range can significantly impair neuromuscular and neurological function" and that the "impact of hypocalcaemia occurring has profound effects on the nervous system, contributing to neuromuscular irritability including tetany arrhythmia, cognitive dysfunction, brain fog, seizures, and mood disorders, all of which significantly impair quality of life" (p21), the EAG considers that this deficiency in CT may result in a bias favouring palopeg.

Routine care treatments are often prohibited in clinical trials because they affect efficacy outcomes; the EAG assumes that to be the case in PaTHway, given the absence of an alternative reason. The

company's Delphi panel concluded that permitting the use of thiazide diuretics in PaTHway would have had a negligible impact overall on patient outcomes. The Delphi panel also noted that thiazide diuretics are not widely used. However, the EAG's clinical adviser considered that many patients who were genuinely NAC would be offered thiazide diuretics. In PaTHway 13% of patients had some record of prior thiazide diuretic use; this figure should be interpreted in the context that the mean baseline calcium and active vitamin D doses in the PaTHway cohort suggest that some PaTHway patients would likely be considered as having adequately controlled (AC) disease.

2.3 Response-based model

The company's response provides a scenario analysis to address the committee's preference for a response-based model structure, whereby the AC and NAC health states are defined based on the primary outcome of the PaTHway trial. However, the company's base case continues to adopt a treatment-based approach, which it argues better reflects the value of palopeg. The primary justification for this position is that utility data from the PaTHway trial do not show a meaningful difference in quality of life between responders and non-responders ([redacted] vs [redacted], respectively).

In implementing the response-based model, the company assumes that 78.7% of patients in the palopeg arm enter the AC health state, consistent with the proportion that met the multi-component primary endpoint at 6 months. Patients receiving CT are structurally assumed to be unable to achieve a response, based on clinical advice from the Delphi panel. Patients who achieve AC are assumed to remain in this health state for as long as they continue treatment, implying a permanent treatment effect, consistent with the company's original base case.

The committee's specification for the response-based model also requested that the utility values in the model be defined by response rather than treatment received. The company's revised model, however, retains utility values based on treatment allocation, although these have now been updated using mixed model repeated measures (MMRM) methodology as requested by the committee. The company justifies this approach on the basis that palopeg demonstrated an improvement in quality of life, which is not evident in the response-based utility values. The response-based model resulted in a comparable ICER at £21,003/QALY compared to the treatment-based model ICER of £20,031 (Section 3.1).

EAG response

Most appropriate model structure

The EAG considers the company's rationale for rejecting the committee's preferred response-based structure to be flawed and factually inaccurate. The utility values cited by the company appear to be derived from a simple, unadjusted comparison of responders and non-responders. This approach is overly simplistic and does not align with the MMRM analysis presented in the clarification response,

which shows that response (as defined by the primary outcome) is positively and statistically significantly associated with HRQL (see Table 2). It is therefore inaccurate to suggest that there is no difference in the HRQL of responders and non-responders.

Table 2 Summary of MMRM regression models

	Model 1: Treatment only	Model 2: Response only	Model 3: Treatment and response
	Coefficient (SE)		
Intercept	[redacted]	[redacted]	[redacted]
Treatment arm: Palopeg	[redacted]	-	[redacted]
Primary responder: Yes	-	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]	[redacted]
BBMI	[redacted]	[redacted]	[redacted]
Aetiology non-surgical	[redacted]	[redacted]	[redacted]

*p<0.05

Evaluation of alternative specifications of the MMRM analysis provides some support for a treatment-based structure. As shown in Table 2, treatment allocation is a statistically significant predictor of HRQL in Model 1. However, in Model 3, where both response and treatment allocation are included in the same regression, neither parameter remains statistically significant. This result is likely driven by collinearity between the two variables and therefore does not provide strong evidence in favour of one economic model structure over the other.

Importantly, these findings do not invalidate a response-based model, nor do they alter the substance of the EAG's critique. A treatment-based structure remains conceptually weak because it does not explicitly link health states to the mechanism through which health benefits are generated. By contrast, a response-based model is anchored in a clinical measure of benefit and permits the implementation of a stopping rule, allowing treatment discontinuation where there is no evidence of response. Consistent with the committee's preferences, the EAG therefore adopts a response-based structure in its base case.

Implementation of the response-based model

Notwithstanding the above, the EAG has several concerns regarding the company's implementation of the response-based model, which it considers of limited value for decision-making. It does not reflect the data from the PaTHway trial, where one patient on CT (out of 21) achieved the multi-component primary endpoint response. While this is justified based on the Delphi panel, the EAG does not consider it appropriate to disregard the observed evidence which clearly contradicts the elicited clinical opinion. Moreover, clinical advice to the EAG, emphasised that patients can achieve

independence from CT over time. Also, the one patient who had a response when receiving CT demonstrates that it is also plausible that a small number of patients in the palopeg arm may achieve a response which may not be attributable to trial treatment. Removing responses from one trial arm, and not the other, therefore creates a bias.

Utility values are not appropriately modelled; they should be updated using the MMRM analysis, which includes response as a covariate. The current implementation of the MMRM, based on treatment allocation, is inconsistent with a response-based structure, and the values reported in the company response do not reflect the MMRM analysis (see Section 3.1).

Patients are categorised as responders or non-responders at model entry. While this may simplify implementation, it does not reflect proposed clinical practice, where response will be assessed after six months, and it implicitly assumes that treatment benefits are instantaneous in responders. The company provides limited discussion of the appropriateness of the six-month assessment period or its acceptability to patients or clinicians working in the NHS. The EAG considers these to be important issues that should have been addressed in the company's response.

Finally, the EAG reiterates its concerns that both the design of PaTHway and the primary composite outcome are inappropriate for evaluating CT and that PaTHway does not allow for a fair comparison of the trial interventions, even using response-based data in the model. From the trial data it seems clear that patients randomised to placebo/CT were worse off at the end of PaTHway than at the start, given that one of the PaTHway inclusion criteria was achievement of serum levels of albumin-adjusted or ionized serum calcium level in the normal range, or just below the normal range, but at week 26 only 48% of CT patients had albumin-adjusted serum calcium within the normal range.

2.4 Independence from calcium endpoint

This comment from the company was in response to the request from the committee for a scenario in which the 'independence from therapeutic doses of calcium' component was excluded from the primary outcome of PaTHway and from the health-state definition that would be used in the response-based model. The company stated that excluding independence from calcium did not alter the proportion of patients that met the primary endpoint and this exclusion criteria had no impact on cost effectiveness in the response-based model.

EAG response

The company provided limited evidence to validate its response by undertaking subsequent analysis stating that excluding 'independence from therapeutic doses of calcium' did not change the number of patients meeting the endpoint. The EAG notes that this refers only to independence from calcium and not independence from conventional therapy as a whole, which would include

independence from Vitamin D analogues. The company subsequently stated that removing independence from Vitamin D as well also has no impact on the proportion of patients meeting the multi-component primary endpoint. However, the EAG has not seen the results to justify these claims.

Even if independence from calcium and independence from vitamin D were both removed from the composite outcome, the EAG considers that results based on the remaining components (i.e. 'Albumin-adjusted serum calcium within the normal range' and 'No increase in prescribed trial drug') would not be an appropriate outcome for reflecting the effect of conventional therapy in the NHS, given the concerns about the use of in conventional therapy in PaTHway.

2.5 Resource use associated with management of chronic HypoPT

The committee requested a scenario in which resource-use costs were informed by the PaTHway trial, which was not provided by the company. The committee considered that the CPRD data could be a reasonable source to inform the management of chronic HypoPT. However, it also concluded that the company's definitions of AC and NAC based on resource use were problematic and did not reflect the patient experience (DG: Section 3.10). Furthermore, the committee agreed with the EAG that the definitions of AC and NAC were not sufficiently supported by empirical evidence.

The company's response stated that resource use in PaTHway was not considered representative of routine care in the NHS. The company, however, made several revisions to their previous base case but did not fundamentally alter the underlying approach. As in the original base case, health-state costs are informed by CPRD data, with NAC and AC defined based on healthcare utilisation. The company stated that clinical advice from the Delphi panel supported this approach in the absence of directly observed clinical measures within the CPRD.

Based on clinical opinion elicited as part of the Delphi exercise, the company redefined the definition of NAC to include patients with ≥1 inpatient admission per year, with HypoPT as the primary or secondary diagnosis. Previously, NAC was defined as >5 outpatient visits and ≥1 inpatient admission per year, without requiring HypoPT to be specified as the primary or secondary diagnosis. The revised definition was informed by Delphi panel input, which indicated that this represents a more clinically valid proxy for identifying NAC patients within the CPRD dataset.

In addition, and to align with the NICE reference case, the company revised the included cost categories to:

- Inpatient admissions coded to a composite of complications associated with chronic hypoPT;
- Outpatient visits coded to relevant specialities;
- All-cause emergency care attendances; and

- Primary care visits coded to a composite of complications associated with chronic hypoparathyroidism.

Total annual costs for NAC were estimated based on [redacted] patients and were [redacted] (2025 prices). Total annual costs for AC were estimated based on [redacted] patients and were [redacted] (2025 prices), derived from the residual costs of the overall population without complications after excluding NAC. Costs were based on combined post-surgical and non-surgical patients and were not reweighted to reflect the distribution observed in the PaTHway trial.

EAG response

The EAG continues to have substantial concerns with the company's approach to modelling health state costs, as the company's revisions do not address the committee's conclusion that the costs generated from the CPRD analysis are not reliable (DG: Section 3.15). The EAG has identified several further issues relating to the CPRD data used to estimate health state costs.

Conceptual and methodological concerns

The EAG's primary concern remains that the AC and NAC definitions used in the CPRD analysis, which continue to classify patients into AC and NAC without reference to objective clinical criteria, do not align with definitions used to define the model health states. The former is based on resource utilisation, whereas the latter reflects treatment allocation. As outlined in the EAR, this relies on a circular rationale in which patients are stratified based on healthcare resource utilisation, and this stratification is subsequently used to infer a causal relationship between resource use and disease severity (EAR, p.19). The EAG does not consider Delphi panel opinion sufficient to validate this assumption, particularly given that the predicted cost savings exceed the equivalent of [redacted] QALYs at a £25,000 per QALY threshold, and considers that a higher level of evidence is required to support benefits of this magnitude.

The EAG is also concerned that inpatient costs may be double-counted within the model, as the same utilisation data appear to inform both the baseline health-state costs and the event-specific costs associated with adverse events (Section 2.6) raising the possibility that hospitalisations are captured twice.

Definition of NAC

The EAG has further concerns regarding the revised definition of NAC, which is not clearly justified. The definition appears overly narrow and likely captures only the most severe patients with the highest resource use. This is reflected in the limited sample size used to estimate costs. The EAG is particularly concerned that the high inpatient costs, which account for [redacted] of total costs, may be driven by a very small number of patients, potentially even a single outlier. This is supported by the large variation in inpatient costs (mean [redacted]; standard deviation [redacted]). Mean inpatient

costs are markedly higher in the revised NAC population (£[redacted] vs [redacted]), consistent with the possibility that a small number of patients with exceptionally high costs are driving the estimate. Comparisons with other relevant subgroups further highlight this issue. Under the previous NAC definition (n=[redacted]), mean inpatient costs were [redacted]. This demonstrates that the revised NAC costs are unusually high relative to both the previous definition and other clinically similar subgroups.

Aetiology of CPRD cohort

It is unclear whether the revised health-state costs account for the mixed aetiology of patients with hypoparathyroidism (HypoPT) or the disparity in the proportion of non-surgical cases relative to those reported in the PaTHway trial and observed in NHS practice. As described in the EAR, the aetiological composition of the CPRD cohort differs substantially from PaTHway, with [redacted] of patients classified as non-surgical compared with 15% in the trial. Clinical expert advice to the EAG indicates that, in NHS practice, the majority of HypoPT cases are of surgical aetiology, consistent with the distribution reported in PaTHway.

Reweighting the health-state costs to reflect this distribution previously resulted in a substantial reduction in the estimated costs associated with the NAC health state. The provided documentation, however, does not report the necessary data for the new NAC definition. The EAG is therefore unable to establish how costs have been weighted or whether reweighting would impact estimated costs.

Conclusion

Taken together, these issues indicate that the estimated costs associated with the NAC health state are highly uncertain and likely overstated, which in turn inflates the cost offsets attributed to treatment within the model. As per the original EAR base case, the EAG prefers to remove all health state costs, acknowledging that this is likely conservative.

2.6 Modelling of adverse events

To support its decision-making, the committee asked the company to provide evidence that the risk of adverse events would be higher in clinical practice than in PaTHway. The company states that hypocalcaemia and hypercalcaemia are clinically impactful treatment-emergent events and asserts that the PaTHway trial is likely to underestimate the frequency of events requiring acute intervention in routine clinical practice. However, the company notes that there is a lack of literature to inform the specific risk of both symptomatic hypocalcaemia and hypercalcaemia.

Clinical opinion elicited through the Delphi panel suggested that a typical NAC patient in clinical practice would experience at least 2 to 3 symptomatic hypocalcaemia events per year and that these events would require inpatient admission. The company therefore considered that the event rate in the

PaTHway may be artificially low and retains its original base case assumption whereby the event rate is calculated using all hypocalcaemia events regardless of adverse event grade (clarification response - 9 Sept 2025).

As requested in DG: Section 3.16, the company provided a CPRD-based cost estimate for adverse events. The company based their CPRD-based cost estimate on combined post-surgical and non-surgical patients without complications and with ≥1 symptomatic hypocalcaemia IP admissions (N=[redacted]). The company also provided a scenario using an updated Hospitalisation for Heart Failure (HRG) code value but did not consider it relevant in light of the CPRD cost-estimate.

EAG response

Incidence of hypocalcaemia and hypercalcaemia in NAC patients

The company's response offers no further substantial evidence to support its modelled assumptions. The EAG does not regard clinical opinion as sufficiently robust evidence to justify the company's interpretation of the PaTHway trial data, where adverse event rates are based on any-grade events, while associated costs assume hospitalisation.

As outlined in the EAR, the EAG does not accept the company's argument that the PaTHway trial would systematically underestimate the incidence of serious adverse events. Although the more intensive monitoring undertaken in the trial may influence the detection of adverse events, no evidence has been provided to suggest that this would materially affect the incidence of events requiring hospital-based care. In particular, the EAG does not accept the assumption that all grade 1 or 2 events would escalate to a severity requiring hospitalisation. The EAG's position therefore remains unchanged: adverse-event rates should be calculated using only those adverse events that resulted in urgent care visits or hospitalisation (i.e. grade 3 or 4).

The EAG also challenges the company's assertion that patients classified as NAC would experience at least 2–3 symptomatic events per year in clinical practice. This is inconsistent with evidence from the CPRD dataset. Within the CPRD analysis, [redacted] patients experienced [redacted] hospitalisations over [redacted] person-years of follow-up, corresponding to an event rate of approximately [redacted] events per person-year. This observed rate is substantially lower than that suggested by the Delphi panel and does not support the assumption that NAC patients would routinely experience multiple symptomatic events annually.

Costs associated with hypocalcaemia and hypercalcaemia

The EAG agrees with the company that the heart failure HRG scenario analysis value is not relevant and that the CPRD dataset provides a more relevant source of cost and resource use data. However, the EAG has several concerns regarding the specific value applied.

The company's description of the calculation is unclear and does not reproduce the reported value when applying a simple event-level mean. Based on the figures presented [redacted] divided by [redacted] events), the implied cost per admission is [redacted], rather than [redacted] estimated by the company. This suggests that an alternative approach (for example, patient-level averaging) may have been used. However, such an approach would not align with the model structure, which requires a cost per admission, and may introduce bias if admission frequency is associated with cost. Therefore, it is unclear how the applied value has been derived and whether it is appropriate. To explore this uncertainty, the EAG presents scenario analysis using the mean cost per event (Section 3.2).

The EAG is also that the number of patients considered is limited (n=[redacted]; [redacted] events), with substantial variation in individual event costs. The standard deviation is larger than the mean. This indicates considerable uncertainty around the parameter, which is particularly relevant given the substantial cost savings predicted in the company's base case.

2.7 Modelling of complications and mortality

The company's response states that literature searches were conducted to identify evidence supporting the modelled surrogate relationships between complication risk and disease control, but no suitable studies were found. The company further explains that it is not possible to revise the estimated complication risk from the CPRD dataset, as the data cannot be mapped to the response-based health state definitions. Consequently, the company retains its original base-case assumptions using CPRD with health states defined by resource use.

Similarly, literature searches did not identify evidence to inform impacts on mortality. The company, therefore, updated its base case in line with EAG's preferred assumptions, applying a hazard ratio of 2.89 to both model arms.

EAG response

The company's response does not address the underlying issues. While the company notes the inability to identify any appropriate literature sources for complication risk or surrogate relationships to include in the cost-effectiveness model, it has provided no new substantive evidence to support the modelled impact on complication rates. As noted in the EAR, the EAG is concerned that the apparent treatment benefits are not supported by the PaTHway trial, which shows no meaningful differences in complication rates. Furthermore, the company relies on surrogate relationships that are unsubstantiated and involve strong assumptions, specifically, that resource use serves as a proxy for complication rates and that reductions in resource use will directly translate into reductions in complications. Given that no further evidence has been supplied to justify these assumptions, the EAG retains its preferred approach of setting complication rates to zero.

2.8 Uncaptured utility benefit

The company cites a recent systematic review,[3] to highlight that EQ-5D does not directly assess cognitive aspects such as memory, attention or executive function. They argue that omitting cognitive capacity may lead to underestimation of health-related quality of life improvements, noting that cognitive impairment or "brain fog" is a well-documented symptom of chronic HypoPT. [4] On this basis, the company claims that modelled utilities do not fully capture the total benefits of palopeg, and that the ICER may be overestimated.

EAG response

The EAG acknowledges that the EQ-5D does not include a specific domain for cognitive function, though some impacts may be partially captured through other domains, particularly self-care and usual activities. Nonetheless, the EAG agrees that cognitive function is not explicitly captured in EQ-5D and that some benefits of palopeg are likely not captured in the current evaluation.

2.9 Additional issues raised by the company

The company raised the prospect of managed access, stating that NHS England has confirmed availability of interim funding for palopeg via the Innovative Medicine Fund (IMF).

EAG response

According to the NHS England webpage on the IMF, only the eligible patient population, as recommended by NICE, will receive treatments funded by the IMF. Establishing the eligible population for palopeg in treating chronic HypoPT is therefore necessary. Furthermore, the EAG is uncertain how further data collection, other than a new trial, would be informative, given the substantive uncertainties with the current evidence.

2.10 Additional issues raised by the EAG

The company's revised model makes several small changes to parameter values and functionality without documenting or justifying them, including rounding certain values and making minor absolute adjustments, see Table 3 for a full list of changes. While the majority of these undocumented adjustments have a limited impact on the ICER, the changes to the adverse event rate have a more substantive impact on the ICER, as applying the old values to the company's current model reduces the ICER from £20,031 to £16,019. The EAG considers that this lack of transparency represents poor modelling practice and has required additional effort from the EAG to identify all the changes. The EAG is satisfied that the model is suitable for decision making, but the committee may wish to enquire as to the reason for these changes to the economic model.

Table 3 Description of undocumented changes

#	**Description of change**
1	Dose of Ca carbonate changed from [redacted] mg to [redacted] mg
2	Disutility associated with Symptomatic hypercalcaemia/hypocalcaemia changed from 0.208 to 0.21
3	eMIT cost value for alfacalcidol used - was [redacted] now [redacted]
4	Adverse event rates for symptomatic hypercalcaemia update from [redacted] to [redacted] in the palopeg arm. Adverse event rates for symptomatic hypocalcaemia update from [redacted] to [redacted] in the palopeg arm.
5	Drug wastage scenario implemented every 6 rather than 7 cycles
6	EAG correction to the calculation of mortality and state occupancy in the palopeg arm is not incorporated into the model.

3 UPDATED MODELLING ASSUMPTIONS

3.1 Company's revised base case

The results of the company's revised base case and analysis provided in response to the DGD and committee requests are summarised below.

The revisions to the company base case are as follows:

- Health state utilities calculated by treatment from PaTHway using the MMRM approach
- Health state resource use costs informed by updated CPRD analysis (see Section 2.5)
- Adverse event cost based on mean cost for a symptomatic hypocalcaemia inpatient admission from CPRD (see Section 2.6)
- 100% relative dose intensity (RDI) and drug wastage applied
- Mortality risk updated (HR: 2.89)
- Health-state utilities calculated by treatment from PaTHway using a MMRM approach.

The EAG can replicate the company's revised base-case and additional scenario analyses provided in the company's appendix. As outlined in Section 2.3, the company reiterates its preference for a treatment-based (on/off) model but presents scenario analysis using a response-based model. Table 4 presents the results of the company's revised base case. Table 5 presents a scenario analysis using the response-based model structure.

Table 4 Revised company base case (Deterministic)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,031
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Table 5 Revised company base case: Response-based model structure

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,003
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Table 6 presents the additional scenario analyses conducted by the company in response to DGD.

Table 6 Treatment-based model: Scenario analyses

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Alternative health state costs based on all-cause costs						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,025
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Alternative health state costs based on removal of inpatient costs from the AC health state						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,970
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Revised adverse event costs based on the Cardiac HRG code						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,311
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.						

3.2 EAG scenario analysis

The following deterministic exploratory analyses were conducted by the EAG.

1 Response-based model

The EAG updates the response based analysis implemented by the company to remove the structural assumption preventing response in the CT arm of the model and updates the utility value using to utilise the MMRM regression model, including response as a covariate (Model 2 in Table 2). The utility of a responder is therefore updated to be [redacted] and a no-responder is updated to be [redacted].

2 Health state maintenance costs

The company provides no compelling evidence to support the modelled health state costs. As per the EAR, the EAG sets the applied health state costs to zero, thereby removing all (health state-related) cost savings associated with palopeg.

3 Use Grade 3/4 AEs

The company provides no additional substantive evidence to support its assumptions, and the EAG does not consider clinical opinion sufficient to justify modelling hospitalisation costs based on any-grade adverse event rates from the PaTHway trial. The EAG therefore models AE rates based on

grade 3/4 hypercalcaemia and hypocalcaemia events requiring hospital care, as reported in the PaTHway trial.

4 Revised AE costs

The company provided an AE for hypocalcaemia estimated from the CPRD (£[redacted]). The EAG still has concerns about how this value was derived and presents an exploratory scenario where the cost per event is calculated by dividing total costs by the number of events. This reduces the cost per event to £[redacted].

5 Exclude complication rates (set to 0)

The company provided no further evidence to support the modelled benefits associated with the avoidance of complications. This scenario, therefore, sets the complication rates applied in the model to zero.

Table 7 Results of EAG-conducted scenario analyses

Scenario		Technology	Total		Incremental		ICER
			Costs	QALYs	Costs	QALYs	
	Company base-case	Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	£20,031
		Conventional therapy	[redacted]	[redacted]			
1	**Response-based model**	Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	£40, 178
		Conventional therapy	[redacted]	[redacted]			
2	**Remove health state maintenance costs**	Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	£128,850
		Conventional therapy	[redacted]	[redacted]			
3	**Use grade 3/4 AEs**	Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	£82,852
		Conventional therapy	[redacted]	[redacted]			
4	**AE costs - CPRD alternative**	Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	£26,802
		Conventional therapy	[redacted]	[redacted]			
5	**Exclude complications from model**	Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	£21,321
		Conventional therapy	[redacted]	[redacted]			

3.3 EAG base-case analysis

The cumulative impact of the EAG's preferred assumptions is presented in Table 8 below.

The EAG base case adopts the following scenarios described in Section 3.2

- Scenario 1: Response-based model,
- Scenario 2: Remove health state maintenance costs,
- Scenario 3: Use grade 3/4 AE rates,

- Scenario 5: Exclude complications from the model.

Table 8 EAG's preferred model assumptions (Deterministic)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£304,487
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

3.3.1 Additional scenario analysis on the EAG base case

Table 9 presents the EAG base case for the treatment-based model.

Table 9 EAG's preferred model assumptions for the treatment-based model (Deterministic)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£214,168
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

REFERENCES

1. Bollerslev J, Buch O, Cardoso LM, Gittoes N, Houillier P, Van Hulsteijn L, et al. Revised European Society of Endocrinology Clinical Practice Guideline: Treatment of Chronic Hypoparathyroidism in Adults. *Eur J Endocrinol* 2025;193:G49-G78.

2. European Medicines Agency. *Assessment report: Yorvipath - International non-proprietary name: palopegteriparatide. Procedure No. EMEA/H/C/005934/0000*. Amsterdam: EMA; 2023.

3. Rencz F, Pangestu S, Mulhern B, Finch AP, Janssen MF. Development and Use of Cognition Bolt-Ons for the EQ-5D-3L and EQ-5D-5L: A Systematic Review. *Value Health* 2025;28:1752-69.

4. Tmava-Berisha A, Fahrleitner-Pammer A, Stross T, Geiger S, Geiger C, Fellendorf F, et al. Cognitive Function in Individuals with Chronic Hypoparathyroidism-A Prospective Observational Study. *J Clin Endocrinol Metab* 2025;110:2157-63.

APPENDIX

Summary of the EAG key issues

The company responded using a comments format. The EAG has aligned these comments with the key issues presented in the EAR. Table 10 a reproduces the key issue table and provides a summary assessment of whether the company's DGD response adequately addresses these concerns.

Table 10 Summary of EAG key issues and company response

ID	Summary of issue	Report sections	Addressed by Company in DGD response
1.	Uncertain definition of the "Not Adequately Controlled" population: Submission proposes limiting population to patients not adequately controlled by conventional therapy (CT). This population is not consistently defined and may be a small minority of patients with hypoparathyroidism (HypoPT).	2.3.1 3.2.1.2	NO
2.	Uncertainty in the patient-reported quality of life outcomes in PaTHway trial: Participants may have experienced "functional unblinding" due to their awareness of calcium and vitamin D doses received. This could bias results of quality-of-life outcomes in favour of palopegteriparatide (palopeg). The company also used an Analysis of Covariance (ANCOVA) model to analyse EQ-5D data rather than a Mixed Model Repeated Measures analysis (MMRM). This approach is less efficient and more vulnerable to bias.	3.2.1.1 3.2.2 4.2.7.2	Partly Utility values updated to MMRM analysis
3.	Use of sub-optimal conventional therapy in the PaTHway trial: The PaTHway trial mandated a large reduction in active vitamin D dose and prohibited the use of thiazide diuretics, so the CT arm may not reflect treatment use in practice.	2.3.2 3.2.1.2	NO
4	Primary outcome in PaTHway trial does not permit a fair comparison with conventional therapy: The trial used independence from CT as a key component of its primary outcome, which is innately not achievable with CT, and does not measure actual clinical benefits.	3.2.1.2 3.2.2	NO

5.	Model structure: The model structure uses an on/off treatment approach and does not use the primary outcome report in the PaTHway trial.	4.2.2	PARTLY A response-based model is presented
6.	Lack of direct evidence for complication and mortality benefits: The PaTHway trial does not provide direct evidence supporting the modelled reductions in complications and mortality. Instead, the model relies on surrogate relationships between disease control and clinical outcomes, which are inadequately justified.	4.2.2 4.2.6.3 4.2.6.4	PARTLY Company accepts committee/EAG position
7.	Modelling of adverse event rates and costs: Adverse event (AE) rates are modelled based on all grades of severity, while associated costs are derived from cases requiring emergency hospital care. AE costs for hypercalcaemia and hypocalcaemia are based on hospitalisation costs for heart failure.	4.2.6.5 4.2.8.3	PARTLY CPRD data provided
8.	Drug wastage assumptions: The model assumes no drug wastage and presumes that dose reductions and skipped doses directly translate into reduced drug acquisition costs	4.2.81	YES
9	Self-administration of palopeg: The company model assumes all patients will be able to self-administer palopeg. It is unclear if this is appropriate with implications for both costs and equity of access.	4.2.8.1	Committee did agree
10.	Non–reference case approach to healthcare resource use: The model adopts a non–reference case approach by including background care costs that are not attributable to HypoPT.	4.2.8.2	YES Disease specific costs updated using CPRD data
11.	Modelling of healthcare resource use: Reductions in resource use are not directly supported by data from the PaTHway trial and instead rely on a poorly justified surrogate relationship between disease control and resource utilisation. Clinical Practice Research Datalink (CPRD) data used to inform resource use does not reflect the mix of surgical and non-surgical patients in the modelled population.	4.2.8.2	PARTLY Delphi survey states aetiology not a factor in healthcare resource use.

Single Technology Appraisal

Hypoparathyroidism (chronic) - palopegteriparatide [ID6380]

EAG critique – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG critique to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 14 April** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Overarching comment by Ascendis Pharma

After reviewing the EAG critique of the Draft Guidance Document responses, Ascendis Pharma would like to highlight the following emerging themes:

- The critique does not adequately reflect the appraisal process or the prior exchange of information that has already taken place. This omission risks introducing unnecessary duplication, contributing to delays, and slowing overall decision-making.
- There appears to be limited consideration of previously addressed points, leading to repeated requests for clarification on issues that have already been discussed and resolved during earlier stages of the process.
- The language used throughout the document is, at times, overly critical and does not adequately reflect the evidence that has been provided. This may lead readers to assume that relevant information was not submitted, or that decisions were made without appropriate supporting evidence. Furthermore, several statements appear to contradict conclusions reached during the first committee meeting, as well as positions outlined in the initial EAG report. This divergence does not present a fair or balanced assessment of the evidence provided.
- There is a consistent lack of acknowledgement of the methods and findings of the Delphi Panel report, which was developed in response to the request for additional robust and transparent clinical opinion from the first Committee Meeting, particularly given that hypoparathyroidism is a rare disease and the challenges of evidence generation were recognised by the Committee.
- The EAG frequently refers to input from its clinical adviser; however, the adviser's specific expertise and relevant experience are not described. In contrast, it is not acknowledged that the company sought input from nine clinical experts actively working in the field and treating patients with hypoparathyroidism on a routine basis. The use of a Delphi Panel reflects a robust and systematic approach to evidence generation and demonstrates methodological rigour in ensuring that the company's position is informed by current clinical practice

Issue 1 Revised clinical guideline on the management of chronic hypoparathyroidism (DGD Section 3.2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.1 page 6, the EAG states "We note that the population in the original NICE scope was "adults with chronic hypoparathyroidism" and was not restricted to people who are not adequately controlled with conventional therapy."	Please reword this section as it fails to acknowledge that acceptance of the proposed positioning of palopegteriparatide for patients who are not adequately controlled (NAC) on conventional therapy. .	The omission of this important point means that this section does not accurately reflect the scope or intent of the appraisal and may lead to misinterpretation. In the draft guidance (DG) published following the first meeting, the committee stated that it was appropriate to restrict use of palopegteriparatide to the NAC on standard treatment (P.26) in line with the company submission. Furthermore, the DG document states "The EAG agreed with restricting the population to people with NAC chronic hypoparathyroidism" p.7, further justifying the proposed amendment.	Not a factual inaccuracy. We clearly state that this was the original scope population. [see NICE scope Sept 2024] We note also that the company trial was not in a specifically NAC population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.1 page 6, the EAG states “The EAG notes the criteria defined in the ESE guideline are more specific than those used by the company for defining NAC in their submission, with respect to:”	Please make it clear that the definition of NAC referenced in the company submission was based on the Second International Workshop 2022 guidelines, which were the current clinical guidelines at the time and the committee was satisfied with this approach.	The current wording is misleading as it implies that the company have been deliberately vague whereas the NAC definition used in the company submission was based on available clinical guidelines at the time. In addition, the committee “was satisfied that the criteria suggested by the company based on the Second International Workshop 2022 guidelines would be appropriate for determining eligibility for palopegteriparatide and broadly aligned with how clinical experts would use it in clinical practice.” P.8 DG.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.1 page 6, the EAG states "The EAG notes the criteria defined in the ESE guideline are more specific than those used by the company for defining NAC in their submission, with respect to: 1. Impaired quality of life – the company says this is met by an SF-36 score of less than 40 (a broad criterion), whereas ESE say impaired quality of life should be attributable to chronic hypoparathyroidism (HypoPT). The company's definition of impaired quality of life may include patients whose SF-36 is <40 for reasons other than chronic HypoPT (i.e. due to comorbidities).	The statement should be amended to reflect that an SF-36 score of <40 is an indicator of impaired quality of life and consistent with the ESE guidelines.	Although the ESE guidelines highlight that impaired quality of life should be attributable to hypoPT, they offer no guidance on how this should be measured. HypoPT is a multisystem disease and associated with a wide range of effects on health. SF-36 is a quality-of-life measure designed to capture overall quality of life. Therefore, the company's use of an SF-36 threshold should be interpreted as a relevant assessment tool.	Not a factual inaccuracy. We consider that impaired quality of life specifically attributable to hypoparathyroidism is more appropriate, as per ESE guidelines.

In section 2.1 page 6, the EAG states "The EAG notes the criteria defined in the ESE guideline are more specific than those used by the company for defining NAC in their submission, with respect to: … 2. Renal insufficiency – ESE 2025 refers only to reduced kidney function, defined as being an eGFR < 60 mL/min per 1.73m², whereas the company expands this to also include a history of renal insufficiency or kidney stones."	Please remove the section on renal insufficiency.	The ESE guidelines explicitly state that patients with hypoparathyroidism who have nephrolithiasis and hypercalciuria despite optimised conventional therapy are candidates for PTH replacement therapy (R.3.6). R.3.6 further emphasises the importance of managing hypercalciuria, with escalation to PTH therapy where this cannot be controlled. This demonstrates that ESE recognises kidney stones as a clinically meaningful manifestation of renal complications in chronic hypoparathyroidism. The company's approach does not diverge from the ESE guidance when considered in their entirety, so it is not factually correct for the EAG to focus on eGFR in isolation or suggest that the company have inappropriately expanded	Not a factual inaccuracy. The ESE guideline does not specify "history of renal insufficiency or kidney stones" as an eligibility criterion for treatment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		the definition.	
In section 2.1 page 7, the EAG states "The EAG therefore considers it likely that if the revised ESE guideline criteria for NAC were applied to the PaTHway cohort, fewer patients would be classed as being NAC."	Please remove this statement as it appears to be based on assumption rather than supporting evidence.	The existing statement is misleading and not factually supported. The statement does not cite evidence of ESE guideline criteria being applied to the cohort and its direct impact on classification. Instead, it relies on probability of the statement being true without evidence supporting this.	Not a factual inaccuracy. We encourage the company to provide the evidence on how many patients would be classed as NAC under ESE guidelines

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Appendix - Table 10, ID 1 Uncertain definition of the "Not Adequately Controlled" population: The EAG states "NO" under 'Addressed by Company in DGD response'.	Please adjust the statement that is factually inaccurate in 'Addressed by Company in DGD response' from "NO" to "YES" .	Based on the committee's conclusion that the Second International Workshop 2022 guidelines would be appropriate for determining eligibility for palopegteriparatide and therefore correctly reflect the evidence submitted by the company and positive consensus from the committee as per the draft guidance.	Not a factual inaccuracy We note that the EAG is not bound by the draft guidance and acts independently of the committee.

Issue 2 Effectiveness of standard treatment in the NHS vs. standard treatment in PaTHway (DGD Section 3.6)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.2 page 7, the EAG states "The EAG's position on this issue remains unchanged, given that the company's Delphi exercise constitutes the lowest level of evidence (i.e. expert opinion) in evidence-based medicine, and so does not address the fundamental concerns the EAG has with the PaTHway trial…".	Please amend the statement to acknowledge the value of the NICE-requested Delphi Panel.	The EAG's characterisation of the Delphi Panel as representing the lowest level of evidence is not fully accurate. While Delphi Panel methods are based on expert input, they are a structured and systematic approach to achieving consensus, rather than informal expert opinion. The evidentiary value of such exercises depends on their design and conduct, and they are commonly used in situations where empirical data are limited. Therefore, it is not appropriate to categorise the Delphi Panel in overly simplistic terms within the evidence hierarchy. In addition, the EAG's failure to acknowledge or review the Delphi Panel report, which was conducted in response to the Committee's request following the	Not a factual inaccuracy. The role of the EAG is to assess the clinical trial evidence for a technology. Expert evidence, including Delphi panels, while useful, are not clinical evidence and so evaluating them is not part of the EAG's remit, nor should they influence our interpretation of the evidence. Nor is it the role of the EAG to find "common ground" with the company. We consider it essential that the EAG uphold the highest standards of evidence-based medicine, which requires evidence from well-conducted clinical trials. Opinions, no

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		first Committee meeting, is factually incomplete and unprofessional. The Delphi Panel was specifically designed to provide Committee members with additional clinical feedback and insight from experts actively treating patients, ensuring that model assumptions were clinically validated. By disregarding this robust and structured evidence, the EAG did not attempt to find common ground and instead chose to discredit a well-conducted exercise, which unnecessarily complicates the appraisal process and misrepresents the available evidence.	matter how carefully sought, do not meet that required level of evidence. We therefore reject in the strongest possible terms any suggestion that our work has been unprofessional. This is unacceptable behavior by the company, and we request that the committee clearly oppose and reject any such accusations.
In section 2.2 page 7, the EAG states “The EAG’s position on this issue remains unchanged… (the company) does not address	Please remove the statement as the use of CT not reflecting NHS practice is not	The company’s approach to the applicability of the placebo (CT) arm of PaTHway to NHS practice has been validated through	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the fundamental concerns the EAG has with the PaTHway trial, particularly: 1) Use of CT, which does not reflect NHS practice.	factually accurate and substantiated.	consultation with multiple clinicians through the Delphi Panel, confirming that the makeup of conventional therapy in the trial is reflective of clinical practice in the UK. Furthermore, no evidence has been provided by the EAG to demonstrate that the use of CT in the trial is not representative of NHS practice.	We note that CT use in the trial not reflecting standard practice was also an issue raised by the EMA.
In section 2.2 page 7, the EAG states "The EAG's position on this issue remains unchanged… (the company) does not address the fundamental concerns the EAG has with the PaTHway trial, particularly: 3) The applicability of PaTHway trial outcomes to the NHS setting, i.e. use of a surrogate primary outcome which does not allow for a fair comparison of	Please remove this statement as the statement "the use of a surrogate primary outcome not allowing for a fair comparison of conventional therapy with palopeg".	The use of a surrogate primary outcome in clinical trials is a standard and widely accepted practice, particularly when direct clinical endpoints are difficult to measure within the trial timeframe. Additionally, the concern that the outcome was not able to show people in the standard-treatment arm meeting the independence from therapeutic doses of calcium component of the primary outcome had been addressed within the company's response to the Draft	Not a factual inaccuracy. Our concerns in this area have been extensively discussed in our reports and by the committee.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
conventional therapy with palopeg.		Guidance, Comment 5. It was found that excluding independence from therapeutic doses of calcium did not alter the proportion of patients that met the primary endpoint and excluding this component had no impact on cost effectiveness in the response-based model.	
In section 2.2 page 7, the EAG states “The EAG maintains its concern that the reduction in active vitamin D and calcium doses meant that the CT arm of the PaTHway trial did not represent how CT would be used in the NHS and that this could potentially adversely affect serum calcium levels and quality of life.”	EAG to please amend the sentence to reflect that calcium doses in PaTHway were not reduced and could be titrated and acknowledge that the company provided evidence showing CT patients not having adversely affected quality of life outcomes over time.	Titration of calcium was not restricted within the PaTHway trial; therefore, the suggestion that reductions in active vitamin D and calcium dosing would adversely affect serum calcium levels is not supported. Furthermore, the EAG has not provided evidence to substantiate its claim that these reductions in vitamin D did negatively impact patients’ quality of life. In contrast, the company has presented data	Not a factual inaccuracy. Our concerns in this area have been extensively discussed in our reports and by the committee. Specifically, we noted in our report that in the palopeg group there was an increase in serum calcium at week 26 of 0.30 mg/dL compared with a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		demonstrating that quality of life outcomes remains stable over time (Baseline, n=[redacted], [redacted]; Week 26, n=[redacted], [redacted]). As such, the assertion of a potential adverse impact is not supported by the available evidence.	reduction of 0.39 mg/dL in the placebo group. We note that, according to Table 10 in the original company submission, the mean EQ-5D was: Baseline, n=[redacted], [redacted]; Week 26, n=[redacted], [redacted].
In section 2.2 page 7, the EAG states “although one of the PaTHway inclusion criteria was “optimization of supplements prior to randomization to achieve the target serum levels of albumin-adjusted or ionized serum calcium level in the normal range, or just below the normal range”, at week 26 in PaTHway only 48% of CT patients had albumin-adjusted serum calcium within the normal range. Given that the CS notes (on p20) that “even mild deviations below the normal calcium range can significantly	Please amend this statement as hypocalcaemia is a known complication of chronic hypoparathyroidism and serum calcium levels can vary despite ongoing conventional therapy. This cannot be interpreted as a deficiency in CT arm and as potentially favouring palopegteriparatide arm.	While it is reported that only 48% of patients in the CT arm had albumin-adjusted serum calcium within the normal range at week 26, this finding is not unexpected as the inclusion criteria was a normal **or just below** albumin adjusted serum calcium levels in a chronic and fluctuating condition such as hypoparathyroidism. This should also be considered alongside the observation that quality of life (QoL) in the placebo arm remained consistent throughout the trial, with some indications of marginal	Not a factual inaccuracy See also response immediately above regarding EQ-5D numbers. For context, we also note that normal range is 8.3mg/dl to 10.6mg/dl and that the CSR reports that “serum calcium at baseline was within normal range and comparable across treatment groups, with a median of 8.76 mg/dL (range: 7.00 to 10.90) in palopegteriparatide-treated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
impair neuromuscular and neurological function" and that the "impact of hypocalcaemia occurring has profound effects on the nervous system, contributing to neuromuscular irritability including tetany arrhythmia, cognitive dysfunction, brain fog, seizures, and mood disorders, all of which significantly impair quality of life" (p21), the EAG considers that this deficiency in CT may result in a bias favouring palopegteriparatide."		improvement (Baseline, n=[redacted], [redacted]; Week 26, n=[redacted], [redacted]). As noted in Committee paper section 1.3.4.1, hypocalcaemia is a well-recognised complication of chronic hypoparathyroidism, and serum calcium levels may vary despite ongoing conventional therapy. Therefore, the week 26 results reflect the expected clinical variability of the condition rather than any limitation in trial design or conduct. It is also factually inaccurate to suggest that patients randomised to CT/placebo were worse off at the end of the trial period. The EAG's interpretation is based on a narrower range of albumin-adjusted serum calcium at week 26 than that used in the trial's inclusion criteria. When the same range is applied consistently, there is no statistically significant	subjects and 8.48 mg/dL (range: 7.70 to 10.40) in placebo subjects."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		difference between the proportion of patients within the normal range at baseline and at week 26 in the placebo/CT arm.	
In section 2.2 page 8, the EAG states “The company’s Delphi panel concluded that permitting the use of thiazide diuretics in PaTHway would have had a negligible impact overall on patient outcomes. However, the company does not provide a rationale as to why thiazide diuretics were prohibited in PaTHway.”	Please remove the reference to the company not providing a rationale for prohibiting the use of thiazide diuretics in the PaTHway trial.	The current EAG statement is factually inaccurate. The company clearly articulated the rationale for prohibiting thiazide diuretics in the PaTHway trial, explaining that not only was their use expected to have a negligible impact on overall patient outcomes but that thiazide diuretics were prohibited due to their potential confounding effect on the assessment of urinary calcium endpoints (Clarification Question A5 in the Committee papers). In addition, the expected negligible impact of prohibiting thiazide diuretics was reviewed and confirmed with clinical experts	The sentence starting “However, the company…” on page 8 has been deleted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		during the Delphi Panel.	
In section 2.2 page 8, the EAG states “The Delphi panel also noted that thiazide diuretics are not widely used. However, the EAG’s clinical adviser considered that many patients who were genuinely NAC would be offered thiazide diuretics.”	Please consider revising the wording as current phrasing appears to give greater weight to a single unquantified clinical expert versus the output from the Delphi Panel, which was informed by nine experienced clinical experts in the management of hypoparathyroidism.	The reader has the right to know that EAG relied on feedback from one clinical expert whilst the company addressed the request from the committee to provide more robust clinical insight by conducting the formal Delphi Panel.	Not a factual inaccuracy. It is standard practice for the EAG to seek expert advice. That advice is clearly stated here and in our other reports. The clinical expert is named and acknowledged in the original EAG report.
In section 2.2 page 8, the EAG states “In PaTHway 13% of patients had some record of prior thiazide diuretic use; this figure should be interpreted in the context that the mean baseline calcium and active vitamin D doses in the PaTHway	Please remove the statement that prior thiazide diuretic use in the PaTHway population reflects adequate disease control or suggests that patients were	Thiazide diuretics are not indicated for treating chronic hypoparathyroidism or for achieving overall disease control. It is factually inaccurate and misleading to equate the presence of prior thiazide diuretic use in 13% of PaTHway patients to imply	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
cohort suggest that some PaTHway patients would likely be considered as having adequately controlled (AC) disease.”	adequately controlled at baseline.	that these patients were adequately controlled or that thiazides would be routinely used in genuinely non-adequately controlled patients.	
Appendix - Table 10, ID 3 Use of sub-optimal conventional therapy in the PaTHway trial: The EAG states “NO” under ‘Addressed by Company in DGD response’.	Please adjust the statement in ‘Addressed by Company in DGD response’ from “NO” to “YES” based on the above factual inaccuracies.	To correctly reflect the evidence submitted by the company.	Not a factual inaccuracy

Issue 3 Response-based model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3 page 8, the EAG states “In implementing the response-based model, the company assumes that 78.7% of patients in the palopeg arm enter the AC health state, consistent with the proportion that met the multi-component primary endpoint at 12 months.”	Please revise the statement to change the proportion that met the endpoint from 12 months to 6 months.	Statement is factually incorrect. The company use the proportion that met the multi-component primary endpoint at 6 months to determine the percentage of patients in the palopegteriparatide arm entering the AC health state.	This was a typo in our text. It has been corrected to: “… consistent with the proportion that met the multi-component primary endpoint at 6 months.”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3 page 9, the EAG states “The EAG considers the company’s rationale for rejecting the committee’s preferred response-based structure to be flawed and factually inaccurate.”	Please rewrite the statement to reflect the company’s provision of a response-based model upon request from the committee.	A response-based model was provided in response to the committee’s request and therefore not “rejected”, and a clear evidence-based rationale is provided under the company’s answer to Clarification Question B3.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3 page 8-9 the EAG states “The utility values cited by the company appear to be derived from a simple, unadjusted comparison of responders and non-responders. This approach is overly simplistic and does not align with the MMRM analysis presented in the clarification response, which shows that response (as defined by the primary outcome) is positively and statistically significantly associated with HRQL (see **Error! Reference source not found.**). It is therefore inaccurate to suggest that there is no difference in the HRQL of responders and non-responders”.	EAG to amend the sentence “It is therefore inaccurate to suggest that there is no difference in the HRQL of responders and non-responders”. There is no HRQoL differences among responder and non-responder in the palopegteriparatide arm. Therefore, the argument in favour of the treatment-based model remains.	To clarify, the utility data presented in the DG response is based on observed, descriptive statistics utility differences among responder and non-responder patients on palopegteriparatide **only**. For context, the MMRM analysis presented at the CQs examined quality of life data for both; palopegteriparatide and CT patients in the PaTHway trial. The results did show that there are differences in HRQoL between responders and non-responders across **all** patients, regardless of treatment.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3 page 9, the EAG states “Importantly, these findings do not invalidate a response-based model, nor do they alter the substance of the EAG’s critique”	The EAG to please acknowledge the MMRM model with treatment arm as a covariate has better statistical fit to the observed data compared to the primary response model based on the previously provided data.	The EAG claim is misleading and incomplete as it does not report the associated model statistical fit (marginal R-squared, Akaike/Bayesian Information Criterions), which shows the importance and impact of the covariates on utility data. Table 17 of the CQs indicate that the treatment arm performed better within the MMRM analyses; it has better statistical fit compared to the primary response model based on all the metrics above. These statistical outcomes provide a measure of validity to the treatment-based model, and this must be acknowledged to avoid reporting bias.	Not a factual inaccuracy. Our text here is about the problems inherent in using a treatment-based model generally, and is not dependent on the results of the MMRM model.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3 page 9, the EAG states “A treatment-based structure remains conceptually weak because it does not explicitly link health states to the mechanism through which health benefits are generated”	Please rewrite the sentence to acknowledge the supportive evidence the company has provided on this topic.	This statement is factually inaccurate. It has been clearly documented in the submission and during the clarification question stage how health states in the model are linked based on AC/NAC definitions, which in turn define how health benefits arise depending on the treatment patients are on. Therefore, the assertion that a treatment-based structure does not link health states to the mechanism of benefit is misleading and does not reflect the detailed rationale provided by the company during the appraisal process.	Not a factual inaccuracy.
In section 2.3 page 10, the EAG states “Removing responses from one trial arm, and not the other, therefore creates a bias.”	Please revise the statement to remove the sentence that	The EAG statement is factually inaccurate. The Delphi Panel, conducted at the request of additional clinical input, confirmed that achieving an adequate response on CT is not clinically plausible, a	Not a factual inaccuracy. The EAG strongly rejects any suggestion that actual data from a clinical trial can be ignored or overridden based

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	removing responses from one trial arm creates bias.	context not reflected in the EAG's assessment. Incorporating the full Delphi Panel findings supports removal of the single adequate response on conventional therapy and validates the company's treatment-based modelling approach; this adjustment reflects clinical reality and does not introduce bias.	on the opinions of an unknown Delphi panel.
In section 2.3 page 10, the EAG states "In addition, the company provides no discussion of the appropriateness of the six-month assessment period or its acceptability to patients or clinicians."	Please remove the statement.	Clinical trial data demonstrate that a clear response to palopegteriparatide can be observed within six months. In the absence of contrary evidence, this criticism is unsupported and creates unnecessary confusion. The company's approach is therefore reasonable and	This has been amended to: "The company provides limited discussion of the appropriateness of the six-month assessment period or its acceptability to patients or clinicians working in the NHS."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		aligned with the available evidence. Importantly, relevant clinical guidance supports this position. As stated in ESE guidelines (R.3.5.3): “If PTH replacement therapy is initiated, we suggest evaluating the treatment effects after 6–12 months, depending on treatment goals (Good clinical practice).” This further reinforces that a six-month assessment is appropriate and consistent with accepted clinical practice.	
In section 2.3 page 10, the EAG states “From the trial data it seems clear that patients randomised to placebo/CT were worse off at the end of PaTHway than at the start”	Please remove this sentence as it is factually inaccurate.	PaTHway trial outcomes show that the observed quality of life (QoL) in the placebo arm remained consistent throughout the trial, with some indications of marginal improvement (Baseline, n=[redacted], [redacted]; Week 26, n=[redacted], [redacted]).	Not a factual inaccuracy: We note that serum calcium levels were worse in the CT

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Therefore, it is incorrect to say CT patients were worse off.	after the trial than at randomisation. See also response on page 11-12 regarding EQ-5D numbers.

Issue 4 Effectiveness of standard treatment in the NHS vs. standard treatment in PaTHway (DGD Section 3.6)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.2 page 7, the EAG states "The EAG's position on this issue remains unchanged, given that the company's Delphi exercise constitutes the lowest level of evidence (i.e. expert opinion) in evidence-based medicine, and so does not address the fundamental concerns the EAG has with the PaTHway trial…".	Please amend the statement to acknowledge the value of the NICE-requested Delphi Panel.	In line with the above comment, the EAG's characterisation of the Delphi Panel as representing the lowest level of evidence is not fully accurate. While Delphi Panel methods are based on expert input, they are a structured and systematic approach to achieving consensus, rather than informal expert opinion. The evidentiary value of such exercises depends on their design and conduct, and they are commonly used in situations where empirical data are limited. Therefore, it is not appropriate to categorise the Delphi Panel in	Not a factual inaccuracy. See also response on page 8 and 9 above.

		overly simplistic terms within the evidence hierarchy. In addition, the EAG's failure to acknowledge or review the Delphi Panel report, which was conducted at the request of additional clinical input, is factually incomplete and unprofessional. The Delphi Panel was specifically designed to provide Committee members with additional clinical feedback and insight from experts actively treating patients, ensuring that model assumptions were clinically validated. By disregarding this robust and structured evidence, the EAG did not attempt to find common ground and instead chose to discredit a well-conducted exercise, which unnecessarily complicates the appraisal process and misrepresents the available evidence.	

Issue 5 Independence from calcium endpoint

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 2.4 page 10 “The company provided no new evidence to validate its response.”	Please adjust the wording as the company provided evidence to validate its response.	This statement is factually inaccurate and should be adjusted. In response to the Committee’s request to exclude the ‘independence from therapeutic doses of calcium’ as a component of the primary outcome and health-state definitions in the response-based model, the company undertook this analysis and confirmed the exclusion did not change the number of patients meeting the endpoint, hence it had no impact on the cost-effectiveness.	This sentence (page 11) has been amended to read: The company provided limited evidence to validate its response by undertaking subsequent analysis stating that excluding ‘independence from therapeutic doses of calcium’ did not change the number of patients meeting the endpoint.

In Section 2.4 page 10 “It is unclear to the EAG whether only independence from calcium was considered by the company, or independence from conventional therapy as a whole, which would include independence from Vitamin D analogues”	Please remove this statement.	It was explicit in the committee’s request and the company response that the analysis was based on removing independence from calcium only. However, the company can confirm that removing independence from Vitamin D as well also has no impact on the proportion of patients meeting the multi-component primary endpoint.	This was accurate at time of writing, but we have amended the document (EAG response, Page 11) to reflect the information supplied by the company here.

Issue 6 Resource use associated with management of chronic hypoPT

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 12, the EAG states “The EAG continues to have substantial concerns with the company’s approach to modelling health state costs, as the company's revisions do not address the committee’s conclusion that the costs generated from the	Please remove the following part of the statement: “the company's revisions do not address the committee’s conclusion”.	Following the first Committee meeting, the company updated the approach to analysing the CPRD data to meet the committee concerns that the definitions used to differentiate the health states were not appropriate.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
CPRD analysis are not reliable (DG: Section 3.15).”		The updated approach aligns with NICE reference case by only including the additional costs associated with chronic HPT and excluding patients with prior CKD and CVD.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 12, the EAG states “The EAG does not consider Delphi panel opinion sufficient to validate this assumption,”	Please remove this statement.	The statement fails to acknowledge the challenges in evidence generation recognised by the committee due to the rarity of the disease and their request for additional clinical expert opinion. The Delphi Panel was conducted in response to the request of the committee for robust transparent clinical expert opinion (DG Page 17), particularly in the absence of literature sources given the rarity of the disease. The statement fails to acknowledge this important context, which explains why the Delphi Panel was conducted in the first place and the role it played in validating assumptions after the first committee meeting.	Not a factual inaccuracy. See also response on Page 8 and 9 above.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 12, the EAG states “the predicted cost savings exceed the equivalent of [redacted] QALYs at a £25,000 per QALY threshold and considers that a higher level of evidence is required to support benefits of this magnitude.”	Please revise this statement as the translation of predicted cost savings into QALY values at a threshold is inappropriate.	This figure is not based on the company’s submitted data or the model and has no connection to the decision problem. Predicted cost savings should not be converted into QALYs, and the assertion inflates the perceived impact of the treatment without any evidential basis.	Not a factual inaccuracy. This is only a statement that the large cost savings must be justified by clear clinical evidence and not clinical opinion, just as substantial QALY gains must.
In section 2.5 page 12, the EAG states “The EAG has further concerns regarding the revised definition of NAC, which is not clearly justified.”	Please remove this statement.	The definition of NAC used to identify patients in the CPRD data was conclusively justified through the Delphi Panel.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 12, the EAG states “The definition appears overly narrow and likely captures only the most severe patients with the highest resource use.”	Please remove the claim the definition appears overly narrow.	It is considered factually incorrect to describe the definition as overly narrow given the generalisability of the data to the NAC population was confirmed by the clinical experts in the Delphi Panel. The definition is deliberately specific to ensure costs were attributable to chronic hypoparathyroidism in patients NAC on conventional therapy, with the methodology validated by clinical experts through the Delphi Panel.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 13, the EAG states "The revised NAC population (n=[redacted]) is of a very similar size to a subgroup defined by ≥1 inpatient admission for symptomatic hypocalcaemia (n=[redacted]), suggesting substantial overlap between the groups."	Please remove this statement.	It is inappropriate to assume overlap based on sample size alone. Particularly as there are only [redacted] patients who were in both groups, further confirming that hypocalcaemia is under reported in the CPRD data.	This statement was valid at time of writing, but has been removed, given the clarification supplied by the company.
In section 2.5 page 13, the EAG states "However, mean inpatient costs are markedly higher in the revised NAC population (£[redacted] vs £[redacted]), consistent with the possibility that one patient with exceptionally high costs is driving the estimate."	Please revise the statement.	It is inaccurate to speculate that one patient with exceptionally high costs has possibly been responsible for the cost differences. The maximum relevant inpatient cost for a patient is reported at £[redacted], which corresponds to less than 10% of the relevant total inpatient costs.	Not a factual inaccuracy. Given the substantial change in costs it is perfectly reasonable for the EAG to speculate on possible causes; our text is clear that this is only a possible cause. For clarity we have amended "one patient" to "a small number".

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 13, the EAG states “It is unclear whether the revised health-state costs account for the mixed aetiology of patients with hypoparathyroidism (HypoPT) or the disparity in the proportion of non-surgical cases relative to those reported in the PaTHway trial and observed in NHS practice.”	Please revise this statement to include the expert clinical opinion that aetiology did not impact health state costs.	This statement should be amended to include reference to the clinical consensus from the Delphi Panel confirming from the impact of aetiology on total healthcare resource use for NAC patients is small (score of 2), and that aetiology is not a significant driver of differences in total healthcare resource use (score of 8).	Not a factual inaccuracy.

In section 2.5 page 13, the EAG states “As per the original EAR base case, the EAG prefers to remove all health state costs, acknowledging that this is likely conservative.”	Please revise the statement to reflect that this is highly conservative.	The conclusion to remove all health state costs is not factually consistent with the arguments presented by the EAG in their EAR. The company’s updated approach aligns with the NICE reference case, as it incorporates hypoparathyroidism specific costs. This is the very basis on which health state costing should be calculated and undermines a major EAG critique. In addition, the EAG’s conclusion contradicts its own earlier statement in the EAR that “it is plausible that improved disease control may result in modest reductions in healthcare resource use.” (p.70) This acknowledgement explicitly supports the existence and relevance of hypoparathyroidism related costs in the clinical practice. Removing all health state	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		costs is therefore inconsistent with the EAG's position that disease control influences resource use. These inconsistencies demonstrate that the removal of all health state costs is extremely conservative and against common understating that any progressive chronic disease is more costly to the healthcare system. Eliminating these costs introduces a substantial imbalance where economic consequences of uncontrolled hypoparathyroidism are underestimated.	

Issue 7 Modelling of adverse events

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 page 13, the EAG states "To support its decision-making, the committee asked the company to provide evidence that the risk of adverse events would be higher in clinical practice than in PaTHway. The company states that hypocalcaemia and hypercalcaemia are clinically impactful treatment-emergent events and asserts that the PaTHway trial is likely to underestimate the frequency of events requiring acute intervention in routine clinical practice. However, the company notes that there is a lack of literature to inform the specific risk of both symptomatic hypocalcaemia and hypercalcaemia."	Please revise this opening statement to also include reference to the company's provision of additional supportive evidence through the Delphi Panel.	The company did provide evidence explaining why the PaTHway trial likely underestimates the frequency of clinically impactful adverse events via expert opinion from the Delphi Panel.	Not a factual inaccuracy.

In section 2.6 page 14, the EAG states “The EAG does not regard clinical opinion as sufficiently robust evidence to justify the company’s interpretation of the PaTHway trial data, where adverse event rates are based on any-grade events, while associated costs assume hospitalisation.”	Please remove this statement.	This statement does not reflect the robust evidence collection of the Delphi Panel, which was conducted in response to the committee's request for robust transparent clinical opinion. The EAG fails to acknowledge the additional clinical validation and expertise supporting the modelled assumptions including the interpretation of PaTHway data trial data and the clinical impact of adverse events. Evidence from a Delphi Panel of nine clinicians, each experienced in managing over 70 patients with HypoPT, was incorporated to support assumptions regarding the underestimated incidence of severe adverse events.	Not a factual inaccuracy.

Issue 8 Modelling of complications and mortality

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.7 page 16, the EAG states “Given that no further evidence has been supplied to justify these assumptions, the EAG retains its preferred approach of setting complication rates to zero.”	Please amend this statement to reflect that there was no further available evidence to be provided.	The company could not identify any further evidence rather than it was not provided. The modelled complication rates are supported by peer-reviewed evidence. The EAG’s statement is also contrary to their previous conclusion that it was plausible that palopegteriparatide could reduce the risk of complications (DG Page 20). It is therefore unclear why the EAG has reverted to setting complication rates to zero, as this does not reflect the evidence or the previously cited data.	Not a factual inaccuracy.

Issue 9 Additional issues raised by the EAG and EAG scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 2.10 page 15 the EAG states "The company's revised model makes several small changes to parameter values and functionality without documenting or justifying them, including rounding certain values and making minor absolute adjustments, see Table 3 for a full list of changes"	N/A – no action for the EAG.	The company would like to clarify the undocumented changes to avoid time being taken up in the committee meeting. • Numbers 1 and 2 are due to version control and rounding errors • Number 3 is due to implementing the EAG preference as stated in the EAR to use the eMIT cost for alfacalcidol • Number 4 is due to identification of	None required We note that any model changes should be clearly documented should additional analysis or model amendments be required in future.

		a calculation error in the first-round exposure-adjustment adverse event analyses. Specifically, AEs from patients who did not complete Week 156 were inadvertently excluded due to a programming issue related to the identification of AEs within the reporting period. The updates AE rates reflect the correct and updated analyses. As the EAG notes, the new rates are detrimental for the ICER but nevertheless, the	

		company did incorporate them to include the most up to date values for the analyses. • Number 5 is due to implementing drug wastage as confirmed in the company's draft guidance response. The implementation every 6 cycles rather than 7 appears to be due to a difference in interpretation of how the EAG thought wastage should be incorporated • Number 6 is not an undocumented	

		change rather the company have not implemented the EAG correction because it impacts mortality risk from complications, which is not considered in the base case. We would like to apologise for any inconvenience caused as a result of these changes.	
In section 3.2 page 19, the EAG states “The company provides no compelling evidence to support the modelled health state costs. A per the EAR, the EAG sets the applied health state costs to zero, thereby removing all (health state-related) cost	Please amend this statement as it fails to acknowledge the previously provided evidence (economic SLR) showing higher healthcare costs in patients derived from CPRD data and patients diagnosed with chronic hypoparathyroidism.	Previously provided published evidence shows that patients with a diagnosis of chronic hypoparathyroidism incur higher healthcare costs than matched members of the general population, even when excluding patients with	Not a factual inaccuracy

savings associated with palopeg.”		cardiovascular or chronic kidney disease risk factors. Please see the economic SLR for detail. Additionally, the health-state costs used in the model are derived from CPRD data from real-world patients, which is a well-recognized and credible source of information.	
In section 3.2 page 19, the EAG states “The company provides no additional substantive evidence to support its assumptions, and the EAG does not consider clinical opinion sufficient to justify modelling hospitalisation costs based on any-grade adverse event rates from the PaTHway trial.”	Please remove this statement as it fails to acknowledge clinical validation from the Delphi Panel.	The company provided clinical validation for its assumptions by conducting a Delphi Panel, which was conducted following a committee request for further clinical input. The purpose of the panel was to provide additional expert input on the interpretation of PaTHway trial data and the modelling of	Not a factual inaccuracy.

		hospitalisation costs. Therefore, the EAG's assertion that no substantive evidence was provided and that clinical opinion is insufficient does not accurately reflect the robust evidence and validation undertaken at the Committee's request.	
Appendix - Table 10, ID 9 <u>Self-administration of palopeg:</u> The EAG states "Committee did not agree" under 'Addressed by Company in DGD response'.	Please adjust the statement in 'Addressed by Company in DGD response' from "Committee did not agree" to "Committee **did** agree" based on the above factual inaccuracies.	Draft guidance document, section 3.18 "The committee concluded that additional administration costs did not need to be included in the model" p.25	This typo has been corrected.

Typographical errors

Location of incorrect marking/typographical	Description of incorrect marking	Amended marking	EAG response
Section 2.5 page 14: "The company based their CPRD-based cost estimate on combined post-surgical and non-surgical patients without complications and with ≥1 symptomatic hypocalcaemia IP admissions (N=[redacted]). "	Please remove the additional space after the period of the sentence.	The company based their CPRD-based cost estimate on combined post-surgical and non-surgical patients without complications and with ≥1 symptomatic hypocalcaemia IP admissions (N=[redacted]).	Corrected, although this is not an error.
Section 2.6 page 16: "The company's response does not address the underlying issues. "	Please remove the additional space after the full stop of the sentence.	The company's response does not address the underlying issues.	Corrected, although this is not an error.
Section 3.2 page 19: "The EAG updates the response based analysis implemented by the company to remove the structural assumption preventing response in the CT arm of the model and updates the utility value using to utilise the MMRM regression model, including response	Please remove the additional space between "Model 2 in" and "Table 2".	The EAG updates the response based analysis implemented by the company to remove the structural assumption preventing response in the CT arm of the model and updates the utility value using to utilise the MMRM regression model, including response as a covariate (Model 2 in Table 2).	Corrected

as a covariate (Model 2 in Table 2).”			
Section 3.2 page 20: “A per the EAR, the EAG sets the applied health state costs to zero, thereby removing all (health state-related) cost savings associated with palopeg.”	Please amend the “A” in the sentence to “As”.	As per the EAR, the EAG sets the applied health state costs to zero, thereby removing all (health state-related) cost savings associated with palopeg.	Corrected
Section 3.2 page 19: “The utility of a responder is therefore updated to be [redacted], and a no-responder is updated to be [redacted] “	Please add a full stop at the end of the sentence.	The utility of a responder is therefore updated to be [redacted], and a no-responder is updated to be [redacted].	Corrected
Appendix - Table 10 ID 5: Model structure, Addressed by Company in DGD response: “PARTLY A response based model is presented”	Please include a hyphen between “response” and “based”.	PARTLY A response-based model is presented	Corrected

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EAG ADDENDUM

Committee requests following ACM2: Palopegteriparatide for treating chronic hypoparathyroidism [ID6380]

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None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

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1 OVERVIEW

The External Assessment Group (EAG) was requested by NICE to provide additional critique and analysis following appraisal committee meeting two (ACM2).

NICE request that the EAG provide a critique of the company's updated response-based model provided in additional documentation dated: 9 April, 5 May and 8 May 2026 submitted by the company prior to ACM2 (12 May 2026). The updated model was provided by the company in response to the EAG's critique to the company's response to the consultation on the draft guidance document (DGD) published following ACM1 but was not subject to critique by the EAG prior to ACM2 due time constraints.

NICE have further requested that the EAG provide additional analysis to inform committee decision making. This includes further analysis to reflect the committee's preferred base case assumptions; scenario analysis exploring alternative assumptions regarding modelled response rates, health state costs and adverse event rates and costs applied; and threshold analysis exploring the impact of health state costs applied to the not adequately controlled health state.

Finally, NICE also requested that the EAG to review additional information provided by the relating to redefining the trial primary outcome to exclude independence from calcium and from calcium and vitamin D combined.

2 DESCRIPTION AND CRITIQUE OF COMPANY'S RESPONSE-BASED MODEL

The additional documentation provided by the company prior to ACM1 outlines an updated company base case which makes the following changes to the company's preferred assumptions:

- Model structure updated to response-based structure using the primary trial endpoint to inform health state occupancy.
- Revised model health state utilities estimated from a mixed model for repeated measures (MMRM) with response included as a covariate.
- Updated model health state costs to address concerns raised by the EAG regarding the double counting of costs attributable to symptomatic hypocalcaemia.

The EAG has conducted high-level checks of the provided model and has been able to replicate the results presented by the company (ICER: £28,862).

The response rate in the company's revised analysis was informed by an adjusted analysis of observed outcomes in the PaTHway trial. This analysis set the response rate in the conventional therapy (CT)

arm, to 0% and 73.9% in the palopegteriparatide (palopeg) arm. This analysis adjusts the response rates applied in both arms by subtracting 4.9% from both arms. The rationale for this adjustment was that the company did not consider biologically plausible or reflective of real-world clinical practice to model response in the CT arm. It is suggested that the observed response in the trial may be attributable to recovery of residual parathyroid gland function following down-titration of CT in accordance with the trial protocol. On this basis, the company assumes that a similar proportion of patients in both arms would experience restored gland function and therefore removes an equivalent proportion of responders from both treatment arms.

The EAG acknowledges what the company is trying to achieve in aligning to the EAG response-based model framework. However, the EAG is concerned by the company's post hoc adjustments to the response rates. While the EAG acknowledges that spontaneous recovery may be rare, it considers that any adjustment to observed trial outcomes requires strong empirical justification. Where such adjustments are applied, they should preserve the relative treatment effect observed in the trial rather than re-specifying effects in terms of absolute differences between arms. The latter approach assumes that the treatment effect is additive and separable from the background response rate and implicitly assumes that the observed response in the CT arm contaminates the treatment arm to an equivalent degree, neither of which is demonstrated by the trial evidence or clearly supported by the underlying clinical structure of the outcome.

The company did not provide additional CPRD data or supporting documentation to enable the EAG to verify the removal of potential double-counting. In the absence of such evidence, the EAG can only infer that costs in the not adequately controlled (NAC) population attributed to the composite complication category for hypoparathyroidism are not primarily driven by inpatient admissions related to symptomatic hypocalcaemia. This uncertainty weakens the company's assumption that any-grade symptomatic hypocalcaemia necessarily results in hospitalisation.

3 ADDITIONAL INFORMATION REQUESTS

In their response to request (8 May 2026), the company provided a table showing that percentage of participants meeting the composite primary endpoint at week 26 with independence from calcium excluded was equal to the percentage of participants meeting the primary endpoint in both arms. The EAG notes that, even with independence from calcium excluded, the primary outcome remains effectively unattainable on standard treatment. We note that 10 patients (46.7%) in the placebo arm maintained serum calcium in the normal range, and 5 (23.8%) achieved independence from active vitamin D (without independence from calcium).

The committee additionally requested that the EAG provide further details on the health costs applied in the economic analysis using the ACM1 and ACM2 definitions of adequately controlled (AC) and NAC from the CPRD dataset. Table 1 provides details of the definitions used, the cost categories included, the health costs applied and the proportion of costs that are attributable to inpatient stays.

The EAG notes that the figures reported in Table 1 are based on the health state costs applied in the company's ACM1 response and do not account for updates made in the latest company base case, in which the company states that costs attributable to symptomatic hypocalcaemia were removed. The EAG is unable to provide details for these updated costs as it is unclear what changes have been made and the EAG has not been supplied with updated CPRD analyses or supporting documentation.

Table 1 Details of health state costs applied in ACM1 and ACM2

	Previous ACM1 definitions		**Updated ACM2 definitions**	
	AC	**NAC**	**AC**	**NAC**
Definition	*≤5 outpatient visits and <1 inpatient visit per patient per year*	*>5 outpatient visits and ≥1 inpatient visit per patient per year*	*All patients without complications who do not meet definition of NAC*	*≥1 inpatient visit per patient per year, with hypoPT as the primary or secondary diagnosis*
Included cost categories*	primary care consultations, outpatient attendances, inpatient admissions, emergency visits, and kidney replacement therapy.		primary care consultations/visits (coded to a composite of complications associated with chronic hypoPT), outpatient attendance/visits (coded to any speciality of interest), inpatient admissions (coded to a composite of complications associated with chronic hypoPT), all-cause emergency visits, and kidney replacement therapy (KRT)*.	
n	[redacted]	[redacted]	[redacted]	[redacted]
Total annual costs	[redacted]	[redacted]	[redacted]	[redacted]
Total inpatient costs	[redacted]	[redacted]	[redacted]	[redacted]
Inpatient costs as % of total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total per cycle costs	[redacted]	[redacted]	[redacted]	[redacted]

*Total costs were the same with and without KRT in ACM1 but did differ in ACM2 for both AC and NAC costs.
^The total annual costs were provided on the 8 May 2026; the inpatient costs were ascertained from the 13 March CPRD dataset available to the EAG.

4 COMMITTEE PREFERRED BASE CASE ASSUMPTIONS AND SCENARIOS

Following ACM2, the committee's preferred base case assumptions for the response-base model were as follows:

- Responders: 1% for standard treatment, 74.9% (78.7% - 4.8% + 1%) for palopeg
- Health state costs based on original CPRD analysis with AC/NAC definitions from ACM1
- No additional inclusion of AEs or complications in the model

The committee also requested the following scenarios on the committee's base case:

- Responders: 4.8% for conventional therapy; 78.7% for palopeg
- Responders: 0% for conventional therapy; 73.9% for palopeg
- Adverse events: Grade 3/4 AEs only and EAG's alternative CPRD cost
- Complications: Company's assumptions for complication rates

Threshold analysis – based on committee's other base case assumptions, what is the minimum NAC health state cost (holding AC costs constant) that would result in palopeg being cost-effective.

5 UPDATED RESULTS

Results inclusive of the committee's preferred assumptions are presented in Table 2. The results are based upon amendments to the EAG base-case model (i.e., excluding complications and using MMRM utility values based on response). Table 3 presents the equivalent probabilistic ICER. All results are inclusive of all relevant confidential discounts.

Table 2 Committee preferred assumptions (Deterministic)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,376
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Table 3 Committee preferred assumptions (Probabilistic, 10,000 simulations)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£144,296
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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

Table 4 shows the deterministic ICERs for the scenario analyses requested by committee, and Table 5 the equivalent probabilistic ICERs.

Table 4 Scenario analyses (deterministic)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Responders: 4.8% for conventional therapy; 78.7% for palopegteriparatide						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£144,420
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Responders: 0.0% for conventional therapy; 73.9% for palopegteriparatide						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£135,486
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Adverse events: Grade 3/4 AEs only and EAG's alternative CPRD cost						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,533
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Company's assumptions for complication rates						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£128,757
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Table 5 Scenario analyses (Probabilistic, 1,000 simulations)

Technology	Total costs	Total LYGs	Total QALYs	Incremental QALYS	Incremental costs	ICER
Responders: 4.8% for conventional therapy; 78.7% for palopegteriparatide						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£152,971
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Responders: 0.0% for conventional therapy; 73.9% for palopegteriparatide						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139,261
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Adverse events: Grade 3/4 AEs only and EAG's alternative CPRD cost						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£142,319
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Company's assumptions for complication rates						
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£131,597
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Threshold analysis

The threshold analysis seeks to identify the minimum NAC health state cost required for palopeg to be considered cost-effective. As shown in Table 2, the committee's base-case ICER is £140,376 per QALY. Assuming the committee's preferred AC health state of [redacted] and all other base case assumptions (see Section 4), the results presented in Table 6 identifies the minimum NAC health state costs required to achieve different ICER thresholds. This is set between £20 to £35K reflecting the range of the NICE cost-effectiveness (ICER) thresholds over the period of this evaluation. For example, at the £25K ICER threshold, the minimum per cycle NAC health state costs required for palopeg to be considered cost-effective are [redacted] per month or [redacted] per annum. Note, this substantially exceeds the health state costs applied in the company's revised base case analysis which assumed a cost of [redacted] per month or [redacted] per annum. The primary reason that such high NAC health-state costs are required, compared with the company's base case, is that the committee's preferred base case does not simultaneously include AE costs, which are associated with substantial cost savings.

Table 6 Threshold analysis

ICER Threshold	Minimum per cycle NAC costs	Minimum annual NAC costs
£20,000	[redacted]	[redacted]
£25,000	[redacted]	[redacted]
£30,000	[redacted]	[redacted]
£35,000	[redacted]	[redacted]