Medicinrådet

Bilag til Medicinrådets vurdering af palopegteriparatid til behandling af voksne med kronisk hypoparatyroidisme

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. palopegteriparatid
2. Forhandlingsnotat fra Amgros vedr. palopegteriparatid
3. Ansøgers endelige ansøgning vedr. palopegteriparatid

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Kommentar til Medicinrådets vurdering af palopegteriparatide til behandling af voksne med kronisk hypoparatyroidisme (hypoPT)

Ascendis takker for muligheden for at kommentere på Medicinrådets udkast til vurderingsrapport for palopegteriparatide i behandlingen af kronisk hypoPT. Ascendis finder, at vurderingsrapporten i sin nuværende form desværre indeholder både fejl og misforståelser, der gør, at den ikke er egnet for Medicinrådets beslutning. Der opfordres derfor til, at de aktuelle fejl rettes og at sagen sættes i clock-stop på foranledning af Ascendis. Dette vil give mulighed for at have en dialog om afgrænsning af den aktuelle patientpopulation. Ascendis har forståelse for at vurderingsforløbet skal følge bestemte processer og tidslinjer, men finder det samtidig utilstedeligt, hvis processer og tidslinjer ender med at overskygge patienters mulighed for at få adgang til et livsforandrende lægemiddel. De konkrete kritikpunkter og forslag uddybes herunder.

Beskrivelsen af effektmål

I vurderingsrapporten indikeres det, at det primære effektmål i det randomiserede kliniske studie ikke er patientrelevant. Ascendis vil gerne påpege, at det primære effektmål er vurderet klinisk relevant og adækvat af EMA.[1] Vi finder, at der er åbenlyse patientrelevante sammenhænge mellem at have normale serum calcium værdier og være symptomfri, blive uafhængig af konventionel behandling og have en nedsat risiko for komplikationer. Kritikken fremstår i vurderingsrapporten ubalanceret, når det ikke også fremhæves, at det valgte effektmål er det bedst mulige, når det drejer sig om en behandling, der som en væsentlig effekt gør at patienter netop ikke behøver konventionel/ symptomatisk behandling.

Det fremhæves i vurderingsrapporten, at de patientrapporterede livskvalitetsmål i PaTHway studiet er usikre, da patienterne trods blinding potentielt bliver klar over, hvilken behandlingsarm de er med i. Dette er begrundet i at palopeparateride har en signifikant effekt på afhængigheden af calcium og vitamin D. Kritikken fremstår også her ubalanceret i vurderingsrapporten, når det ikke samtidig fremhæves, at intet i data tilsiger at dette er tilfældet. Der ses således - på tværs af instrumenter - et meget begrænset fald i livskvalitet i placebo-armen og en konsekvent høj livskvalitetsgevinst i palopegteriparatide armen - både i den randomiserede periode og i de efterfølgende tre års follow-up. Yderligere påpeges det i flere studier, at selv i open-label trials, har det begrænset betydning for patientrapporterede outcomes at patienter ved hvilken behandling de får[2].

Omkostninger forbundet med monitorering og komplikationer

Kronisk hypoPT er en relativt sjælden lidelse. Det er dog veldokumenteret, at tilstanden er forbundet med en lang række komplikationer i hele kroppen[3,4,5]. Ascendis finder det derfor meget overraskende, at det fra vurderingsrapporten kan konkluderes, at patienter med kronisk hypoPT som ikke er i tilstrækkelig sygdomskontrol har lave årlige omkostninger forbundet med monitorering af behandling samt behandling af medfølgende symptomer og komplikationer.

Ascendis har i ansøgningen baseret omkostninger forbundet med monitorering og komplikationer på et engelsk registerstudie. Studiet estimerer hypoPT patienters sygdomshenførbare merforbrug i sundhedsvæsenet. På den baggrund virker det inkonsistent, at Medicinrådet vurderer omkostninger forbundet med patienter, der ikke er i tilstrækkelig sygdomskontrol, til at være mere end [redacted] gange lavere end hvad, der er dokumenteret baseret på registerdata. Ascendis antager, at dette enten skyldes, at Fagudvalget er blevet spurgt til den specifikke sygdomsmonitorering og ikke til det samlede ressourceforbrug, der inkluderer de sygdomsrelaterede komplikationer. Alternativt må forklaringen være, at det er en forkert patientpopulation, der er blevet vurderet, da ressourceforbruget ikke kan afspejle det samlede ressourceforbrug for patienter, der ikke er i tilstrækkelig sygdomskontrol. Ascendis har efter indsendelsen til Medicinrådet fået resultatet

[1] EMA assessment report. Yorvipath: "The primary endpoint is regarded meaningful and adequate to investigate the efficacy of palopegteriparatide"
[2] Lord-Bessen J, Signorovitch J, Yang M, Georgieva M, Roydhouse J. Assessing the impact of open-label designs in patient-reported outcomes: investigation in oncology clinical trials. JNCI Cancer Spectr. 2023 Mar 1;7(2):pkad002. doi: 10.1093/jncics/pkad002. PMID: 36661326; PMCID: PMC10023242.
[3] Noori et al. Adv Ther 42, 4881–4903 (2025). https://doi.org/10.1007/s12325-025-03265-w
[4] Narendra *et al.* Endocrine and Metabolic Science, Volume 19,2025, https://doi.org/10.1016/j.endmts.2025.100258.
[5] Chen *et al.* Journal of Medical Economics, 22(11), 1141–1152. https://doi.org/10.1080/13696998.2019.1624081

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fra et begrænset pilotstudie af danske registerdata. Her ses tal for sygehuskontakter som er sammenlignelige med dem fra det engelske register. Danske patienter med ikke-velkontrolleret hypoPT (cirka 30% af alle hypoPT patienter) havde i gennemsnit mere end fire indlæggelser og mere end 19 ambulante kontakter per år.

Ascendis anerkender, at det er svært at opgøre antallet af indlæggelser og kontakter præcist, men mener dog som minimum, at estimaterne fra det engelske studie bør indgå i vurderingen, da de udgør den bedst tilgængelige evidens og kan valideres af danske data. Det bør desuden afklares med Fagudvalget, hvad den nuværende forskel i det observerede og det vurderede ressourceforbrug er.

Livskvalitet og QALY estimat

Ascendis finder vurdering af nytteværdier og dermed estimering af QALY er fejlbehæftet. I den sundhedsøkonomiske vurdering halveres behandlingseffekten på livskvalitet i forhold til hvad der er dokumenteret i det randomiserede studie. Rationalet for denne reduktion er at Medicinrådet noterer, at patienter i PaTHway som er i sygdomskontrol har en livskvalitet som er højere end populationsnormen, hvilket ikke er korrekt. Som begrundelse for justering anvendes en forkert, historisk populationsnorm, som er baseret på et andet instrument og andre præferencevægte. Den faktiske populationsnorm er således 0,90 og ikke 0,834, som det angives i vurderingsrapporten[6]. Patienter behandlet med palopegteriparatide i PaTHway oplevede en forbedring af livskvalitet over 26 uger mens patienter i kontrolarmen havde en lille forringelse (ΔCFB= [redacted]; p = [redacted]). I modellen anvendes baseline for begge grupper med tillæg af den dokumenterede behandlingseffekt på [redacted]. Dette giver en værdi i modellen som for begge arme ligger over niveauet ved 26 uger i PaTHway. Da ICER er inkrementel påvirkes den kun af ændringen i nytteværdi. Det er således faktuelt forkert at justere behandlingseffekten på livskvalitet i den sundhedsøkonomiske model. Ascendis forventer, at denne fejl bliver korrigeret inden rådet træffer beslutning om ibrugtagning af palopegteriparatide.

Patientpopulation

Ascendis har på baggrund af vurderingsrapporten en opfattelse af, at der ikke har været klarhed omkring, den aktuelle patientpopulation. I ansøgningen beskrives det, at den aktuelle patientpopulation for palopegteriparatide er patienter, som ikke kan opnå tilfredsstillende sygdomskontrol med nuværende symptombehandling. Dette drejer sig om en afgrænset population og falder i tråd med de nyligt publicerede internationale guidelines[7]. PaTHway studiets patientpopulation udgøres i høj grad af danske patienter (24%), hvorfor der er danske klinikere, der har erfaring med behandling. Også her peges på den afgrænsede patientpopulation. F.eks. skriver Peter Schwarz, Ordførende Professor, Overlæge dr. med. Rigshospitalet og klinisk studieleder i det kliniske program for palopegteriparatide:

"Hovedparten af mine patienter har ingen eller kun få gener og behandles med calcium og aktiv vitamin D. Når denne velbehandlede gruppe vurderes, er generne som oftest kun lette paræstesier (summen og prikken) i læberne, i finger og tåspidser og behandlingen enkel. Imidlertid er der en gruppe patienter (15-30%), der er betydeligt mere udfordret med større udsving i biokemi, større kompleksitet med symptomer, og nogle har ligeledes bidrag fra anden sygdom, som gør gruppen vanskelig."

Afslutningsvis vil Ascendis understrege, at der er et klart behov for afklaring omkring patientpopulationen mellem Ascendis, Medicinrådets sekretariat og Fagudvalget før der kan skabes et tilfredsstillende beslutningsgrundlag for Medicinrådet. Ascendis håber, at alle parter er interesserede i at indgå i en sådan dialog og at vurderingsprocessen sættes i clock-stop på foranledning af Ascendis. Ascendis har tilbudt en [redacted] pris for palopegteriparatide for at sikre at de patienter i Danmark, som ikke er velkontrollerede på konventionel behandling, får adgang til behandling. Den årlige omkostning per patient (13 pakker) bliver dermed ca. [redacted] kr/patient.

[6] Jensen *et al*. Scand J Public Health. 2023 Mar;51(2):241-249. doi: 10.1177/14034948211058060
[7] Bollerslev et al. European Journal of Endocrinology, 2025, 193, G49–G78. https://doi.org/10.1093/ejendo/lvaf222

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23.02.2026

DBS, KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.03.2026
Leverandør	Ascendis Pharma
Lægemiddel	Yorvipath (palopegteriparatide)
Ansøgt indikation	Substitutionsbehandling til voksne patienter med kronisk hypoparatyroidisme.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Yorvipath (palopegteriparatide):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Yorvipath	168 mikg/0,56 ml (2 stk.)	54.550,30	[redacted]	[redacted]
Yorvipath	294 mikg/0,98 ml (2 stk.)	54.550,30	[redacted]	[redacted]
Yorvipath	420 mikg/1,4 ml (2 stk.)	54.550,30	[redacted]	[redacted]

Prisen er fortrolig og betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Yorvipath, indkøbes lægemidlet til AIP.

[redacted]

Information fra forhandlingen

[redacted]

Konkurrencesituationen

Den nuværende behandling består af tilskud af calcium og aktivt D-vitamin samt supplerende behandling med thiazid og tilskud af magnesium ved behov. To nye lægemidler, eneboparatide og encalerat, forventes markedsført til behandling af kronisk hypoparatyroidisme. Endelig indikation og tidshorisont for lancering er dog endnu ikke kendt.

Tabel 2 viser lægemiddeludgifter pr. år pr. patient ved behandling med Yorvipath. Udgifterne til den nuværende behandling er så lave, at de ikke er medtaget.

Tabel 2: Sammenligning af lægemiddeludgifter pr. år pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år SAIP, DKK)
Yorvipath	420 mikg/1,4 ml (2 stk.)	Startdosis på 18 mikrogram én gang dagligt med mulighed for dosisjustering i intervaller på 3 mikrogram hver 7. dag. Dosis kan variere fra mellem 6 og 60 mikrogram om dagen, s.c.	[redacted]	[redacted]

*) Der anvendes i gennemsnit 13 pakninger pr. år pr. patient, jf. Medicinrådets vurderingsrapport afsnit 4.3.1.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
England	Under vurdering	Link til status
Sverige	Ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of Palopegteriparatide (Yorvipath®) for chronic hypoparathyroidism

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Text to be redacted

Contact information

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Tables and Figures

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Abbreviations

Overview of abbreviations	
AC	Adequately controlled
AE	Adverse event
ANCOVA	Analysis of covariance
BMD	Bone mineral density
Ca	Calcium
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
CKD	Chronic kidney disease
COA	Clinical outcome assessment
CTx	C-telopeptide
DMC	Danish Medicines Council
DXA	Dual-energy X-ray absorptiometry
ED	Emergency department
EMA	European Medicines Agency
EQ-5D	EuroQol Five Dimension Scale
ER	Emergency room
ESE	European Society of Endocrinology
FECa	Fractional excretion of calcium
GFR	Glomerular filtration rate
GI	Gastrointestinal
HCRU	Healthcare resource utilization
HPES	Hypoparathyroidism patient experience scales
HypoPT	Hypoparathyroidism
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
MOA	Mechanism of action
N	Number
N/A	Not applicable
NAC	Not adequately controlled
NICE	National Institute of Health and Care Excellence
OLE	Open-label extension
P1NP	Procollagen type 1 N-terminal propeptide
PBO	Placebo
PK	Pharmacokinetics
PRO	Patient-reported outcome
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related peptide
QALY	Quality-adjusted life year
QD	Every day
QoL	Quality of life
RCT	Randomized controlled trial
rhPTH	Recombinant human parathyroid hormone
RR	Relative risk or relative ratio
RWE	Real-world evidence

Overview of abbreviations	
SAE	Serious adverse event
SC	Subcutaneous
sCa	Serum calcium
SD	Standard deviation or stable disease
SE	Standard error
SF	Social functioning
SF-12	12-item Short Form Survey
SF-36	36-item Short Form Survey
SLR	Systemic literature review
sMg	Serum magnesium
sP	Serum phosphate
TBS	Trabecular bone score
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States
VAS	Visual analog scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Yorvipath®
Generic name	Palopegteriparatide
Therapeutic indication as defined by EMA	Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism[1].
Marketing authorization holder in Denmark	Ascendis Pharma A/S
ATC code	H05AA05
Combination therapy and/or co-medication	Patients receiving the maximum Yorvipath dose of 60 mcg per day who experience ongoing hypocalcaemia may require co-administration of therapeutic calcium and/or active forms of vitamin D
Date of EC approval	17 November 2023 [2]
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes (19 October 2020): EU/3/20/2350
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the Danish Medicines Council (DMC) (yes/no)	No
Joint Nordic assessment (JNHB)	Due to the different treatment landscape and due to the different comparators available in the Nordics (i.e. Norway) this submission only concerns Denmark.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	Palopegteriparatide 168 micrograms/0.56 mL solution for injection in pre-filled pen (1 pre-filled pen + 15 disposable needles). Each pre-filled pen contains palopegteriparatide equivalent to 168 micrograms of parathyroid hormone (PTH)(1-34) in 0.56 mL of solvent. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 6, 9, or 12 micrograms of PTH(1-34). Palopegteriparatide 294 micrograms/0.98 mL solution for injection in pre-filled pen (1 pre-filled pen + 15 disposable needles). Each pre-filled pen contains palopegteriparatide equivalent to 294 micrograms of PTH(1-34) in 0.98 mL of solvent. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 15, 18, or 21 micrograms of PTH(1-34). Palopegteriparatide 420 micrograms/1.4 mL solution for injection in pre-filled pen (1 pre-filled pen + 15 disposable needles). Each pre-filled pen contains palopegteriparatide equivalent to 420 micrograms of PTH(1-34) in 1.4 mL of solvent. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 24, 27, or 30 micrograms of PTH(1-34).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	The approved EMA indication is: Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism [1]. The patient population for this reimbursement application is: Adult patients with chronic hypoparathyroidism (HypoPT) who are not adequately controlled on conventional therapy.
Dosage regiment and administration	Palopegteriparatide is administered subcutaneously, and the recommended starting dose is 18 mcg once per day with dose adjustments in 3 mcg increments thereafter every 7 days. The dose range is 6 to 60 mcg per day [1]. The dose should be individualised based on serum calcium. The optimal dose after titration is the minimum dose required to prevent hypocalcaemia. without the need for oral calcium or active vitamin D beyond recommended nutritional supplementation for the general population (generally less than 600 mg per day).
Choice of comparator	Conventional therapy consists of oral calcium and active vitamin D treatments. This adheres to the guidelines published by the Danish Society of Endocrinology and is in alignment with Danish medical practice, according to which the treatment for hypoparathyroidism involves a combination of calcium and active vitamin D treatments. The conventional therapy involves the administration of tablet calcium carbonate of 400-500 mg twice per day and the initiation of active vitamin D with a daily capsule of alfacalcidol at 1 microgram. Higher doses can be given twice per day in cases of new-onset postoperative hypoparathyroidism. Additionally, cholecalciferol tablets of 20-40 micrograms per day are recommended [3].
Prognosis with current treatment (comparator)	Conventional therapy of chronic HypoPT with calcium and active vitamin D is intended to increase serum calcium and relieve classical symptoms of hypocalcaemia [4, 5]. Conventional therapy does not replace PTH or any of the physiological functions associated. This results in disrupted calcium and phosphate homeostasis, leading to a range of severe and potentially life-threatening short and long-term complications HypoPT affects multiple organ systems, causing debilitating physical and cognitive symptoms. Chronic HypoPT is associated with serious long-term complications, such as renal impairment (e.g., nephrocalcinosis, kidney stones), cardiovascular disease, neurocognitive dysfunction (e.g., memory loss), and ectopic calcifications. Morbidities are related directly to hypocalcaemia and/or hyperphosphatemia or indirectly to treatment due to excessive amounts of calcium and active vitamin D and increased load of filtered calcium in the kidneys.[6]Increased mortality is also related to chronic HypoPT. [7] Chronic HypoPT affects the health-related quality of life; pain, fatigue, cognitive symptoms

Summary	
	(such as “brain fog” and difficulty concentrating), anxiety and depression are often reported by patients and are independent of serum calcium levels.[6, 8, 9]
Type of evidence for the clinical evaluation	Phase 3, placebo-controlled, trial of Yorvipath (palopegteriparatide) demonstrating superior effect to conventional therapy.
Most important efficacy endpoints (Difference/gain compared to comparator)	The primary endpoint from the phase 3 PaTHway clinical trial (TCP-304) was a multi-component efficacy endpoint of the proportion of patients, at week 26, who achieved all of the following: serum calcium levels in the normal range (8.3 to 10.6 mg/dL), independence from conventional therapy defined as requiring no active vitamin D and ≤ 600 mg/day of calcium supplementation, and no increase in prescribed study treatment within 4 weeks prior to week 26 [10]. The response rate difference was 74% (95% CI 60.4%, 87.6%), p<0.0001.
Most important serious adverse events for the intervention and comparator	5 patients (8.2%) in the palopegteriparatide group reported SAEe, one of which was considered related to treatment. In the conventional therapy group, 3 patients (14%) reported SAEs [4].
Impact on health-related quality of life	A statistically significant and clinically relevant difference between palopegteriparatide and conventional therapy was reported on the hypoparathyroidism symptom-specific quality of life score, Hypoparathyroidism Patient Experience Scale (HPES-Symptom) in the physical and cognitive domains; on the hypoparathyroidism impact-specific score (HPES-Impact) in the domains of physical functioning, daily life, psychological well-being and relational social life. In addition, a statistically significant and clinically relevant difference was reported on the physical functioning subscale of the SF36 generic quality of life score. The least square mean change from baseline to week 26 in EQ-5D-5L index was statistically significant higher in the palopegteriparatide group compared to conventional therapy group.
Type of economic analysis that is submitted	Cost-utility analysis Markov model
Data sources used to model the clinical effects	PaTHway clinical trial [10].
Data sources used to model the health-related quality of life	PaTHway clinical trial [10].
Life years gained	[redacted]

Summary	
QALYs gained	[redacted]
Incremental costs	[redacted] DKK/patient
ICER (DKK/QALY)	[redacted] DKK/QALY
Uncertainty associated with the ICER estimate	Main uncertainties of the CEM were HS utilities and assumption on excess mortality of HypoPT relative to the general population
Number of eligible patients in Denmark	Incidence: 47 patients (See Section 3.2) Prevalence: 1,749 HypoPT patients in 2023 Prevalence: 437 HypoPt patient eligible
Budget impact (in year 5)	[redacted] DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Hypoparathyroidism (HypoPT) is a rare endocrine disease characterized by an absence or insufficient levels of parathyroid hormone (PTH), resulting in abnormal calcium and phosphate homeostasis and a range of severe and potentially life-threatening short-term and long-term complications. [11, 12]. HypoPT may be transient, which is generally reversible, or chronic/permanent [11, 13, 14]. Among cases of HypoPT, 78% are a result of neck surgery, while 7% are familial, 9% have other secondary causes, and 6% have unknown aetiology [15]. Patients with chronic HypoPT require lifelong treatment to try to reduce debilitating muscular, cardiovascular, renal, and neurologic symptoms, as well as potentially life-threatening complications.

The most common types of surgery leading to HypoPT are partial or complete thyroidectomy, parathyroidectomy, and neck dissection [16]. According to a United States (US) claims database from 2007 to 2008, 7.6% of neck surgeries led to HypoPT (75% transient, 25% chronic)[16]. Across surgical centres with experienced endocrine surgeons, rates of postsurgical permanent hypoparathyroidism have been reported to range from 0.9% to 1.6%

HypoPT affects multiple organs, causing physical and mental symptoms that have a significant impact on patients' lives [17]. Symptoms include mainly:

- paresthesias of the extremities and perioral regions,
- increased muscle tone with cramps and stiffness,
- severe hypocalcemia can sometimes be associated with bronchial and/or laryngeal spasms [18]. Management of these episodes may require emergency hospitalization [19].

Chronic asthenia, observed in 40% of cases, is one of the most common physical manifestations of chronic HypoPT [20]. Cognitive impairment is observed in a third of patients. It mainly manifests as impairment of higher functions [20]. In some cases, comitial seizures occur; motor impairment (extrapyramidal syndrome, bradykinesia) is also observed in approximately 15% of patients [21].

The clinical manifestations of HypoPT, both short and long-term, have a significant negative impact on patients' quality of life, with chronic physical and mental comorbidities that affect the patients [22].

In a systematic review of the literature by Smith et al (2021) [23], 33 studies assessing the quality of life of patients with chronic HypoPT were analysed. In studies conducted in the USA, the UK and Norway, patients with chronic HypoPT had significantly lower quality of life scores than those in the general population. In ten other studies, an increase in the severity of HypoPT -related symptoms was shown to be associated with a decrease in patients' general health. Finally, the utility scores obtained from the EQ-5D-5L questionnaire, administered to patients with moderate to severe symptoms, were 0.7 and 0.4 respectively.

Using data from medical records analysed between 2007 and 2020, a population of 203 patients with HypoPT was compared with a control cohort (n= 414) from the WHO (World Health Organization) MONICA (MONItoring of trends and determinants in Cardiovascular disease) project in Sweden [8]. Of the 203 patients identified, 164 patients were alive at the time of analysis, and 65% of them completed the quality-of-life questionnaire SF-36. Significant differences between mean scores of the HypoPT patient population and the control population were observed on the physical component: 40 vs. 51.2 ($p<0.001$) and the mental component: 43.1 vs. 56.1 ($p<0.001$), with evidence of a limitation in daily activities such as work or domestic tasks.

According to the study by Underbjerg et al. [24], based on a cohort of 688 patients with post-surgical HypoPT recorded in the Danish National Patient Registry (DNPR) between 1988 and 2012, HypoPT has a significant impact ($p<0.01$) on patients' mental health, with a 2-fold higher risk of depression or bipolar disorder compared with a control population of 2,064 individuals.

In the United States (US), a survey via electronic questionnaire was conducted among 374 adult patients with HypoPT in 2012 (mean age 49 ± 12 years, time since diagnosis 13 ±12 years), 85% of whom were women [6]. Results revealed, among other things, that hospital stays, or emergency room visits had been required in the previous year for 79%

of patients, 45% reported significant interference with their lives, 85% reported an inability to perform household tasks and 20% experienced a change in professional status related to the disease.

3.2 Patient population

Chronic HypoPT is a rare disease with scarce reporting on its incidence and prevalence in many countries. Chronic HypoPT is more common in women than men (approximately 4:1 ratio), [15, 16, 25-27] likely because of the increased prevalence of thyroid surgery in this population. Multiple studies have reported an increased risk of developing postoperative transient and/or permanent HypoPT among women [25, 28-31]. Across studies that included patients with nonsurgical HypoPT, more females were affected than males, with proportions ranging from 53% to 59% of the study population [25, 32, 33].

In Denmark, Underbjerg et al. [34] reported a prevalence for postsurgical chronic HypoPT of 22/100,000 persons [34] meaning 1,284 patients, for nonsurgical chronic HypoPT the prevalence was 2.3/100,000 persons [33], meaning 134 patients. Based on this, the overall prevalent number of estimated patients was 1,418 in 2015 in Denmark.

For postsurgical patients, Underbjerg et al [34] also calculated an incidence rate of 0.8 per 100,000. Assuming that incidence and prevalence rates stay constant, and applying it to the entire HypoPT patient population, it can be assumed there are 40-55 new patients with chronic HypoPT each year, leading to a total number of 1,749 patients in 2024 (see Table 2).

Based on existing international treatment guidelines [5], parathyroid hormone replacement therapy could be considered for patients who are not adequately controlled on conventional therapy, defined as patients:

- With inadequate control of serum calcium concentrations.
- In whom elemental calcium doses exceed 2.0 g per day or in whom large quantities of active vitamin D analogues are required to control calcium concentrations or symptoms.
- With hypercalciuria, kidney stones, nephrocalcinosis or reduced renal function.
- With hyperphosphatemia and/or increased phosphocalcic product.
- With disorders of the gastrointestinal tract associated with malabsorption.
- With a significant reduction in quality of life.

Building upon these criteria, [redacted] patients enrolled in Ascendis Pharma's clinical trial PaTHway, would be considered not adequately controlled at baseline. According to Danish clinical experts, the definition of not-adequately controlled patients by Chen et al. (2019), Bollerslev et al. (2022), and most recently Khan et al. (2022))[5, 35, 36] overall align with the definition applied in Danish clinical practice.

A post hoc analysis of the PaTHway trial baseline data was conducted using the Khan criteria to identify patients with not adequately controlled HypoPT. This analysis showed

that [redacted] of patients enrolled in the trial met the criteria for not adequately controlled HypoPT at baseline.

Table 1 Classification of not adequately controlled (NAC) patients at baseline in the PaTHway trial using the clinical definition by Khan et al. (2022)

Khan's Criteria	Frequency
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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

Furthermore, as per findings from a study conducted by Iqbal et al. [37], Delphi panellists across UK, Sweden and Portugal estimated that approximately 75% of patients are adequately controlled on conventional therapy (defined as having normal biochemical levels and feeling well). This implies that about 25% are not adequately controlled on conventional therapy. If 25% of HypoPT patients are not adequately controlled (which is a conservative estimate), approximately 430-445 patients would be considered not adequately controlled on conventional therapy in 2024 in Denmark.

Table 2 Incidence and prevalence of HypoPT in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	47	47	47	47	47
Prevalence in Denmark	1,561	1,608	1,655	1,702	1,749
Not adequately controlled*	390	402	414	425	437

Notes: *Assuming that 25% [37] of patients are inadequatelly controlled under conventional therapy
Abbreviations: HypoPT, hypoparathyroidism

The patient population relevant for this application corresponds to HypoPT patients not adequately controlled on conventional therapy. The base-case budget impact analysis will consider [redacted] patients at year 5 (Table 3). Patients on treatment with palopegteriparatide is expected to gradually increase over the next five years, with a maximum 40% share of patients treated. Not all eligible patients are expected to receive active treatment with PTH and new treatment options may enter the market.

Table 3 Estimated number of patients eligible for treatment

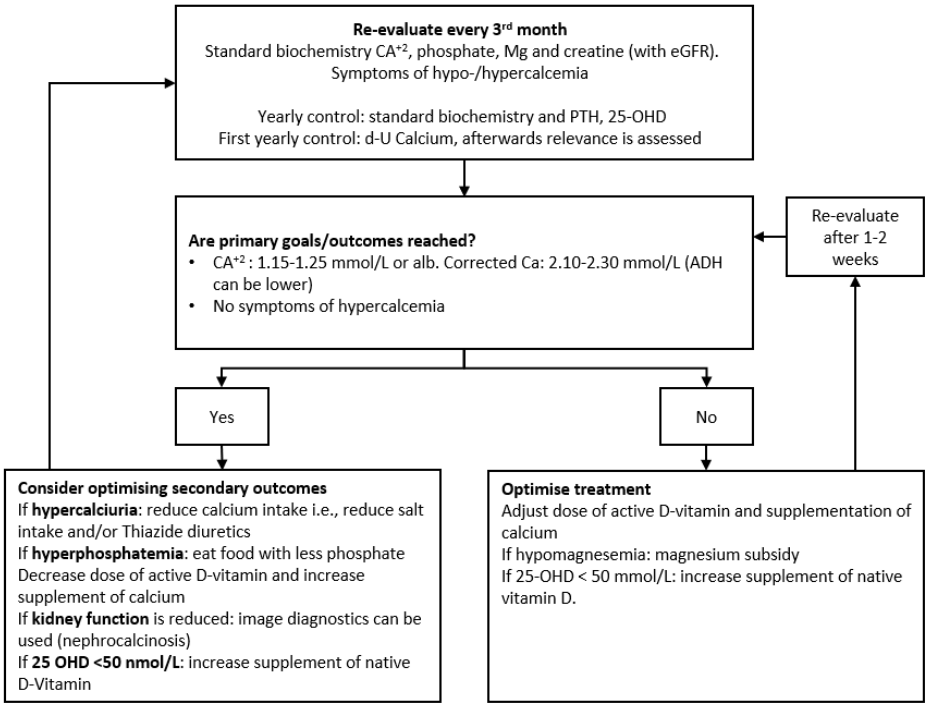
Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for treatment in the coming years	437	449	461	473	485
Patients expected to be treated by Ascendis in case of approval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corresponding market share in case of approval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

No DMC treatment guideline is available for this condition. Therefore, Denmark-specific guidelines from the Danish Society of Endocrinology (last updated in 2022) have been utilized to inform the choice of comparator and other relevant decisions.

The Danish treatment guidelines, outline that conventional therapy involves a combination of calcium-containing preparations and activated vitamin D. However, in some cases, PTH substitution is also offered [38]. These recommendations are in line with European treatment guidelines, where the majority of patients are treated with substantial doses of calcium and active vitamin D, while routine PTH is not recommended [39].

Figure 1. Flow chart of treatment pathways in Danish guidelines



Source: Underbjerg, 2022 [3]

The purpose of HypoPT treatment is to achieve normal levels of serum calcium and ensure adequate levels of activated vitamin D aiming at reducing symptoms and restoring normal calcium dependent physiologic function.

All patients with symptomatic hypocalcaemia or s-CA2+ below 1.15-1.25 mmol/L (or Albumin-corrected calcium below 2.10-2.30mmol/L) receive treatment. The first treatment option is calcium carbonate (400-500 mg, twice per day); however, calcium citrate can also be used as an alternative. The dose is individually titrated, with the recommended dose being 800-1,000 mg/day, while adjusting the dose of active vitamin D.

Because PTH is responsible for converting vitamin D to a biologically active form, patients with HypoPT also require supplementation with active vitamin D, at a dose of 1 microgram per day. In case of acute hypocalcaemia, higher doses are often needed initially.

In case of extensive excretion of calcium in the urine, and no specific hyponatremia or other contra-indicated medication, a thiazide diuretic is included in the treatment, such as Centyl® with KCl, once per day. If the effect is insufficient, the dose can be increased to twice per day or switched to indapamide. During ongoing diuretic treatment, fluid levels must be checked frequently.

Patients with HypoPT may also need magnesium supplementation to ensure that magnesium is within reference range. Magnesium is given to patients with deficiency; the recommended dose is 1 g divided into 2-3 doses. However, if the treatment is followed by hypermagnesaemia, then treatment with Sparkal® twice daily is given [38].

In patients with hyperphosphatemia, it is recommended that phosphate-rich foods are reduced. If this is not sufficient, the dose of calcium supplements can be increased, and the dose of activated vitamin D reduced. Currently, PTH substitution is a treatment option not recommended as standard of care. However, it represents an option for patients with severe symptoms despite optimized conventional therapy. This option is contraindicated in patients with previous bone malignancies, and treatment can only be carried out by an endocrinologist.

New international treatment guidelines
Recently new guidelines and recommendations including palopegteriparatide have been published. Furthermore, an update of the European Society of Endocrinology's clinical guideline on chronic hypoparathyroidism in adults (from 2015), is expected in October 2025. While the exact wordings are not known at this point, the overall framework was presented by the guideline group at the Joint Congress of ESPE and ESE 2025, and revealed that palopegteriparatide is included as a treatment to consider in patients with optimized conventional treatment and one of the following: Frequent fluctuations in calcium levels, or symptomatic hypocalcemia, impaired quality of life attributable to chronic hypoparathyroidism, reduced kidney function (eGFR less than 60 mL/min per 1.73m2), hypercalciuria, hyperphosphatemia. In other words, in patients which are not well controlled. The guideline will include specific guidance for how to initiate treatment (starting dose, titration etc).

In the publication 'Best practice recommendations for the diagnosis and management of hypoparathyroidism' by Khan et al 2025[40], the authors provide updated international best practice recommendations for the diagnosis and management of hypoparathyroidism, building on the 2022 international guidelines and incorporating new evidence and expert consensus. This best practice recommendation includes palopegteriparatide and states, that 'palopegteriparatide is now approved for adults with hypoparathyroidism, offering normalization of calcium/phosphate balance and reducing pill burden when conventional therapy is inadequate'.

Another publication from the same author is the publication 'Hypoparathyroidism: diagnosis, management and emerging therapies' [41], which describes that 'PTH replacement therapy (i.e. palopegteriparatide) offers a physiological approach to therapy in hypoparathyroidism, as compared with conventional therapy. It also addresses the hypercalciuria and hyperphosphataemia that can result in long-term complications of this condition and are exacerbated by conventional therapy' and 'the lack of PTH on the brain and other organs also undoubtedly results in symptoms and complications, and replacing the missing hormone is now possible with palopegteriparatide'. This review article emphasizes the importance of PTH replacement therapy for patients with hypoparathyroidism, owing to the challenges associated with conventional therapy. It closely aligns to the 2022 Second International Workshop on the Evaluation and

Management of Hypoparathyroidism, summarizing previous published data on the pathophysiology, evaluation, and management of hypoparathyroidism.[42]

The Turkish Association of Endocrinology and Metabolism has shared an update to their 2025 edition of the diagnosis and treatment guideline for Osteoporosis and Metabolic Bone Disease. In this update, palopegteriparatide has been officially included in the section dedicated to management of hypoparathyroidism. There is a clear articulation that palopegteriparatide should be considered in patients who cannot reach target values with conventional treatment, cannot tolerate conventional treatment, or who develop acute or chronic complications.[43]

The Hellenic Endocrine Society (2025) independently provide updated clinical practice recommendations, reinforcing diagnostic and treatment principles as recent guidelines, with added emphasis on monitoring parameters including renal, bone mass density and quality of life assessment as well as a structured treatment algorithm. The recommendation presents a stepwise treatment algorithm: from calcium + alfacalcidol to escalation with trans-con PTH if control is not achieved after 3–6 months. It also identifies specific criteria for transitioning to PTH replacement therapy, including persistent hypocalcemia, hypercalciuria, CKD, nephrolithiasis, hyperphosphatemia, and poor QoL (SF-36 <50 or HPES). Regarding PTH replacement therapy, including palopegteriparatide, it states that it is indicated in cases with symptomatic hypocalcemia, significant hyperphosphatemia, or development of complications, initially for 6 months. It is furthermore stated that PTH replacement therapy can be continued long-term under close monitoring, provided it results in sufficient clinical benefits.[44]

Andrea Palermo et al. have recently published a review article in Current Osteoporosis Reports, 12 February 2025. In this publication they emphasise that treatments designed for PTH replacement therapy should be based on administering the hormone which is missing and an optimal pharmacokinetic approach for delivery, which closely mimics the physiology of native PTH. The authors conclude, that while conventional therapy with calcium and active vitamin D effectively normalize calcium level and alleviates symptoms it is often associated with unpredictable fluctuations in calcium levels, hypercalciuria, complications related to the kidney and reduced QoL. When compared to the previous PTH analogs; palopegteriparatide seems to consistently improve QoL and ameliorate kidney function with the fully independence from the conventional therapy in addition to the adequate bone safety profile.[45]

Hence, new updates of treatment guidelines and best practice recommendations include palopegteriparatide and emphasis the importance of PTH replacement therapy for patients with hypoparathyroidism, owing to the challenges associated with conventional therapy.

3.3.1 Unmet need

Despite treatment with conventional therapy, patients may develop complications as although a treatment goal is to try and stabilise serum calcium, it does not replace the physiological function of PTH, leading to potential long-term risks. The risk of complications (frequency and severity) is increased for patients whose disease is not adequately controlled on conventional therapy (requiring a high dose of calcium,

experiencing severe symptoms and/or high healthcare use, renal impairment or history of renal complications.[46, 47]

Individuals with chronic HypoPT managed with conventional therapy experience a significant symptomatic and treatment-related burden that profoundly affects the health-related quality of life.[8, 47, 48] Patients experience significant short-term symptoms and long-term complications that interfere with their daily functioning [6]. Neuromuscular irritability is usually the most prominent feature affecting day-to-day life, with symptoms ranging from paraesthesia and muscle cramps to life-threatening laryngospasm, bronchospasm, seizures, and arrhythmias. Individuals with HypoPT are likely to report pain, fatigue, cognitive symptoms (such as “brain fog” and difficulty concentrating), anxiety and depression [9]. Other possible complications include an increased propensity for infections, heart failure, renal failure, ectopic calcifications (e.g., of the basal ganglia, and lenses), cataracts and abnormal skeletal dynamics [49].

Data from a recent patient-centred, qualitative study comprising semi-structured individual telephone interviews with 42 adult participants with idiopathic or post-surgical HypoPT found that symptoms commonly include muscle cramping (86%), physical fatigue (83%), paraesthesia (88%) [11, 12]. Less frequent but potentially life-threatening consequences include seizures, cardiac arrhythmias, laryngospasm and tetanic seizures [12]. The symptoms, manifestations, and complications of HypoPT affect multiple organ systems, including detrimental effects on the renal system caused by conventional therapy consisting of calcium and active vitamin D [9, 11, 49].

A recent Swedish study demonstrates that patients with chronic HypoPT have higher risk of cardiovascular diseases and fatal cardiovascular disease compared to matched controls [50].

Insufficient PTH is confirmed to be associated with reduced bone turnover and high bone mineral density. Intestinal absorption of calcium and phosphate are both impaired in the setting of insufficient PTH [11, 51]. Low PTH levels also decrease renal phosphate excretion and impair renal reabsorption of calcium which can result in hyperphosphatemia and hypercalciuria.

Data from case-control studies suggest that individuals with HypoPT who receive calcium and active vitamin D are at around a 4 -fold increased risk of kidney stones, chronic kidney disease and/or impaired renal function compared with age-matched controls [52]. Individuals with HypoPT therefore require close monitoring, with blood calcium levels targeted towards the lower end of the normal range, although complications may still occur [52]. A recent UK study compared patients without HypoPT to patients with post-surgical chronic HypoPT and demonstrated a higher adjusted risks of mortality and composite renal complications .[7] The association between current treatment options and associated comorbidities highlights an important unmet need for individuals with HypoPT.

According to a recent international consensus statement with best practice recommendations for the diagnosis and management of HypoPT, conventional therapy is associated with significant limitations. This includes elevations in urine calcium and

serum phosphorus, wide fluctuations in serum calcium, declines in renal function, poor quality of life (QoL) and high pill burden. The expert consensus statement stresses that palopegteriparatide is now approved and available for adults with HypoPT and can normalize serum calcium, phosphorus, and urine calcium. Furthermore, treatment with palopegteriparatide can also significantly reduce the need for active vitamin D and calcium supplements, while improving QoL. [40]

According to Danish clinical experts, a chronic HypoPT patient who is considered uncontrolled despite receiving optimized conventional therapy is unlikely to achieve adequate control by a change in conventional therapy alone. PTH is an important treatment option for these patients.

3.4 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Adult patients with chronic HypoPT who are not adequately controlled on conventional therapy.
Method of administration	Subcutaneous
Dosing	Yorvipath (palopegteriparatide) is administered subcutaneously, and the recommended starting dose is 18 mcg once daily with dose adjustments in 3 mcg increments thereafter every 7 days. The dose range is 6 to 60 mcg per day
Dosing in the health economic model (including relative dose intensity)	Titrated to optimal dose
Should the medicine be administered with other medicines?	At the beginning of treatment palopegteriparatide is administered alongside calcium supplements and active vitamin D. During titration conventional therapy is stopped and palopegteriparatide is given as monotherapy as per indication.
Treatment duration / criteria for end of treatment	Chronic, unless: Persistent hypocalcemia Persistent hypercalcemia Persistent vasodilatory symptoms that cannot be corrected with adjustments to treatment Any other drug related severe adverse event
Necessary monitoring, both during administration and during the treatment period	The patient's serum calcium concentration must be monitored during titration, 7 days after the first dose, after any subsequent change in dosage, and when maintenance dose is achieved.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Routine care costs were informed using the literature and included physician visits and metabolite assays necessary to treat HypoPT
Package size(s)	Palopegteriparatide 168 micrograms/0.56 mL solution for injection in pre-filled pen (1 pre-filled pen + 15 disposable needles). Each pre-filled pen contains palopegteriparatide equivalent to 168 micrograms of parathyroid hormone (PTH) (1-34) in 0.56 mL of solvent. The concentration based on PTH (1-34) is 0.3

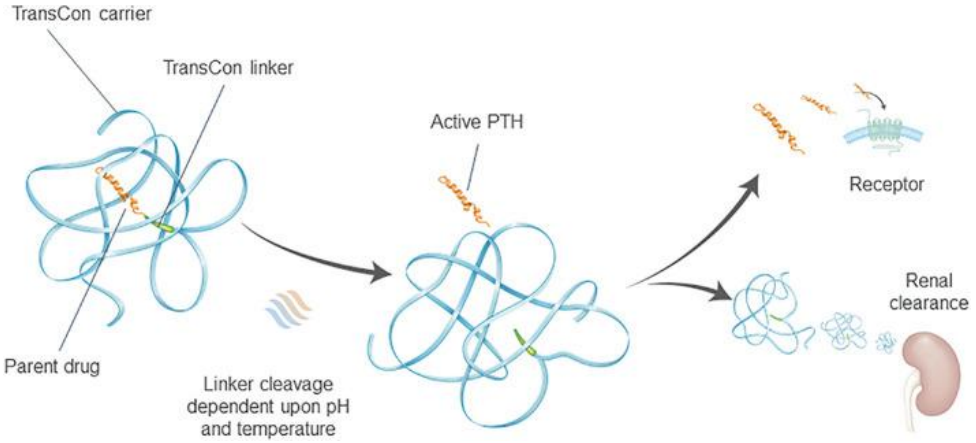
Overview of intervention	
	mg/mL. Each pre-filled pen delivers doses of 6, 9, or 12 micrograms of PTH(1-34). Palopegteriparatide 294 micrograms/0.98 mL solution for injection in pre-filled pen (1 pre-filled pen + 15 disposable needles). Each pre-filled pen contains palopegteriparatide equivalent to 294 micrograms of PTH(1-34) in 0.98 mL of solvent. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 15, 18, or 21 micrograms of PTH (1-34). Palopegteriparatide 420 micrograms/1.4 mL solution for injection in pre-filled pen (1 pre-filled pen + 15 disposable needles) Each pre-filled pen contains palopegteriparatide equivalent to 420 micrograms of PTH(1-34) in 1.4 mL of solvent. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 24, 27, or 30 micrograms of PTH(1-34).

3.4.1 Mechanism of action

Endogenous parathyroid hormone (PTH) is secreted by the parathyroid glands as a polypeptide of 84 amino acids. PTH exerts its action via cell-surface parathyroid hormone receptors, for example, expressed in bone, kidney and nerve tissue. Activation of PTH1R stimulates bone turnover, increases renal calcium reabsorption and phosphate excretion and facilitates synthesis of active vitamin D.

Palopegteriparatide is a prodrug, consisting of PTH(1-34) conjugated to a methoxypolyethylene glycol carrier (mPEG) via a proprietary TransCon Linker. PTH(1-34) and its main metabolite, PTH(1-33), have similar affinity to and activation of PTH1R as endogenous PTH. At physiological conditions, PTH is cleaved from palopegteriparatide in a controlled manner to provide a continuous systemic exposure of active PTH.[1]

Figure 1 Mechanism of action of palopegteriparatide



Source: Karpf, 2020 [53]

After daily subcutaneous administration, palopegteriparatide provides a sustained release of active PTH designed to deliver PTH levels in the physiological range for 24 hours, after which the linker and carrier are freely filtered and excreted by the kidneys [1].

3.4.2 The intervention in relation to Danish clinical practice

PTH substitution therapies are not recommended in routine treatment, however, they are endorsed for patients who are not adequately controlled on conventional therapy [5, 54]. This supports the rationale for this submission, which will refer to the subgroup of HypoPT patients who are not adequately controlled on conventional therapy.

Findings from three European Delphi panels show that approximately 75% of patients are managed in a satisfactory way with conventional therapy. This implies that a remaining 25% lack the required treatment to be symptom-free and achieve normal biochemical levels [37].

3.5 Choice of comparator(s)

The current standard treatment for HypoPT is made up of oral calcium and active vitamin D. The patient group targeted by palopegteriparatide consists of patients whose symptomology and biochemistry cannot be managed with conventional therapy. For this subgroup of not adequately controlled patients, no other treatment exists, as Natpar (recombinant human parathyroid hormone rhPTH (1-84)) indicated only as adjunctive treatment, was withdrawn from the market in October 2022. Because of these reasons, the most appropriate comparator to palopegteriparatide, in Denmark and in this submission, is conventional therapy as described above.

Tabel 1. Overview of comparator

Overview of comparator	
Generic name	Oral calcium and vitamin D
ATC code	NA
Mechanism of action	NA
Method of administration	Oral
Dosing	Individualized doses of Calcium and active vitamin D
Dosing in the health economic model (including relative dose intensity)	Mean daily dose (week 26) PaTHway[55]: Oral calcium: 1847mg Active vitamin D: 0.618ug
Should the medicine be administered with other medicines?	Combination of oral calcium and vitamin D during initial titration period
Treatment duration/ criteria for end of treatment	Treatment is lifelong
Need for diagnostics or other tests (i.e. companion diagnostics)	Biochemistry should be performed to monitor response.
Package size(s)	Ca carbonate pack: 180 tablets, 400mg strength Alfacalcidol pack: 30 tablets, 0.25ug strength

3.6 Cost-effectiveness of the comparator(s)

There is no evidence of the cost-effectiveness of conventional therapy in the sub-population relevant for the submission (not adequately controlled); however, the treatments are routinely used and recommended in Danish clinical guideline.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The efficacy endpoints relevant for this submission are the primary multi-component endpoint and the QoL (EQ-5D-5L) endpoint of the PaTHway trial. Additional secondary endpoints from the trial (i.e., HPES) are presented in Section 6.

Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Primary multi-component endpoint	26 weeks	Proportion of subjects who met all of the following criteria at 26 weeks of blinded treatment: • Albumin-adjusted serum calcium measured within 4 weeks prior to and on Week 26 visit within the normal range (8.3 to 10.6 mg/dL) *; and • Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of PRN ≤ 7 days during the 4 weeks); and Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤ 600 mg AND use of PRN doses on ≤ 7 days during the 4 weeks) and • No increase in prescribed study drug within 4 weeks prior to Week 26 visit	See details in Appendix D
QoL	26 weeks	Change from baseline at 26 weeks of treatment for the following parameters: • HPES - Symptom - Physical domain score • HPES - Symptom - Cognitive domain score • HPES - Impact – Physical Functioning domain score • HPES - Impact – Daily Life domain score • 36-Item Short Form Survey (SF-36) - Physical Functioning subscale score EuroQol 5-dimensional questionnaire (EQ-5D-5L)	See Section 6, Appendix B and Appendix G

* Time point for data collection used in analysis (follow up time for time-to-event measures)

4. Health economic analysis

The type of health economic analysis relevant for this submission is a cost-effectiveness analysis (CEA). The CEA is based on a Danish adaptation of an Excel-based decision analytic model. Data from the clinical trial is applied. Since the trial ITT population consists of more than XXX not adequately controlled patients, we modelled the ITT population to preserve power and trial integrity. Therefore, the objective of the CEA is to assess the cost-effectiveness of palopegteriparatide versus conventional therapy (CT) in the ITT population. The estimated effect of palopegteriparatide is based on the PaTHway clinical trial. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained. The following section (4.1) introduces the model structure and its features.

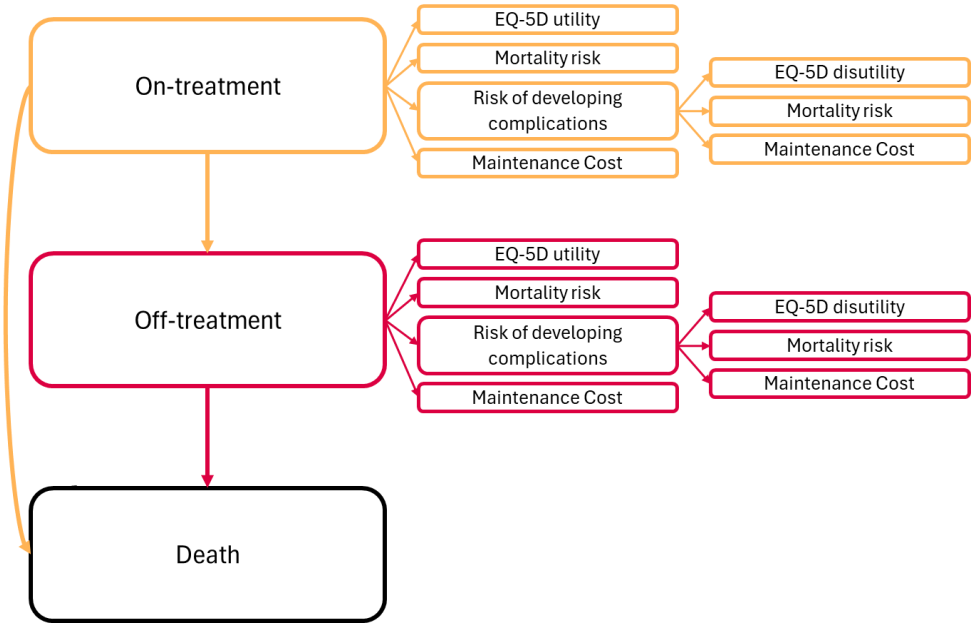
4.1 Model structure

A de-novo three state on/off treatment model was developed with the purpose of extrapolating the clinical efficacy observed in the PaTHway trial and estimating long-term cost and quality adjusted life-years. Hence, the model contains two arms based on treatment allocation to palopegteriparatide (palopeg) and conventional therapy (CT): on-treatment (palopegteriparatide treatment associated with patients achieving disease control – adequately controlled, or AC), off-treatment (CT associated with patients remaining inadequately controlled – not achieving adequate disease control, or NAC)

Clinical outcomes were modelled using three primary health states in each arm. Figure 2 presents the model structure diagram for the three mutually exclusive health states:

- **On-treatment:** Patients on palopegteriparatide associated with patients achieving disease control enter the model in this state. These patients may transition to off-treatment over time based on treatment discontinuation.
- **Off-treatment:** Patients receiving CT associated with patients failing to achieve disease control enter the model in this state and remain in this state while alive.
- **Death:** All-cause mortality, adjusted by health state mortality risk.

Figure 2: Palopegteriparatide model structure overview



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

Classifying patients by disease control (AC, which is on-treatment in the model vs NAC, which is off-treatment in the model) was essential to reflect meaningful clinical differences. From engagement with UK clinical experts guiding the model development, AC patients are expected to have better HRQoL, fewer complications, lower resource use requirements, and reduced mortality, whereas NAC patients experience persistent burden, higher long-term risk and have a higher use of healthcare. Danish clinical experts validated that Danish patients who are NAC are more likely to require higher healthcare resource usage than patients who are AC. Event and outcome differences were therefore modelled based on stratification by control health state.

The model structure was selected based on several key considerations:

- Chronic HypoPT is a rare disease, and data availability is limited, particularly for long-term outcomes and transitions between health states.
- The primary effect of palopegteriparatide is hormone replacement, restoring physiological PTH levels and regulating calcium homeostasis. This is expected to reduce the clinical burden and resource use compared with CT.

- Relevant evidence was available from both the PaTHway clinical trial and United Kingdom (UK) RWE study (CPRD analysis) to support differences in utility, costs, and complication risks between on-treatment and off-treatment health states.
- The on/off treatment model structure offered simplicity, transparency, and flexibility while allowing direct use of trial data to estimate time spent as AC and NAC.

Patients are assumed to be AC while on treatment (i.e., in the on-treatment health state) and NAC when not on treatment (i.e., in the off-treatment health state).

All patients off-treatment receiving CT were assumed to be NAC, as NAC reflects the target population of the model and the proposed positioning of palopegteriparatide: *Patients with chronic HypoPT who are not adequately controlled on CT*. It is not the use of CT that defines NAC status; rather, patients are classified as NAC because their disease remains not adequately controlled despite being on CT. As CT is currently the only widely available treatment, all patients are expected to be receiving it, but clinical feedback indicates that some patients remain not adequately controlled despite ongoing CT, and there is no expectation that these patients would become adequately controlled without a change in therapy. This population aligns with those most likely to benefit from palopegteriparatide, is appropriately reflected in the model, and corresponds with the clinical definition of NAC—supported by the high proportion of patients in PaTHway who met NAC criteria.

The assumption of all patients being AC while on-treatment was based on the clinical response observed in the PaTHway trial. A patient is classified as AC if they meet any of the following:

1. Albumin-adjusted serum calcium within the normal range (8.3–10.6 mg/dL).
2. Independence from active vitamin D, defined as:
    a. A daily standing dose of zero on all days.
    b. Use of any PRN active vitamin D on no more than 7 days during the 4 weeks prior to the Week 26 visit.
3. Independence from therapeutic doses of calcium, defined as:
    a. ≤600 mg/day of elemental calcium.

In addition to the primary endpoint, the following secondary and exploratory endpoints from the PaTHway trial further support the classification of patients as AC:

- 24-hour urine calcium within the normal range (≤250 mg/day for women, ≤300 mg/day for men).
- Improvement in HRQoL.
- Stabilisation of bone turnover markers (e.g. P1NP and CTx).
- Improved renal function (e.g., reduction in urinary calcium excretion).

From the PaTHway intent-to-treat (ITT) population, most of the patients treated with palopegteriparatide achieved multiple responses across all of these endpoints. This assumption is further supported by the mechanism of action of palopegteriparatide. As a PTH replacement therapy, it addresses the underlying hormonal deficiency in HypoPT and restores physiological regulation of calcium and phosphate. This contrasts with CT, which provides passive supplementation without correcting the root cause. Through its action on PTH receptors, palopegteriparatide is expected to improve renal calcium handling, stabilise serum calcium levels, and normalise bone turnover—mechanisms consistent with a sustained and broad treatment benefit.

Further, the assumption that patients on treatment would remain AC while receiving palopegteriparatide was supported by three key factors:

- In the PaTHway OLE, 97% of patients maintained normal serum calcium levels through 156 weeks, and the frequency of treatment-related AEs (hypocalcaemia and hypercalcaemia) declined over time. Similarly, in the PaTH Forward study, by Week 214, 98% of patients maintained normal albumin-adjusted serum calcium, and 93% remained independent from CT. These findings support the assumption that patients who initially respond to palopegteriparatide are likely to sustain biochemical control and treatment benefit with continued long-term use.
- The physiological rationale for sustained benefit is supported by the mechanism of action of palopegteriparatide, which restores the missing PTH. Unlike CT, which supplements calcium and active vitamin D without correcting the hormonal deficiency, palopegteriparatide acts directly on PTH receptors to regulate calcium and phosphate homeostasis, likely leading to better renal calcium handling, more stable serum calcium, and more normal bone turnover.
- Although some patients treated with palopegteriparatide did not meet the composite primary endpoint response definition, EQ-5D data indicate that patients who did not meet this endpoint still experienced improvement in HRQoL. When utility was analysed by responder status, non-responders had a higher EQ-5D value at Week 26 than at baseline, suggesting a meaningful benefit despite not achieving full response. This reflects the difficulty of the multi-component response definition and supports the assumption that initiating treatment with palopegteriparatide provides clinical benefit for most patients.

Patients who discontinued or lost treatment response were assumed to move from on-treatment to off-treatment, reflecting the return to a state of inadequate disease control.

As such, the transition from on-treatment to off-treatment was applied only for those patients discontinuing therapy, and patients who remained on treatment were assumed to maintain an adequately controlled state unless discontinued. Patients in the off-treatment state were assumed not to transition to the on-treatment state without a treatment change, experts, including Danish clinical experts, indicated that reversal of

not adequate control was highly unlikely in chronic HypoPT without initiating a new therapy. The PaTHway trial did contain a patient on the comparator arm of the trial achieving the primary endpoint (4.9%), however, given the low sample size of the analysis and input from clinicians, this was considered not to be reflective of clinical practice. Complications to (not adequately controlled) HypoPT are modelled using a linked sub-model captured occurrence of comorbidity as discrete events. Each event allowed for an assigned disutility. Complication risks were stratified by health state based on HRs applied to general population incidence derived from UK RWE study (CPRD analysis). Complications were included only as repeatable events with associated disutility.[56-64]

Hypocalcaemia and hypercalcaemia were modelled separately by treatment arm using exposure-adjusted rates from the PaTHway trial, to reflect an additional benefit of palopegteriparatide not captured by UK RWE study (CPRD analysis) derived inputs given these are based on AC and NAC receiving CT. By applying exposure-adjusted, treatment-specific event rates within the model, these outcomes were incorporated in a way that preserved comparability while avoiding double counting. Although formally an efficacy measure, the assumptions are presented in the safety section as the data was sourced from the PaTHway safety assessment. Each event was assigned a cost, disutility, and duration of event. These were treated independently of the complication sub-model to reflect trial-observed treatment differences, which were indicated to better reflect likely rate of events that would be expected in clinical practice.

A 28-day cycle length was chosen to align with the marketed presentation of palopegteriparatide, which is supplied as two 14-day injection pens per monthly pack and allowed sufficient granularity to capture the impact of repeatable events. Costs and outcomes were discounted at 3.5% per annum for years 0-35 and 2.5% thereafter using annual discounting. Half-cycle correction was applied to all costs and outcomes to account for mid-cycle transitions.

4.2 Model features

The structure and rationale of the model is described in the section above. This section describes the model features for the base-case.

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	HypoPT patients (ITT population of PaTHway)	ITT population consists of XXX meeting the Khan criteria [54]for not adequately controlled patients
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (51 years)	Assuming patients with chronic hypoparathyroidism remain on treatment indefinitely
Cycle length	28-days	In line with the intended pack size of palopegteriparatide (Yorvipath)

Model features	Description	Justification
Half-cycle correction	Yes	According to DMC guidelines
Discount rate	3.5% p.a. year 0-35 2.5% p.a. year 36-70	Finansministeriets anbefalede samfundsøkonomiske diskonteringsrente[65]
Intervention	Yorvipath (Palopegteriparatide)	NA.
Comparator(s)	CT (oral calcium and active vitamin D)	Danish clinical practice (see section 3.3)
Outcomes	Costs LY QALYs Incremental cost per QALY	Main outcomes of interest for cost-effectiveness analyses

Abbreviations: CT, conventional therapy; QALY, quality adjusted life year; LY, Life-years; ICER, incremental cost effectiveness ratio

4.3 Model limitations

Limitations include the lack of long-term direct clinical outcomes from the trial, which necessitated extrapolation of discontinuation and treatment benefit. This limitation is unavoidable due to trial ethical reasons and rarity of disease, that prohibit long-term outcome studies as a basis for regulatory approval.

In addition, the classification of disease control status in CPRD analysis was based on healthcare resource use due to the lack of data on clinical markers, introducing potential misclassification. However, this was mitigated through expert validation.

Not all complications could be included due to data limitations (e.g. mental health outcomes). Cognitive deficits are commonly associated with HypoPT [48]. However, EQ-5D is insensitive to changes in cognitive impairment[66]. This is an important consideration because palopegteriparatide demonstrates favourable benefits compared to conventional therapy/placebo in reducing cognitive domain symptoms [36]. Preference-based disutility for impaired cognitive processing is considerable [67].

Several aspects of the model reflect a conservative approach:

- The costs and outcomes associated with the AC state are based on patients achieving control with conventional therapy within the CPRD study and may therefore underestimate the potential benefits for patients achieving control with palopegteriparatide.
- The impact of complications is limited to a quality-of-life impact only. While some costs of treating complications are captured within the UK RWE study (CPRD analysis), the costs incurred due to complications were found to be below what was reported in literature for treating these events. Therefore, there could be an underestimation of the impact of complications
- Reduction in pill burden not captured. Managing HypoPT effectively often means that patients have a high number of pills to take every day – 27% take

three to five pills every day[68]. More than a quarter of patients find the number of pills they are required to take challenging, resulting in measurable direct treatment disutility [68, 69]. Moreover, managing blood calcium levels effectively can require patients to change the number of calcium pills and active Vitamin D capsules that they take daily: 21% of patients find the regular changes to the number of calcium pills to be challenging, and the figure is 16% of patients for active Vitamin D capsules [68, 69].

5. Overview of literature

5.1 Literature used for the clinical assessment

The pivotal evidence supporting palopegteriparatide for the treatment of HypoPT is provided by the Phase III PaTHway trial and its open-label extension (OLE), which are the focus of this submission. The PaTHway trial compares palopegteriparatide to placebo. In both treatment arms patients were treated with oral calcium and active vitamin D, which is considered standard of care in Denmark and hence is the relevant comparator in Denmark. Hence, no SLR has been conducted

5.2 Literature used for the assessment of health-related quality of life

The assessment of health-related quality of life was based on results from the PaTHway (see Section 10). Additional utilities for adverse events, and disease long term complications were sourced from literature. Table 6 provides an overview.

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Wester V, de Groot S, Versteegh M, Kanters T, Wagner L, Ardesch J, et al. Good Days and Bad Days: Measuring Health-Related Quality of Life in People With Epilepsy. Value in Health. 2021;24(10):1470–5. [70]	Disutility of neurological complication	Section 10.3.4
Andayani T, Kristina S, Hidayaturahmah R. Comparison and validation of EuroQol-5 Dimension level and Short Form-6 Dimension in cataract patients. Pharmacy Education. 2022;22(2). [57]	Disutility of cataract	
Conrad N, Molenberghs G, Verbeke G, Zaccardi F, Lawson C, Friday JM, et al. Trends in cardiovascular disease incidence among 22 million people in the UK over 20 years: population based study. Bmj. 2024;385:e078523. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. Health Qual Life Outcomes. 2010;8:13.	Calculation of disutility of cardiovascular complications	

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Golicki D, Niewada M, Buczek J, Karlińska A, Kobayashi A, Janssen MF, et al. Validity of EQ-5D-5L in stroke. Qual Life Res. 2015;24(4):845–50. [58-60]		
Jesky MD, Dutton M, Dasgupta I, Yadav P, Ng KP, Fenton A, et al. Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. PLoS One. 2016;11(11):e0165675. [61]	Chronic kidney disease disutility	
Van Wilder L, Rammant E, Clays E, Devleesschauwer B, Pauwels N, De Smedt D. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. Qual Life Res. 2019;28(12):3153–61. [62]	Disutility associated with respiratory tract infection (including pneumonia). Disutility associated with bone fracture	
Shingler S, Fordham B, Evans M, Schroeder M, Thompson G, Dewilde S, et al. Utilities for treatment-related adverse events in type 2 diabetes. J Med Econ. 2015;18(1):45–55. [63]	Urinary tract infection disutility	
Eryildirim B, Sahin C, Tuncer M, Sabuncu K, Cetinel C, Tarhan F, et al. Effect of medical expulsive therapy on the health-related quality of life of patients with ureteral stones: a critical evaluation. Int Urol Nephrol. 2015;47(8):1271–5. [64]	Disutility of Nephrolithiasis and Nephrocalcinosis disutility	

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Lin CF, Huang YH, Ju LY, Weng SC, Lee YS, Chou YY, et al. Health-Related Quality of Life Measured by EQ-5D in Relation to Hospital Stay and Readmission in Elderly Patients Hospitalized for Acute Illness. Int J Environ Res Public Health. 2020;17(15). [71]	Disutility of symptomatic events	

5.3 Literature used for inputs for the health economic model

Risk of complications to hypoPT was estimated based on occurrence of complications in a hypoPT population compared to matched controls (Ascendis CPRD study; see section 8.4.1). This study also provided estimates of HCRU attributable to hypoPT (number of visits for hypoPT patients in excess of number of visits for matched controls) and excess mortality of hypoPT patients relative to matched controls. General population was sampled from Danish mortality statistics.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Ascendis data on file (CPRD study)[72]	Risk of complications in general population	Data on file	Section 10.3.4
	Relative risk of complication for hypoPT patients		Section 10.3.4
	Excess mortality of hypoPT patients relative to general population		Section 8.1.2.4
	Attributable HCRU for hypoPT patients		Section 11.4
Danish general population statistics[73]	Age and gender specific mortality rates	DMC guideline	Section 8.1.2.4

6. Efficacy

6.1 Efficacy of palopegteriparatide compared to conventional therapy for patients with HypoPT

6.1.1 Relevant studies

Palopegteriparatide, developed under the name TransCon PTH, is a subcutaneous injection of parathyroid hormone replacement medicine for adults with chronic HypoPT. The efficacy of palopegteriparatide was demonstrated in the PaTH Forward (NCT04009291) and PaTHway (NCT04701203) trials, phase 2 and Phase 3 respectively, comparing palopegteriparatide and placebo adjuvant to conventional therapy of calcium and active vitamin D. The submission is based on the PaTHway trial, the only phase 3 randomized controlled trial. The PaTHway trial is presented in Table 8. The final CSR is expected by end of September 2025. In Appendix B, details about PaTHway are presented.

PaTH Forward is phase 2, randomized, double-blind, placebo-controlled 4-week trial with open-label extension which enrolled 59 individuals with HypoPT. Interventions included TransCon PTH 15, 18, or 21 µg PTH/day or placebo for 4 weeks, followed by a 22-week extension during which TransCon PTH dose was titrated (6-60 µg PTH). The trial demonstrated that by week 26, 91% of participants treated with TransCon PTH achieved independence from standard of care (SoC, defined as active vitamin D = 0 µg/day and calcium [Ca] ≤ 500 mg/day). In addition, patients achieved normal sCa, serum phosphate, uCa, serum calcium-phosphate product, and experienced an improved health-related quality of life. Patient Experience Scale symptom and impact scores improved through 26 weeks. TransCon PTH was well tolerated with no treatment-related serious or severe adverse events. [36] Data from PaTH Forward is available with OLE up to 266 weeks. The trial is not further presented in the submission.

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
PaTHway, NCT04701203	Phase 3, Multicenter, randomized, double-blind, placebo controlled, parallel group trial with an open label extension	Blinded period of 26 weeks, continued with the open-label extension phase up to week 182	Adult patient with chronic hypoparathyroidism from either postsurgical, autoimmune, genetic, or idiopathic origin	Palopegteriparatide (TransCon PTH) was administered once daily by subcutaneous injection, using a pre-filled pen. The starting dose of 18mcg was titrated to an optimal dose that allowed independence from Ca/VitD during the blinded period. The optimal dose is used during the open-label extension period.	Placebo, delivered once daily by subcutaneous injection using a prefilled pen.	**Primary:** Albumin-adjusted sCa (4 weeks prior to and Week 26), active vitamin D and calcium doses (week 26) **Secondary:** HPES Symptom - Physical Domain score (week 26), HPES Symptom – Cognitive domain score (week 26), HPES Impact – Physical functioning domain score (week 26), HPES Impact – Daily life domain score (week 26), SF-36 physical functioning subscale score (week 26) **Other secondary:** The following endpoints will be evaluated at predefined timepoints during the Blinded Treatment and the extension period: sP, Albumin-adjusted sCa x sP product, including proportion of subjects with sCa x sP product $\leq$55 mg^2/dL^2, $\leq$52 mg^2/dL^2, and $\leq$44 mg^2/dL^2, BMD and TBS by DXA, Bone turnover markers (serum P1NP and CTx), sMg, QoL measured by EQ-5D-5L, CGI-S

Abbreviations: mcg, microgram; mg, milligram; dL, deciliter; Ca, calcium; sCa, serum calcium; sMg, serum magnesium; sP, serum phosphate; PTH, parathyroid hormone; P1NP, procollagen type 1 N-terminal propeptide; CTx, c-telopeptide; VitD, vitamin D; HPES, Hypoparathyroidism Patient Experience Scale; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; CGI-S, Clinical Global Impression of Severity; COAs, clinical outcome assessments; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; TBS, trabecular bone score; PEG, polyethylene glycol; FECa, fractional excretion of calcium; AM FECa, morning fractional excretion of calcium

6.1.2 Comparability of studies

NA

6.1.2.1 Comparability of patients across studies

Baseline characteristics of the patient population in the PaTHway trial is presented in Table 9 below. While the application considers patients that are not adequately controlled (NAC), the baseline characteristics are presented for the ITT population since XXX of all patients included in the PaTHway trial were NAC according to predefined criteria (see section 8.1.2.1).

Table 9 Baseline characteristics of patients in the studies included for the comparative analysis of efficacy and safety (PaTHway) [4]

	PaTHway	
	Palopegteriparatide (N=61)	Placebo (N=21)
Age: Mean (SD)	49.0 (13.1)	47.3 (11.4)
Age group (years) - n (%)		
<50	28 (45.9)	14 (66.7)
≥50	33 (54.1)	7 (33.3)
Sex at birth n (%)		
Female	46 (75.4)	18 (85.7)
Body mass index (kg/m2)		
Mean (SD)	27.3 (5.8)	29.5 (5.7)
Menopausal status - n	46	18
Postmenopausal - n (%)	19 (41.3)	3 (16.7)
Race - n (%)		
American Indian or Alaska Native	0	0
Asian	3 (4.9)	2 (9.5)
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	0
White	57 (93.4)	19 (90.5)
Other	1 (1.6)	0
Geographic region - n (%)		
North America	39 (63.9)	12 (57.1)
Europe	22 (36.1)	9 (42.9)
Cause of hypoparathyroidism - n (%)		
Acquired (neck surgery)	52 (85.2)	18 (85.7)
Autoimmune	1 (1.6)	0

	PaTHway	
	Palopegteriparatide (N=61)	Placebo (N=21)
Intrinsic genetic defects of the parathyroid glands	3 (4.9)	0
Idiopathic	4 (6.6)	3 (14.3)
Other	1 (1.6)	0
Duration of hypoparathyroidism (years)		
Mean	12.0	11.1
Min, Max	1, 56	1, 33
Patient history - n (%)		
Renal insufficiency history	5 (8.2)	1 (4.8)
Kidney stones history	15 (24.6)	4 (19.0)
Ectopic calcifications history	0	0
Vascular calcifications history	1 (1.6)	0
Brain calcification history	1 (1.6)	0
Cataract history	3 (4.9)	0
Seizure history	0	1 (4.8)

Abbreviations: n, number; PTH, parathyroid hormone; SD, standard deviation

The baseline characteristics of the patient population enrolled in the clinical study aligns well with Danish patients that are not adequately controlled according to Danish clinical experts.

In the phase 3 trial PaTHway, at baseline, the mean total daily doses (TDDs) of conventional therapy for patients in the palopegteriparatide group were 1748 mg/day for calcium supplementation, 0.76 µg/day for calcitriol, and 2.5 µg/day for alfacalcidol [4]. The mean TDDs of conventional therapy for patients in the placebo group were 2105 mg/day for calcium supplementation, 0.69 µg/day for calcitriol, and 2.0 µg/day for alfacalcidol. The baseline TDD data of conventional therapies are shown in Table 10.

Table 10 Baseline total daily dose of conventional therapies (PaTHway)[74]

Conventional therapy TDD at baseline	Palopegteriparatide (N=61)	Placebo (N=21)
Calcium supplement/TDD (n)	61	21
Mean (mg)	1748	2105
Min, Max (mg)	600, 5000	800, 7200
Calcitriol (active vitamin D)/TDD (n)	53	17
Mean (µg)	0.76	0.69
Min, Max (µg)	0.5, 2.0	0.5, 1.75
Alfacalcidol (active vitamin D)/TDD (n)	8	4
Mean (µg)	2.5	2.0
Min, Max (µg)	1.0, 4.0	1.5, 2.5

Abbreviations: TDD, total daily dose

The mean baseline albumin-adjusted serum calcium for patients in the palopegteriparatide and placebo groups were 8.8 mg/dL and 8.6 mg/dL, respectively [4]. At baseline, the mean 24-hour urine calcium for patients in the palopegteriparatide was 392 mg/dL and in the placebo group was 329 mg/dL [4]. Baseline data for albumin-adjusted serum calcium and 24-hour urine calcium are shown in Table 11

Table 11 Baseline albumin-adjusted serum calcium and 24-hour urine calcium (PaTHway) [4]

Lab summary at baseline	Palopegteriparatide (N=61)	Placebo (N=21)
Albumin-adjusted serum calcium (n)	61	21
Mean mg/dL (SD)	8.8 (0.7)	8.6 (0.6)
24-hour urine calcium (n)	60	21
Mean mg/dL (SD)	392 (175)	329 (140)

Abbreviations: n, number; PTH, parathyroid hormone; SD, standard deviation

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

As described in Sections 3.3 and 3.5, the relevant population in the Danish setting would be that of patients not adequately controlled under CT. Disease control status was not an explicit inclusion criteria, however, post-hoc classification suggest that [redacted] could be categorized as not adequately controlled – see section 8.1.2.1. Because of the number of adequately controlled is small, we believe that PaTHway is a fair representation of patients that are likely to be offered palopegteriparatide in Danish clinical practice.

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	48.6 (Assumption)	48.6 (PaTHway)[74]
Gender	Female 78% (Assumption)	Female 78% (PaTHway)[74]

6.1.4 Efficacy – PaTHway results

6.1.4.1 Primary endpoint

The primary endpoint from the phase 3 PaTHway clinical trial (TCP-304) was a multi-component efficacy endpoint of the proportion of patients, at week 26, who achieved all of the following: serum calcium levels in the normal range (8.3 to 10.6 mg/dL), independence from conventional therapy defined as requiring no active vitamin D and ≤ 600 mg/day of calcium supplementation, and no increase in prescribed study treatment within 4 weeks prior to week 26 [10].

Palopegteriparatide was able to achieve the primary multi-component efficacy endpoint for 79% of the patients after 26 weeks, a significant difference compared to 5% in the placebo group ($p<0.0001$). The proportion of patients that met each component of the primary endpoint was higher in the palopegteriparatide group when compared to placebo (albumin-adjusted serum calcium within the normal range: 80.3% vs 47.6%; independence from active vitamin D: 98.4% vs 23.4%; independence from therapeutic doses of calcium: 93.4% vs 4.8%; no increase in prescribed study drug: 93.4% vs 57.1%) (Table 13) [4, 74].

Table 13 Primary multi-component endpoint at week 26 [4].

	Palopegteriparatide (N=61)	Placebo (N=21)
Number of patients meeting the primary endpoint criteria at week 26 (responders)	48	1
Proportion, % (95% CI)	79 (66.3, 88.1)	5 (0.1, 23.8)
Hypothesis test: p-value (palopegteriparatide vs placebo)†	<0.0001	
Number of patients meeting each component, n (%):		
Albumin-adjusted serum calcium within the normal range‡	49 (80.3)	10 (47.6)
Independence from active vitamin D	60 (98.4)	5 (23.8)
Independence from therapeutic doses of calcium supplements	57 (93.4)	1 (4.8)
No increase in prescribed study drug	57 (93.4)	12 (57.1)

CI = confidence interval; n = number; PTH = parathyroid hormone
†CMH test controlling for etiology of hypoparathyroidism (postsurgical vs other).
‡The normal range for albumin adjusted serum calcium is 8.3 mg/dL to 10.6 mg/dL.
Note: Three patients with missing data for one or more of the components are considered as non-responders.

Table 14 present the comparison of number of patients meeting the primary endpoint in PATYway for the main multi-component efficacy endpoint from the head-to-head evidence.

Table 14 Results from the comparative analysis of palopegteriparatide vs. CT for HypoPT patients

Outcome measure	Palopegteriparatide (N=61)	CT (N=21)	Result
Number of patients meeting the primary multi-component efficacy end point from head-to-head evidence n (%; 95%CI)	48 (79%; CI: 66.3; 88.1)	1 (5% CI: 0.1, 23.8)	Difference: (74 p.p; CI: 60.4; 87.6)

Abbreviations: CT, conventional therapy: p.p. percentage points

The PaTHway trial also demonstrated palopegteriparatide's potential to substitute the intake of active vitamin D and oral calcium. During the trial, all but one patient (60/61) (98.4%) treated with palopegteriparatide discontinued active vitamin D completely in week 4, which was maintained throughout the entire study period. A rapid reduction in calcium supplementation from week 8 through week 26 was also observed. Palopegteriparatide also increased mean serum calcium levels that was maintained within the normal range across study visits [36, 74].

A total of Fifty-seven (93.4%) patients achieved independence from therapeutic doses of calcium. Fifty-seven (93.4%) patients had no increase in prescribed study drug within 4 weeks prior to Week 26 visit.[74]

The effect of Palopegteriparatide on bone turnover markers (P1NP and CTx) had a similar pattern to what was reported in the PaTH Forward trial. Bone turnover markers (P1NP and CTx) were measured at week 12 and week 26 in the palopegteriparatide and placebo groups. CTx levels increased in patients treated with palopegteriparatide from baseline and peaked at week 12, P1NP peaked at week 26. After peaking both trended downward, toward normal ranges [36] (Appendix B).

6.1.4.2 Patient reported outcomes

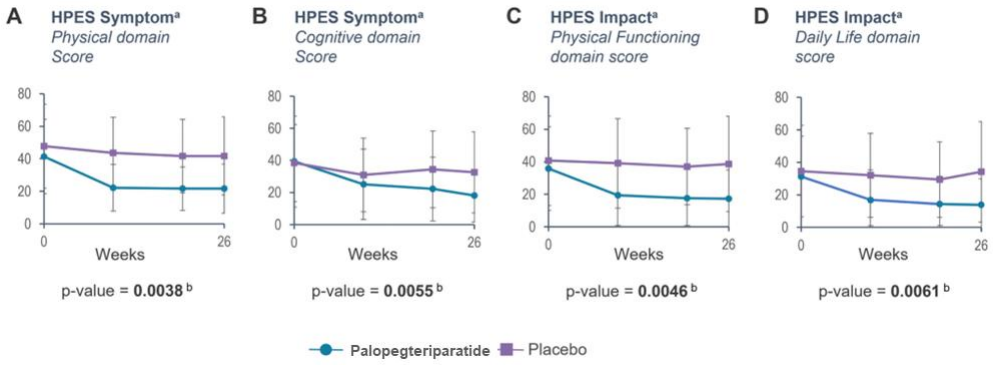
Treatment with palopegteriparatide showed statistically significant and clinically relevant improvements in disease-specific measures of symptoms, functioning and well-being across HPES-Symptom (physical p=0.0038, and cognitive p=0.0055) and HPES-Impact (physical functioning p=0.0046, and daily life p=0.0061) domains at Week 26, versus placebo (Table 15, Figure 3)[4, 74].

Table 15 Change from baseline (CFB) to week 26 in HPES impact and symptom scores (ITT population) [74]

HPES scale	Palopegteriparatide (N=61)	Placebo (N=21)
HPES-symptom scale		
HPES symptom- Physical domain score, n	59	19
CFB	−21.01 (2.20)	−4.81 (5.02)
Treatment difference	-16.20 (5.02)	
P value	0.0038	
HPES symptom- Cognitive domain score, n	59	19
CFB	−20.49 (2.59)	−6.16 (4.71)
Treatment difference	-14.33 (4.67)	
P value	0.0055	
HPES symptom- Physical functioning domain, n	59	19
CFB	−18.29 (2.65)	−1.01 (5.49)
Treatment difference	-17.28 (5.50)	
P value	0.0046	
HPES impact- daily life score, n	59	19
CFB	−17.65 (2.37)	−0.36 (5.68)
Treatment difference	-17.29 (5.682)	
P value	0.0061	

Abbreviations: HPES, Hypoparathyroidism Patient Experience Scale; HypoPT, hypoparathyroidism; SD, standard deviation.
[a]Lower scores reflect improvement in HypoPT-related symptoms, functioning and well-being.
Source: EPAR assessment report

Figure 3 Treatment effect of palopegteriparatide on HPES scores (ITT population) [4]



[a]Lower scores reflect improvement in HypoPT-related symptoms, functioning and well-being;

[b]p-values are from analysis of covariance models assessing change from baseline at Week 26 for palopegteriparatide versus placebo, with aetiology of HypoPT as fixed effects and baseline HPES domain scores as covariates.
Negative error bars (SD) are not displayed for values less than zero.
HPES, Hypoparathyroidism Patient Experience Scale; HypoPT, hypoparathyroidism; SD, standard deviation.
Source: Khan et al 2023

HPES-Symptom (physical and cognitive) and HPES-Impact (physical functioning and daily life) domains showed sustained improvement for participants receiving palopegteriparatide through Week 52 [51].

HRQoL as measured by the SF-36 also improved significantly in the palopegteriparatide versus placebo group for the physical functioning subscale score (p=0.0347 for between-group differences in change from baseline to Week 26) [4, 74]. Mean SF-36 physical functioning subscale scores remained above baseline in the open-label extension period, demonstrating sustained improvement in HRQoL through Week 52 [51].

All changes in QoL measures were greater than MCID values (8.7 - 15.6 points for the different HPES domains and 3 points for SF-36 physical functioning subscale, respectively), thereby showing a clinically meaningful improvement in QoL upon treatment with palopegteriparatide.

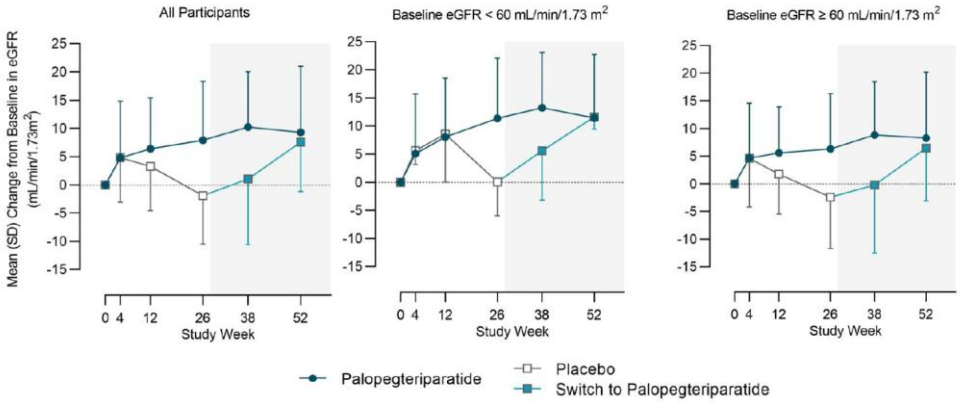
6.1.4.3 Renal function

A *post-hoc* analysis was conducted to examine the impact of palopegteriparatide treatment on renal function in adults with chronic HypoPT [75]. At baseline, mean eGFR was numerically lower in participants randomised to receive palopegteriparatide (67.3 mL/min/1.73m^2) versus placebo (72.7 mL/min/1.73m^2) and the proportion of participants with eGFR <60 mL/min/1.73m^2 (impaired renal function) was numerically higher in the palopegteriparatide (31.1%) versus placebo (19.1%) group [75]

Palopegteriparatide treatment resulted in significant and sustained improvement in renal function in adults with chronic HypoPT in the Phase 3 PaTHway trial [75]. From baseline to Week 26, mean (SD) eGFR increased by 7.9 (10.4) mL/min/1.73m^2 in the palopegteriparatide group and decreased by -1.9 (8.6) mL/min/1.73 m^2 in the placebo group (P<.001 for the difference between groups) [75].

Treatment with palopegteriparatide over 52 weeks resulted in a mean (SD) increase in eGFR of 9.3 (11.7) mL/min/1.73m^2 from baseline (P<0.0001). The mean (SD) eGFR increased by 7.6 (8.7) mL/min/1.73m^2 (P<0.01) from baseline to Week 52 for participants who switched from placebo to palopegteriparatide treatment at Week 26 [75]. The increase was sustained: at Week 104, palopegteriparatide treatment resulted in a mean (SD) increase in eGFR of from baseline of 9.0 (10.3) mL/min/1.73m^2 (P<.0001) [76]. Improvements in the palopegteriparatide arm were consistent for patients with either eGFR <60 and >= 60 at baseline (Figure 4).

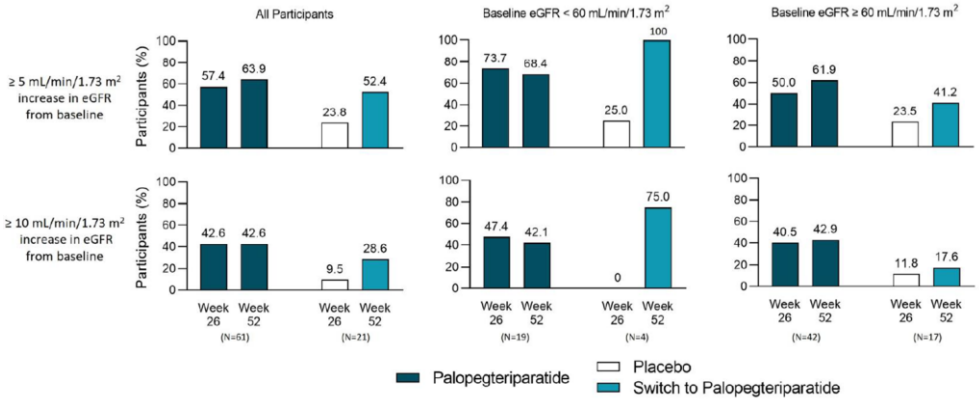
Figure 4: PaTHway – Mean (SD) changes from baseline in eGFR through Week 52 for the overall population and by baseline eGFR sub-group



Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation
Source: Rejnmark *et al.* 2024[75]

At Week 52, 64% (39 of 61) of participants randomised to palopegteriparatide had a clinically meaningful change in eGFR of ≥5 mL/min/1.73 m^2 and 43% (26 of 61) had an increase in eGFR of ≥10 mL/min/1.73 m^2 from baseline (Figure 5) [75]. eGFR response rates, defined as an increase of ≥5 mL/min/1.73 m^2, in participants randomised to placebo increased from 26% at Week 26 (end of the blinded period) to 57% at Week 52 after switching to palopegteriparatide [75].

Figure 5: PaTHway – Proportion of participants with an increase ≥5 mL/min/1.73m² and ≥10 mL/min/1.73 m² in eGFR from baseline to Weeks 26 and 52



Abbreviations: eGFR, estimated glomerular filtration rate
Source: Rejnmark *et al.* 2024 [75].

By Week 104, 61% of participants had an increase in eGFR of ≥5 mL/min/1.73m^2, and 44% had an increase of ≥10 mL/min/1.73m^2 [76].

Participants with impaired renal function at baseline (<60mL/min/1.73m^2) had the greatest improvement in mean eGFR with palopegteriparatide treatment [76].

The mean increase from baseline in eGFR in participants with impaired renal function at baseline randomised to palopegteriparatide (n = 19) was 11.4 mL/min/1.73m^2 at Week 26 and 11.5 mL/min/1.73m^2 at Week 52 [75].

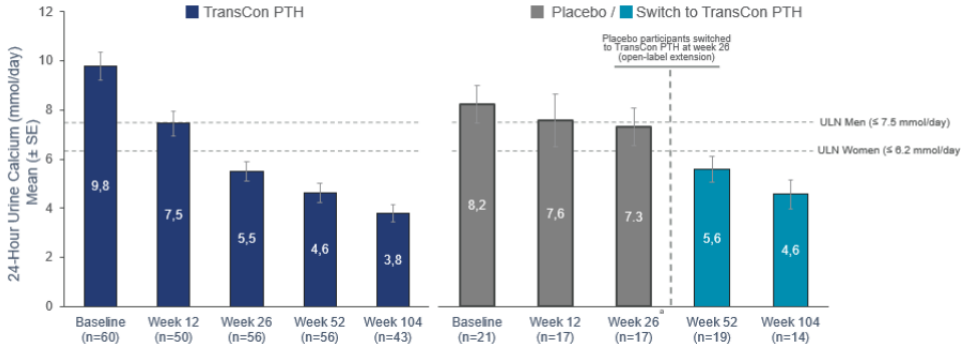
At Week 104 the mean increase from baseline in eGFR in participants with impaired renal function at baseline (n = 23, all receiving palopegteriparatide) was 13.8 (10.0) mL/min/1.73m^2 [76]. Mean increase from baseline in eGFR to Week 52 was 11.7 mL/min/1.73m^2 for participants who had switched from placebo to palopegteriparatide at Week 26 (n = 4) [75].

Among participants randomised to palopegteriparatide with baseline eGFR <60 mL/min/1.73m^2, 68% (13/19) had a clinically meaningful change in eGFR of ≥5 mL/min/1.73 m^2 and 42% (8/19) had an increase in eGFR of ≥10 mL/min/1.73 m^2 at Week 52 [75]. At Week 104, 78% had an increase in eGFR of ≥5 mL/min/1.73m^2 and 57% had an increase of ≥10 mL/min/1.73m^2, respectively [76].

In addition, 24-hour Urinary calcium excretion was evaluated as a safety endpoint in the PaTHway trial. At baseline, participants in the palopegteriparatide and placebo groups had elevated levels of 24-hour urinary calcium excretion (Figure 6).[4] Participants treated with palopegteriparatide showed a mean decrease in 24-hour urinary calcium excretion to the normal range by 26 weeks, which was maintained through week 52 and 104 (Figure 6). [4, 75, 76]

In the first 26-week period, participants in the palopegteriparatide group showed a statistically significant decrease in mean 24-hour urine calcium from baseline versus the placebo group (p<0.0001) (Khan et al. 2023). Urinary calcium continued to decrease nominally until week 104 (Schwarz et al. 2024). In placebo-treated participants who switched to palopegteriparatide after the double-blind period, mean 24-hour urine calcium normalised within 26 weeks of treatment initiation (week 52 of the study) and remained below the ULN until week 104 (Figure 6) [76]

Figure 6. 24-hour urine calcium excretion at 12, 26, 52 and 104 weeks (Schwarz et al. 2024)[76]



7. Comparative analyses of efficacy

Comparative analyses of efficacy in PaTHway are presented section 6.1.4.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

As presented in Section 4, the cost-effectiveness analysis relied on Markov modelling of time on/off palopegteriparatide treatment. The key transitions in the model are time to treatment response, discontinuation from palopeteriparatide treatment and death.

Discontinuation in the palopegteriparatide arm is based on overall discontinuation sourced from PaTHway

Mortality was modelled based on Danish general population mortality with a health state dependent excess mortality related to HypoPT sourced from RWE.

8.1.1.1 Extrapolation of effect measure

Not applicable, no extrapolation of treatment duration or OS using longitudinal data analysis.

8.1.2 Calculation of transition probabilities

Transition probabilities (TPs) have been included in the CEM to describe the likelihood of moving from one state to another in each time step. The base case assumptions and method for deriving TPs are presented in Table 16. Details on estimates are presented in following sections below.

Table 16 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
NAC On palopeg	AC On palopeg	One transition in cycle 0-6 based on palopeg efficacy	PaTHway.
	Death	General Danish population mortality (gender weighted) at modelled age Adjusted for excess mortality in NAC health state	DMC CPRD study (see section 8.4)
AC On palopeg	NAC Off palopeg	<u>General discontinuation:</u> Fixed probability estimated from discontinuation from palopeg Patients will leave AC state 0-12 cycles after discontinuation.	PaTHway and PaTHway OLE Assumption. Base case is 0 cycles
	Death	General Danish population mortality (gender weighted) at modelled age Adjusted for excess mortality in AC health state	
NAC Off palopeg/ NAC On CT	Death	General Danish population mortality (gender weighted) at modelled age Adjusted for excess mortality in NAC health state	

Health state (from)	Health state (to)	Description of method	Reference
NAC On CT	AC On CT	0	Assumption. Patients on conventional therapy or who have discontinued palopeg treatment will remain in NAC state until death.
	Death	General Danish population mortality (gender weighted) at modelled age Adjusted for excess mortality in NAC health state	

Abbreviations: AC adequately controlled; CT, conventional therapy; NAC Not adequately controlled; palopeg Palopegteriparatide

8.1.2.1 Initial health state allocation

All patients enter the model in the NAC state and will transition to the AC depending on treatment arm.

A post hoc analysis of the PaTHway trial baseline data was conducted using the Khan criteria to identify patients with NAC HypoPT. This analysis showed that [redacted] of patients enrolled in the trial met the NAC criteria at baseline. The breakdown of the classification of patients can be found in Table 1.

Although not all patients in PaTHway were classified as NAC according to the post-hoc analysis, it was decided to use the efficacy data from the overall population in order not to break randomization.

8.1.2.2 Time to response

The goal of treatment with palopegteriparatide is to replace the parathyroid function and restore normal calcium homeostasis, removing the need of CT typically given for symptomatic relief. Improvement of health-related quality of life observed in PaTHway was used as surrogate for restoration of physiological PTH function, enabling evaluation of effectiveness of palopegteriparatide as a replacement hormone. Assessment of EQ-5D index over time show that the effect (difference in change from baseline) at week 10 (the first EQ-5D reporting after baseline) was the same as at end of placebo control (see Table 29 and Table 30).

Based on this and for modelling simplicity, patients on treatment were modelled to enter the AC state from the initiation of therapy. A scenario analysis with a three cycle (12 week) delay of effect was conducted.

8.1.2.3 Discontinuation

Discontinuation of palopegteriparatide was based on observed data from the clinical trial. In the OLE phase, 6/79 patients discontinued treatment by Week 156.[55] An annualised discontinuation rate of 2.60% (0.2% per cycle) was calculated, which was applied as a fixed transition probability in the palopegteriparatide arm over the model time horizon.

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

8.1.2.4 Mortality

Transitions to death are time-varying and based on the Danish age and gender tables for 1-year life expectancy [73]. Model population cycle probabilities of general mortality were estimated using the DMC preferred method [73].

Adjustments applied by health state to reflect elevated mortality risk among HypoPT patients. Excess mortality risk associated with HypoPT in the model was informed by real-world evidence from the UK RWE study (CPRD analysis).[72]

Hazard ratios were estimated by comparing mortality in patients with chronic HypoPT against matched general population controls and were stratified by AC and NAC status.[72] These hazard ratios were applied to the Danish general population life tables to generate age-sex-specific mortality rates for each cycle and health state.[73]

Table 17: Hazard ratios for mortality

Mortality	Hazard ratio
AC	[redacted]
NAC	[redacted]

Abbreviations: AC, adequately controlled disease; NAC, not adequately controlled disease; Source: UK RWE study (CPRD analysis)[72]

Any additional mortality risk to account for incident complications to HypoPT was not included within the base case analysis due to the potential risk of double counting mortality risk. Given the UK RWE study (CPRD analysis) excluded patients who had a prior diagnosis of CKD or CVD event, there is a potential risk of underestimating long-term mortality from these complications.

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

Patients discontinuing palopegteriparatide will switch back to CT therapy.

8.4 Other assumptions regarding efficacy in the model

The primary clinical effect in the model is the time to treatment response and implication for disease management status (AC/NAC). In order to estimate downstream effect on mortality, risk of complications and health care resource utilization, Ascendis Pharma have sponsored a real-world evidence (RWE) study using the UK clinical primary care data base (CPRD). This section provides an overview of the study and results. Details are presented in the report [72, 77].

8.4.1 CPRD study

8.4.1.1 Purpose

To describe the healthcare resource use and estimate the risk of complications and mortality for individuals with chronic post-surgical and non-surgical hypoparathyroidism and their matched general population counterparts overall and stratified by controlled and uncontrolled hypoparathyroidism.

8.4.1.2 Data

The study was conducted in linked primary care (CPRD), secondary care (HES) and mortality (ONS) databases. Patients were required to be aged at least 18 years at the time of inclusion in the study and with at least one day of follow-up in the study period. To confirm chronic HypoPT, both non-surgical and post-surgical cohorts were required to have two diagnosis codes, 6 to 36 months apart, or ongoing treatment with calcium salts dosed at >600mg/day or active vitamin D (0.5 mcg/day) analogue replacement in lieu of a second diagnosis code. For incident chronic post-surgical chronic HypoPT, the first HypoPT diagnosis was required to be within 180 days of a relevant neck surgery procedure. General population matched control were matched on 5-year age band, gender and overlapping observation periods.

The study period was April 2008 to March 2020. The study period extends for 1 year beyond the eligibility period to allow all patients to have at least 12-months follow-up. Patients were followed from index until the earliest of end of registration with a contributing primary care practice, last data collection from CPRD practice, death, or the end of the study period.

8.4.1.3 Method

For the analysis of excess mortality and complication risk, patient with a history of CVD or renal insufficiency prior to the index date were excluded. [redacted] patients with post-surgical HypoPT were identified and matched to [redacted] from the general population without HypoPT. [redacted] patients with non-surgical HypoPT were identified and matched to [redacted] patients from the general population without HypoPT.

Included HypoPT patients were classified with respect to level of disease control (AC or NAC). The CPRD analysis does not contain laboratory, medication dosing, or symptom-specific data. As a result, the clinical definition used for the PaTHway trial could not be applied directly. Instead, patients were classified based on intensity of health care contacts needed to manage symptoms as a proxy for disease control.

This approach was developed through engagement with UK clinical experts and based on the observation that patients with poorly controlled HypoPT require more frequent monitoring and acute care. The following thresholds were defined and applied consistently to the UK RWE study (CPRD analysis) population:

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

This definition enabled consistent classification of health states across real-world evidence inputs, including complication risk, resource use, and mortality. It also ensured alignment with the model's assumption that AC reflects better biochemical and symptomatic control with reduced healthcare burden, while NAC reflects continued disease instability.

Hazard ratios (HR) for the risk of HypoPT relevant complications or death were estimated using cox proportional hazard regression comparing patients with HypoPT to matched patients without HypoPT and comparing patients with controlled HypoPT to patients with uncontrolled HypoPT.

In addition, the study estimated overall HRCU (primary care visits, emergency care visits, and inpatient/outpatient hospital visits) per patient-year of follow-up.

8.4.1.4 Results

For the included patients without CVD or advanced renal insufficiency at index date, the mortality hazard rates were similar when comparing HypoPT cases to general population controls within the controlled and uncontrolled definition. For patients with HypoPT in a controlled disease state, the unadjusted hazard ratio (uHR) for mortality was [redacted]) compared to the general population. Similarly, for patients with uncontrolled disease status, the unadjusted hazard ratio (uHR) was [redacted]) compared to general population controls.

Patient with HypoPT (without CVD or advanced renal insufficient) had higher all-cause HCRU across IP, OP, EC and primary care than their respective general population controls. Combined post-surgical and non-surgical cases with HypoPT had [redacted] more all-cause inpatient (IP) admissions, [redacted] more all-cause outpatient (OP) appointments, [redacted] more all-cause emergency care (EC) attendances, and [redacted] more all-cause primary care (PC) consultations compared to general population controls.

Among patients with HypoPT without CVD or advanced renal insufficiency, those with uncontrolled HypoPT disease status had higher all-cause HCRU across IP admissions, OP visits, EC attendances and PC consultation than those with controlled HypoPT. Patients

with uncontrolled HypoPT had [redacted] more all-cause IP admissions, [redacted] more all-cause outpatient appointments, [redacted] more all-cause EC attendances, and [redacted] more all-cause primary care consultations compared to those with controlled HypoPT

8.4.1.5 Discussion

The study concluded that patients with chronic HypoPT had higher total HCRU compared to matched general population controls without HypoPT. Additionally, patients with chronic HypoPT had an elevated risk of mortality and many complications compared to their control counterparts. When comparing patients with controlled versus uncontrolled chronic HypoPT, it was observed that those with controlled HypoPT had lower HCRU, as well as lower risk of mortality and many complications compared to those with uncontrolled HypoPT.

Based on Danish clinical expert input, the study finding was seen as relevant for the modelling of indirect effect of palopegteriparatide treatment. The additional number of contacts (relative to matched controls, contacts attributable to HypoPT) in the CPRD study are considered relevant in a Danish context. However, the Danish clinical experts emphasized that primary care is less used by Danish patients. Instead, specialist out-patient care is the main point of contact.

The baseline characteristics of the patient population enrolled in the clinical study aligns well with a Danish patient population.

The Danish clinical experts hence concluded that the approach for collection of HCRU in the CPRD database seem reasonable and the findings seem to be applicable to a Danish context and emphasised that there is no reason to believe that HypoPT treatment practice in UK differs from that in Denmark.

8.5 Overview of modelled average treatment length and time in model health state

An overview of patients' health state in the palopegteriparatide and CT group is provided in Figure 7 and Figure 8, respectively.

Figure 7 Health state distribution over time in palopegteriparatide

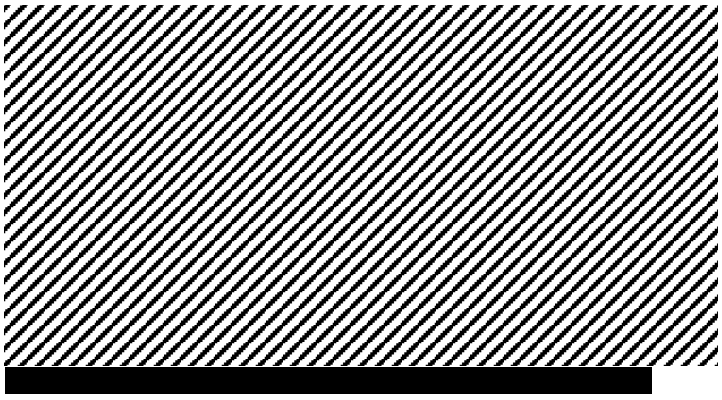
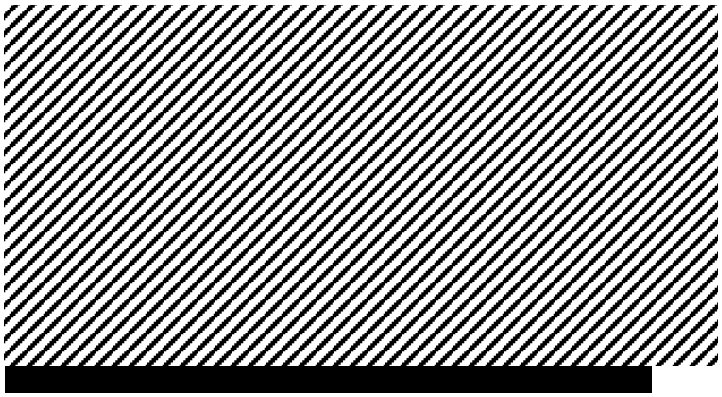

[redacted]

Figure 8 Health state distribution over time in CT



OS and PFS are not states being modelled in this analysis, hence Table 18 is not applicable. Estimates by stage are presented in Table 19.

Table 18 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Palopegteriparatide	NA	NA	NA
CT	NA	NA	NA

Treatment in the comparator group (CT) and in the intervention group (palopegteriparatide) is lifelong, a discontinuation probability is applied to the palopegteriparatide group based on results from the PaTHway trial ( ).

Table 19 Overview of modelled average treatment length and time in model health state, undiscounted

	Duration of treatment	AC	NAC	Total
Palopegteriparatide				
Conventional therapy				

9. Safety

The safety data from the PaTHway trial is described in the tables below [4]. A total of 84 patients fitting the inclusion and exclusion criteria that were randomised into the trial (ITT), with 63 patients randomised into the palopegteriparatide group, and 21 patients into the placebo group. One patient withdrew consent, and another experienced a recurrence of thyroid cancer, unrelated to palopegteriparatide. For the analyses, 82 patients were included, 61 received palopegteriparatide, and 21 patients administered placebo.

9.1 Safety data from the clinical documentation

Overall, palopegteriparatide was well tolerated, there were no treatment discontinuations related to the study drug during the PaTHway trial. Treatment-emergent adverse events (TEAEs) were reported in 82% of patients in the palopegteriparatide group, and 100% of patients in the placebo group.

Table 20 Overview of adverse events in the trial during blinded period

TEAE summary	Palopegteriparatide (N=61) n (%)	Placebo (N=21) n (%)
TEAE	50 (82.0)	21 (100.0)
Serious TEAE	5 (8.2)	3 (14.3)
Severity†		
Grade ≥3	2 (3.3)	1 (4.8)
Grade 2	21 (34.4)	9 (42.9)
Grade 1	27 (44.3)	11 (52.4)
Related TEAE	30 (49.2)	8 (38.1)
Serious related TEAE	1 (1.6)	0
TEAE related to hypercalcemia or hypocalcemia leading to hospitalization and/or an ER/urgent care visit	4 (6.6)	2 (9.5)
TEAE leading to discontinuation of study drug	1 (1.6)‡	2 (9.5)
TEAE leading to death	1 (1.6)‡	0

Abbreviations: ER, emergency room; n, number; PTH, parathyroid hormone; TEAE, treatment-emergent adverse event
†In the severity categories, patients are displayed for the highest severity category only.
‡Death due to cardiac arrest that was unrelated to study drug.

Most of the TEAEs were classified as mild (grade 1) and moderate (grade 2). The one serious related TEAE that occurred was hypercalcemia, attributed to a dosing error that deviated from the titration algorithm used in the trial. One patient death occurred in the palopegteriparatide group. It was due to cardiac arrest and unrelated to the palopegteriparatide treatment. The patient was a 70-year-old male with a history of postsurgical HypoPT and cardiovascular risk factors.

The most commonly reported TEAEs in the palopegteriparatide group included injection site reactions (31.1%), headache (21.3%), paraesthesia (18.0%), and fatigue (14.8%). The details can be found in Table 24. Slightly more placebo subjects experienced at least 1 serious adverse event compared with palopegteriparatide-treated subjects (3/21 [14.3%] versus 5/61 [8.2%]) (see Table 21)

Table 21 Serious adverse events

Adverse events	Palopegteriparatide (N=61)		Placebo (N=21)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Serious TEAE, n (%)	5 (8.2)	NA.	3 (14.3)	NA.
Grade 4, n(%)	1 (1.6)	NA.	0	NA.
Grade 3, n(%)	1 (1.6)	NA.	1 (4.8)	NA.
Serious related TEAE, n(%)	1 (1.6)	NA.	0	NA.

Abbreviations: TEAE, treatment emergent adverse event

In the health economic model hypocalcaemia and hypercalcaemia events were captured as treatment emergent adverse events using treatment exposure-adjusted event rates from the PaTHway trial double blinded phase for CT and both the double blinded and OLE phases for palopegteriparatide (including cross-over patients from the comparator to treatment arm following the end of the double blinded phase). Using exposure adjusted event rates allowed for all available trial data to be used while allowing for event rates to be compared between treatments despite the differing times on treatment.

The model included only hypocalcaemia and hypercalcaemia as adverse events, as these were considered to represent impactful, treatment-emergent events that recur throughout a patient's life and contribute meaningfully to patient burden and healthcare utilisation. All symptomatic hypocalcaemia (including paraesthesia) and hypercalcaemia events were included, regardless of grade, to reflect the expected greater severity in clinical practice where regular monitoring is less frequent. In contrast to the intensive monitoring in PaTHway, real-world detection of calcium imbalance is likely to be delayed, increasing the risk of more serious outcomes. Therefore, trial-based grade 1–4 symptomatic event rates were considered to better represent the real-world incidence of clinically significant (i.e. cost-generating) events. This interpretation is supported by [redacted] serum hypocalcaemia events per patient-year observed during the randomised period of PaTHway [55], compared to [redacted] treatment-emergent hypocalcaemia events per patient-year, indicating a higher frequency of biochemical instability than is captured by reported TEAEs and supporting the plausibility that a subset would require inpatient management outside of the trial context. Table 22 presents the exposure adjusted treatment emergent adverse events per patient per year on the palopegteriparatide and CT arms of the PaTHway trial. The values used to calculate the incidence in the model are

emboldened, with the 26-week CT arm value used, as the latest available values for placebo plus CT treatment, and the combined 156-week value used for palopegteriparatide. The reduction in event rates over time among patients receiving palopegteriparatide further supports the expectation of lower healthcare resource use in the long term and provides additional justification for the assumption of no treatment waning.

Table 22. Exposure adjusted treatment emergent adverse events (per patient per year)

Arm	Exposure adjusted TEAE	Week			
		26	52	104	156
[redacted]					

The model then assumes hypercalcaemia and hypocalcaemia continue to occur over the lifespan as complications, with palopegteriparatide attenuating the disease-attributable excess incidence. Table 23 presents treatment emergent adverse event incidence values used in the model, adjusted for the cycle length (four weekly cycles).

Table 23 Adverse events used in the health economic model

Adverse events	Exposure adjusted annual rate		Rate adjusted for model cycle		Source	Justification
	Palopeg	CT	Palopeg	CT		
Hyper-calcemia	[redacted]				Study CSR	AE rates used life-long to capture symptomatic events associated with HypoPT
Hypo-calcemia	[redacted]				Study CSR	AE rates used life-long to capture symptomatic

Adverse events	Exposure adjusted annual rate		Rate adjusted for model cycle		Source	Justification
	Palopeg	CT	Palopeg	CT		
						events associated with HypoPT

9.2 Safety data from external literature applied in the health economic model

NA.

Table 24 Adverse events that appear in more than 5 % of patients

Adverse events	Intervention (N=61)			Comparator (N=21)			Difference, % (95 % CI)	
	Number of patients with adverse events (%)	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events (%)	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
[redacted]								

10. Documentation of health-related quality of life (HRQoL)

Table 25 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	PaTHway trial	Used to estimate HSUVs in the model

Abbreviations: HRQoL, health related quality of life

10.1 Presentation of the health-related quality of life EQ-5D

10.1.1 Study design and measuring instrument

The EuroQol 5-dimensional (EQ-5D) questionnaire is a widely used generic health measure that can be applied to a wide range of health conditions. This measure is used to quantify health related QoL and measures a patient's health across five different domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The measure consists of two components: health state description and evaluation. In the description part, health status is measured in terms of the five dimensions. The respondents rate the level of severity for each dimension using a five-level (EQ-5D-5L) scale. In the evaluation part, the respondents evaluate their overall health status using a EuroQol visual analogue scale (EQ-VAS).

10.1.2 Data collection

Table 26 summarizes observation points for HRQoL during the PaTHway trial.

Table 26 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 10	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL, health related quality of life

10.1.3 HRQoL results

A summary of EQ-5D VAS at baseline, visit 6 (Week 10), visit 9 (Week, 20), and visit 10 (Week 26) is provided in Table 27. Median EQ-5D VAS at baseline was [redacted] in palopegteriparatide-treated subjects and [redacted] placebo subjects. EQ-5D VAS increased over time in palopegteriparatide-treated subjects, with a LS mean change from baseline of [redacted] at Week 26, while it remained unchanged in placebo subjects.

Table 27 HRQoL summary statistics visual analogue score

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To estimate utility values from Denmark by utilizing the *eq5d* package in R. EQ-5D-5L values were estimated for the Danish value set developed by Jensen et al. (2021). The base line utility index in the overall population (N:82) was [redacted])

Table 28 HRQoL summary statistics EQ-5D-5L index (Denmark)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To analyse the change from baseline to end of placebo-controlled study, an ANCOVA analysis was performed including the covariates:

- Aetiology of HypoPT – (surgical complications or other).
- Baseline EQ-5D Index.

- Randomised treatment arm

The ANCOVA analysis for EQ-5D index was aligned with the prespecified trial analysis of change from baseline outcomes as specified in the PaTHway statistical analysis plan.

Below LS mean change from baseline (palopeg vs CT) is presented for week 10 and week 26. It is clear that the utility benefit of palopeg is substantial already at week 10.

Table 29 Least square mean change from Baseline to week 10. EQ-5D-5L index (DK)

	Including control group responder	
	Palopeg	CT
ANCOVA model		
N		
LS Mean (SE)		
95% CI for LS Mean		
Difference in LS Means (SE)		
95% CI for Difference in LS Means		
P-value (Treatment vs Control)		

Abbreviation: ANCOVA analysis of covariance; CI confidence interval; CT conventional therapy; DK Denmark; EQ-5D-5L EuroQoL 5 Dimensions 5 Levels; ITT intent-to-treat; LS least squares; Max maximum; Min minimum; Palopeg palopegteriparatide; SE standard error

Table 30 Least square mean change from Baseline to week 26. EQ-5D-5L index (DK)

	Including control group responder	
	Palopeg	CT
ANCOVA model		
N		
LS Mean (SE)		
95% CI for LS Mean		
Difference in LS Means (SE)		
95% CI for Difference in LS Means		
P-value (Treatment vs Control)		

Abbreviation: ANCOVA analysis of covariance; CI confidence interval; CT conventional therapy; DK Denmark; EQ-5D-5L EuroQoL 5 Dimensions 5 Levels; ITT intent-to-treat; LS least squares; Max maximum; Min minimum; Palopeg palopegteriparatide; SE standard error

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The model should ideally capture the full effect of replace a missing hormone compared to symptom management. This suggest using the treatment effect on EQ-5D index observed in PaTHway to extrapolate the QALY gain while on palopegteriparatide treatment. In PaTHway, patient on palopegteriparatide achieved a statistically significant improvement in EQ-5D index from baseline to end of the placebo-controlled study while patients on CT had a small - but statistically insignificant – decrease in utility. Patients on conventional therapy – and patients discontinuing palogteriparatide – will maintain baseline level while patients on palopegteriparatide have the added utility estimated as

the difference in change in EQ-5D index change from baseline observed in the palopegteriparatide arm compared to CT in PaTHway.

10.2.1.1 Mapping

Not applicable

10.2.2 Disutility calculation

Not applicable

10.2.3 HSUV results

Table 31 Overview of health state utility values [and disutilities]

	Results [95%CI]	Instrument	Tariff (value set) used	Comments
HSUV				
NAC	[redacted]	[redacted]	[redacted]	[redacted]
Delta	[redacted]	[redacted]	[redacted]	[redacted]
AC	[redacted]			[redacted]

Abbreviations: AC adequately controlled; CI confidence interval; HSUV health state utility value; ITT intention to treat; NA not applicable; NAC not adequately controlled

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Health state utility values were sourced from the PaTHway study. In this section disutility associated with HypoPT and symptomatic events applied in the model is described.

10.3.1 Study design

Multiple designs were used in the underlying literature

10.3.2 Data collection

Not applicable. Data is not sourced from patient level data and missing data/completion rates were not available.

10.3.3 HRQoL Results

Not applicable. Only post-analysis results (i.e. disutilities) are presented. See Table 37.

10.3.4 Disutility results

HypoPT complications

The sources and details on derivation of complication disutility values sourced from literature for each complication are provided in Table 32. Disutility values were assumed to apply for a duration of one cycle representing the disutility of an incident event. This assumption was determined to be conservative given many complications would be expected to have longer term (or even chronic) impacts on patients, therefore, the anticipated benefit of palopegteriparatide reducing complications in underestimated.

Table 32: Complication disutility

Complication	Details
Neurological complications (seizure)	The parameter estimates of adult patients with epilepsy having one seizure daily (0.130) versus those seizure free (0.800) were combined.[61, 70]
Cataract	From Andayani 2022,[57] the weighted disutility of cataract patients (-0.346) with moderate or worse visual acuity was compared to those with mild visual acuity impairment (0.926).[57]
Cardiovascular disease	(0.337) calculated from composite events disutilities from Dyer 2010 (Myocardial Infarction and Heart Failure) and Golicki 2015 (Stroke) weighted by incidence from Conrad 2024 (expanded below).[58-60]
Chronic Kidney Disease	The EQ-5D utility score of all CKD stages combined (0.74) versus the stage G1/G2 utility score (0.85) from Jesky 2016.[61]
Mental health	Excluded from base case
Bone fracture	From the catalogue of EQ-5D scores in chronic disease assembled by Van Wilder et al., the disutility of those with vertebral fracture (-0.490) was compared to the healthy age-matched population norm (0.810).[62]
Urinary tract infection	The TTO utility decrement of mild to moderate UTI in type 2 diabetes (T2DM, 0.090) was compared to the mean utility score for uncomplicated T2DM of 0.920.[63]
Upper respiratory tract infection	From the Van Wilder catalogue, the utility of any respiratory tract disease (0.71) was

Complication	Details
Lower respiratory tract infection including pneumonia	compared with age-matched population norm of 0.85 to derive disutility.[62]
Nephrolithiasis	From Eryildirim 2015, the mean EQ-5D index of 0.72 was compared against the age-gender population norm of 0.910 to calculate disutility.[64]
Nephrocalcinosis	

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

Given the multifactor composition of CVD, the disutility was calculated from a range of sources accounting for the disutility of different CVD events and their respective incidence. Dyer (2010) reports a structured literature search for CVD that includes 66 papers and provides utility estimates across a range of CV subgroups.[58] Due to the systematic approach applied, this source has useful applications for modelling of utilities and QALYs in economic evaluations. Golicki (2015) provides a comprehensive assessment of the validity of EQ-5D in stroke. The study included a large sample size (n=408) with a range of aetiologies.[59]

An incidence-weighted composite acute disutility for CVD was calculated using the difference between best (denominator) and worst (numerator) health state utilities for each of myocardial infarction (MI), heart failure (HF), and stroke (Table 33).

- For MI, this was the utility for Canadian Cardiovascular Society (CCS) grade IV (0.36) versus CCS grade 0 (0.81).[58]
- For HF, this was the utility of moderate to severe states (New York Heart Association Functional Classification [NYHA] Class III/IV, 0.51) versus mild states (NYHA Class II/I, 0.78).[58]
- For stroke, this was the mean utility of hospitalised stroke patients (0.528) versus that for patients with a modified Rankin Scale of zero (i.e. no stroke-related impairments, 0.884).[59]

Numerators and denominators were weighted by the relative UK incidence of each CVD component.[60]

Table 33: Derivation of composite CVD event acute disutility

	Incidence† [60]	Numerator	Denominator	Absolute difference	Source
MI	190	0.360	0.810	-0.450	Dyer 2010[58]
HF	367	0.510	0.780	-0.270	
Stroke	181	0.528	0.884	-0.356	Golicki 2015[59]
CVD	**738**			**-0.337**	Weighted

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

Incidences for complications were sourced from general population controls matched to CT patients in the UK RWE study (CPRD analysis).[72] These were age-gender-stratified

where possible, with weighted averages used when age brackets differed. Incidence rates were applied rather than probabilities to allow for the repeatable nature of any single complication for any given patient. Due to the difficulty of classifying mental health and data limitations, it was excluded from the analysis in base case.

Table 34: Complication general population incidence by age category per cycle

Complication	18-29	29-39	39-49	49-59	59-69	69-79	79+
Neurological complications (seizure)	0.05%	0.04%	0.03%	0.05%	0.07%	0.07%	0.07%
Cataract	0.03%	0.01%	0.05%	0.28%	0.74%	2.64%	5.07%
Cardiovascular disease	0.01%	0.01%	0.19%	0.43%	1.27%	3.01%	6.18%
Chronic Kidney Disease	0.00%	0.01%	0.03%	0.17%	0.58%	1.46%	2.50%
Mental health	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Bone fracture	0.20%	0.09%	0.14%	0.14%	0.34%	0.72%	2.15%
Urinary tract infection	3.42%	2.74%	1.90%	2.08%	2.78%	4.17%	6.77%
Upper respiratory tract infection	0.13%	0.14%	0.17%	0.16%	0.10%	0.23%	0.29%
Lower respiratory tract infection	1.23%	1.65%	1.60%	2.11%	2.79%	3.80%	7.24%
Nephrolithiasis	0.05%	0.13%	0.18%	0.10%	0.13%	0.17%	0.11%
Nephrocalcinosis	0.00%	0.00%	0.01%	0.01%	0.05%	0.08%	0.18%

To reflect the differential burden associated with disease control, relative risks for complications were adjusted using hazard ratios stratified by health state from the UK RWE study (CPRD analysis).[72] Table 35 presents, for each complication, the hazard ratio for AC versus general population, and hazard ratio for NAC versus general population.

Table 35: Complication risk

Complication	AC vs Gen pop	NAC vs Gen pop
Neurological complications (seizure)	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Cardiovascular disease	[redacted]	[redacted]
Chronic Kidney Disease	[redacted]	[redacted]
Mental health	[redacted]	[redacted]
Bone fracture	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]

Complication	AC vs Gen pop	NAC vs Gen pop
Upper respiratory tract infection	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]
Nephrocalcinosis*	[redacted]	[redacted]

Source: UK RWE study (CPRD analysis)[72]
*Notes: The Hazard ratio for nephrocalcinosis was taken from the "Renal complications - includes renal insufficiency, nephrolithiasis and nephrocalcinosis as chronic condition" category.

Adverse events

No appropriate sources were identified specific to the quality of life burden of hypocalcaemia and hypercalcaemia events, therefore, the disutility for these events were estimated from an assumed requirement for emergency hospital admission from Lin (2020), where median EQ-5D utility on admission (0.440) was compared against that at discharge (0.648) to derive the disutility (Table 36).[71] The impact of hypocalcaemia and hypercalcaemia was believed to not be adequately captured within the health state utilities due to two primary reasons: the short comparison period of EQ-5D data not being sufficient to capture the ongoing and consistent nature of events; the consistent monitoring of patients allow hypocalcaemia and hypercalcaemia events to be identified and treated before more severe symptoms develop which would limit the impact of these events compared to the real world setting.

Table 36: Adverse event disutility

Adverse event	Disutility (Lin 2020)[71]	Duration*
Hypercalcaemia	0.21	7.00
Hypocalcaemia	0.21	7.00

*The duration of hypocalcaemia and hypercalcaemia events were taken from the observed period that serum calcium initially increased during study drug titration before returning to within baseline levels during the phase of palopegteriparatide dose titration in PaTHway.

Overview of disutility values applied in the model

Results from external literature are included below (Table 37) for disutility associated with complications and adverse events.

Table 37 Overview of disutility values applied in the model

	Results [SD]	Instrument	Tariff (value set) used	Source
Complications				
Seizure	-0.130	EQ-5D	Netherlands	Wester 2021 [70]
Cataract	-0.346	EQ-5D	Indonesian	Andayani 2022 [57]
Cardiovascular disease	-0.337	EQ-5D-5L	Multi-study approach	Dyer 2010 & Golicki 2015 [58] [59] See Table 33
Chronic kidney disease	0.85	EQ-5D-3L	UK	Jesky et al 2016 [61]
Fracture	-0.300	EQ-5D	Multi-study approach	Van Wilder 2019 [62]
Urinary tract infection utility	-0.090	TTO	UK	Shingler 2015 [63]
Upper respiratory tract infection	-0.140	EQ-5D	Multi-study approach	Van Wilder 2019 [62]
Lower respiratory tract infection	-0.140	EQ-5D	Multi-study approach	Van Wilder 2019 [62]
Nephrolithiasis	-0.220	EQ-5D	NA	Eryildirim 2015 [64]
Nephrocalcinosis				
Adverse events				
Hypocalcaemia	-0.208	EQ-5D-3L	Taiwanese	Lin 2020 [71]
Hypercalcaemia	-0.208	EQ-5D-3L	Taiwanese	Lin 2020 [71]

11. Resource use and associated costs

This submission includes medicine costs, administration costs, disease management costs, costs associated with management of adverse events, and patient time and travel costs which are described in the following sections.

11.1 Medicine costs - intervention and comparator

Table 38 provides an overview of the medicines used in the model.

Table 38 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Palopeg	6-60 mcg*	96.4%**	Daily	NA
Calcium carbonate	284 mg	100%	Daily	NA
Alfacaldiol	0.25 mcg	100%	Daily	NA
CT	-	-	-	-
Calcium carbonate	1847 mg	100%	Daily	NA
Alfacaldiol	0.62 mcg	100%	Daily	NA

Abbreviations CT conventional treatment; palopeg palopegeriparatide; mcg microgram; mg milligram
* [redacted] of patients on treatment after week 26 (52) are assumed to be treated with double pen administration (in dose range 33-60mcg/day)
** Calculated as the number of palogpeg administrations relative to planned administrations (i.e., excluding skipped administrations)

Palopegteriparatide costs consist of the drug cost of palopegteriparatide plus the cost of oral calcium at the dose observed in PaTHway at Week 26 (assumed to be constant thereafter).[78]

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

The flat price structure across available dosage strengths ensures that the palopegteriparatide daily cost is the same for daily doses of 30mcg or less. Because the maximum daily dose is 60mcg, some patients may need to administrate two pens or two injections per day.

The base-case analysis assumes that [redacted] at week 26 will require double pen administration and [redacted] at week 52. The assumption is based on actual dosing observed in [redacted] German HypoPT patients treated with commercially available palopegteriparatide for 26 (52) weeks. A total of [redacted] patients at week 26 and [redacted] patients at week 52 administrated two pens daily. In comparison [redacted] of patient in PaTHway required administration of two pens at the end of the placebo-controlled study (week 26). Dose titration based on data from the PaTHway OLE ([redacted] at week 156) is not applied in the model. The proportion of patients that will require dose titration in clinical practice is expected to be low. Thus, application of PaTHway OLE data would overestimate the percentage of patients who require dose titration in reality. After week 52, the daily dose was assumed to remain stable for all patients continuing treatment.

Compliance was incorporated, with 96.4% compliance rate for palopegteriparatide incorporated from the PaTHway clinical trial.[55]

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

11.2 Medicine costs – co-administration

Palopegteriparatide may be co-administrated with individualized dosing of calcium carbonate and alfacalcidol. This is included in the model based on average dosing observed in PaTHway (end of placebo-controlled study) for the first year of palopegteriparatide treatment. See section above.

11.3 Administration costs

In the CEA, both palopegteriparatide and CT are assumed to be self-administered, with no additional costs. Hence. administration cost for palopegteriparatide and CT during maintenance treatment were assumed to be zero and part of the routine care cost of managing adults with HypoPT.

An initial administration cost is applied to palopegteriparatide patients to represent the six-week titration phase for palopegteriparatide (based on the observation that the median duration to achieve a stable dose took [redacted] within the titration period in the double-blind phase of PaTHway, Table 39).

Table 39: Time to stable dosage of palopegteriparatide

N	Mean	SD	Median	LCI	UCI	Q 25%	Q 75%	Min	Max
[redacted]									

Abbreviations: LCI, lower confidence interval; N, number; SD, standard deviation; UCI, upper confidence interval.

Administration costs are presented in Table 40. A total of 4 additional outpatients visits were included to titration purposes.

Table 40 Administration costs used in the model (one-off titration cost)

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient visit	4 visits during titration period	1992	DRG: 10MA98; Diagnosis A: DE209	PaTHway DRG2025[79]

11.4 Disease management costs

Disease management cost was stratified by control status and the model was designed to capture the full cost of the disease including management of complications to hypoPT. Disease management costs were informed using UK RWE (CPRD study). The design and relevance for Denmark is discussed in section 8.4. For the application of the study in Denmark, data on excess health care visits of HypoPT patients (AC and NAC, respectively) compared to their matched controlled subjects. [79] By only including attributable visits, the estimates include resource utilisation that are related to either hypoPT management or management/ treatment of complications to hypoPT.

Table 41 Disease management costs used in the model

Contact	Visits per year	Unit cost (DKK)	DRG code	Reference
AC health state				
Inpatient visit	[redacted]	44,599	10MA02 *Knoglemetboliske- og kalksygdomme* Diagnosis A: DE209; LOS: >12h	CPRD study DRG2025[79]
Outpatient visit	[redacted]	1,992	DRG: 10MA98; Diagnosis A: DE209	CPRD study DRG2025[79]
Emergency care	[redacted]	327	70AK01 *Lette akutte tilstande* Diagnosis A: DE209; Acute illness; LOS: <12h	CPRD study DRG2025[79]
Primary care	[redacted]	156.39	*PLO §50 0101 (konsultation)*	CPRD study DMC (2024)[80]
NAC health state				
Inpatient visit	[redacted]	44,599	See above	
Outpatient visit	[redacted]	1,992		
Emergency care	[redacted]	327		
Primary care	[redacted]	156.39		

11.5 Costs associated with management of adverse events

Table 42 shows the costs associated with management of adverse events. Unit costs were sourced from *interaktiv DRG* [79] using 2025 tariff set and are reported with the respective DRG code and patient contact assumptions. It was assumed that [redacted] of hypo- and hypercalcemia would lead to hospitalisation and [redacted] would lead to an emergency room visit.

Table 42 Cost associated with management of Adverse Events

	DRG code	Unit cost/DRG tariff [DKK]
Hypercalcemia	**Weighted**	[redacted]
[redacted]	70AK01 *Lette akutte tilstande* Diagnosis A: DE835C; Diagnosis B: DE209; Acute illness; LOS: <12h	327
[redacted]	10MA02 *Knoglemetboliske- og kalksygdomme* Diagnosis A: DE835C; Diagnosis B: DE209; LOS: >12h	44,599
Hypocalcemia	**Weighted**	[redacted]
Emergency room [redacted]	70AK01 *Lette akutte tilstande* Diagnosis A: DE835D; Diagnosis B: DE209; Acute illness; LOS: <12h	327
Hospitalisation [redacted]	10MA02 *Knoglemetboliske- og kalksygdomme* Diagnosis A: DE835D; Diagnosis B: DE209; LOS: >12h	44,599

11.6 Subsequent treatment costs

Not applicable.

11.7 Patient costs

Patients' time and travel costs were included in all health care visits applied in the model (drug administration, health state HRCU and adverse events). Frequency of health care visits are the same as for calculation of direct health care cost. Patients time associated with hospitalisation was estimated to be [redacted] hours per admission based on the average number of days per admission for NAC patients in the CPRD-analysis ([redacted] days).

Table 43 Patient costs used in the model

Activity	Time spent (hours) and travel (km) assumptions and cost per activity instance
Primary care visits	0.75 hours (10 km). 178.90 DKK*.
Time for hospital outpatient visit	1 hour (20 km). 263.80 DKK*
Emergency room attendance	1 hour (20 km). 263.80 DKK*
Hospitalisation	[redacted] hours (20 km). [redacted] DKK*

* Cost per hour 188 DKK; cost per Km 3.79 DKK)[80]

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

12.1 Base case overview

An overview of the base is presented in Table 44.

Table 44 Base case overview

Feature	Description
Comparator	CT
Type of model	Markov model
Time horizon	Lifetime horizon (up to age of 100 years)
Treatment line	Patients not adequately controlled under CT
Measurement and valuation of health effects	HSUV from the trial, literature-based disutility values for AE and complications
Costs included	Medicine costs, administration costs, disease management costs, costs associated with AE, patient time and travel cost
Dosage of medicine	Titrated up to optimal dose (6-60mcg/day). From week 26 (52), [redacted] of patients will require double pen/double administration.
Average time on treatment (years)	Palopegteriparatide [redacted] Conventional therapy [redacted]
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	No
Average time in model health state	AC / NAC Palopegteriparatide [redacted] / [redacted] Conventional therapy [redacted] / [redacted]

12.1.1 Base case results

Table 45 presents the discounted base case results for the treatment of HypoPT, with palopegteriparatide versus CT. The comparison indicates a net QALY gain of [redacted] at an incremental cost of [redacted]. Results indicate that palopegteriparatide is more effective but also more costly than CT, with an overall ICER of DKK[redacted] DKK per QALY when assessed at pharmacy purchase prices.

Table 45 Base case results, discounted estimates

	Palopegteri-paratide	Conventional therapy	Incremental
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	275,585	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]
Patient time and transport costs	[redacted]	[redacted]	[redacted]
Total costs	**9,521,144**	**5,366,704**	**4,154,441**
Total life years	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]			[redacted]

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

12.2.1.1 One-way sensitivity analyses

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available or using standard errors estimated based on ±20% variation around the mean where measures of variance around the base case values were not available. Pairwise one way sensitivity analyses were performed separately for each comparator and are reported for the 10 most influential parameters on the ICER.

OWSA results for palopegteriparatide versus CT are presented in Figure 9 and Table 46. The OWSA showed that the parameters with the greatest influence on the ICER were the treatment effect of palopegteriparatide on utility and excess mortality of hypoPT. Overall, the analysis illustrates robustness to univariant analyses.

Figure 9 Deterministic sensitivity analysis

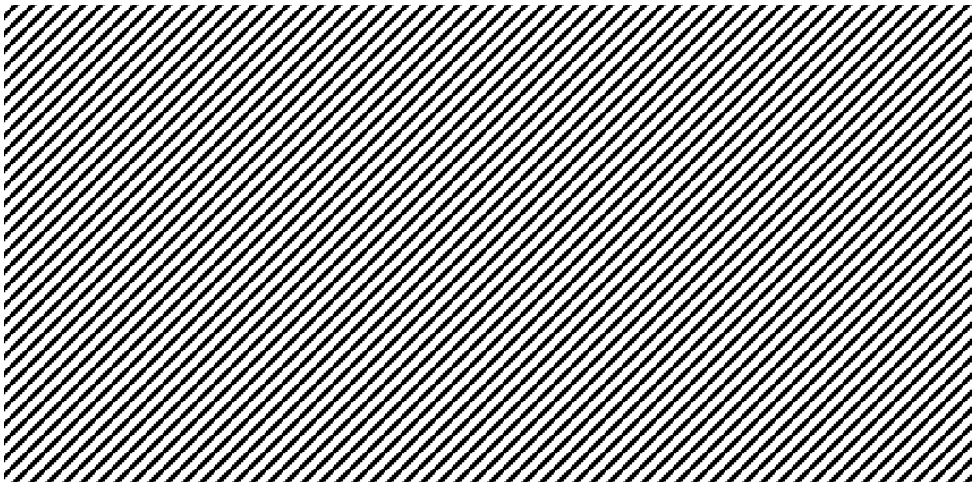


Table 46 One-way sensitivity analyses results

	Input		ICER (DKK/QALY)	
Parameter	Lower value	Upper value	Lower	Upper
[redacted]				

12.2.1.2 Scenario analyses

Efficacy assumptions

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the CE estimates. Table 47 lists the scenarios conducted around the base case analysis presented above.

The results of the scenario analyses (Table 47) illustrate the robustness of the analysis with ICER results varying from [redacted]/QALY to [redacted] DKK/QALY.

Table 47. Scenario analyses for the health economic model

Scenario	Incremental cost	Incremental QALY	ICER (DKK/QALY)
Base case	[redacted]	[redacted]	[redacted]
Response occurs after 1-cycle	[redacted]	[redacted]	[redacted]
Response occurs after 3-cycles	[redacted]	[redacted]	[redacted]
Half discontinuation	[redacted]	[redacted]	[redacted]
Double discontinuation	[redacted]	[redacted]	[redacted]

Subgroup analysis

To test the implication of disease severity on the economic evaluation, a subgroup analysis was performed for patients with moderate to severe hypoPT defined by HPES total score. Results from subgroup ANCOVA of EQ-5D index (DK value set) show that the time to onset of palopegteriparatide treatment effect on EQ-5D in this subgroup (Table 58 through Table 60) is similar to that observed in the ITT population. The treatment effects (change from baseline to week 26) was higher [redacted]) compared to the ITT analysis. The resulting ICER is substantially lower than in the base case analysis ([redacted]K/QALY) (Table 48).

Table 48 Cost-effectiveness results. Subgroup of patients with moderate/ severe hypoPT

	Palopegteriparide	Conventional therapy	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental cost per life years gained			[redacted]
Incremental cost per QALY gained (ICER)			[redacted]

The subgroup result indicates that treatment with palopegteriparatide for patients who may be considered to have a more severe impact on health-related quality of life from

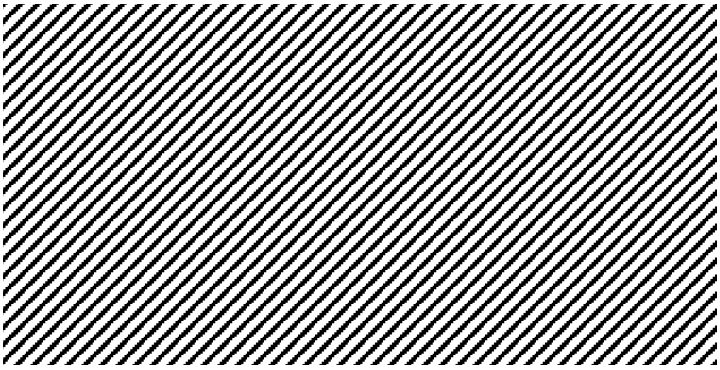
their disease is likely more cost-effective compared to conventional therapy than for the overall population with not-adequately controlled hypoPT.

12.2.2 Probabilistic sensitivity analyses

A probabilistic analysis was conducted to account for the joint uncertainty of the underlying parameter estimates. The choice of distribution (beta, gamma, log-normal, normal) applied to parameters was selected based on recommendations outlined in Briggs et al. 2008[81]. Standard errors (SEs) were taken directly from source data if reported or calculated from published standard deviations (SD) sample size and/ or 95% confidence interval data. If none were reported, SE is estimated as 20% of the default value. Details are presented in Appendix H.

Figure 10 shows the convergence of the ICER (calculated from mean incremental cost and mean incremental QALY by number of simulations). The probabilistic result stabilizes at approximately 500 simulations which supports basing the PSA on 1000 simulations.

Figure 10 Convergence plot (DKK/QALY by number of simulations)



The probabilistic results ([redacted] gained) align well with deterministic results (ICER: [redacted]/QALY gained). The scatterplot of all the PSA iterations is presented in Figure 11, while Figure 12 presents the cost-effectiveness acceptability curves (CEAC). The scatterplot confirms that palopegteriparatide is more efficacious but also more expensive compared to CT in all runs.

Figure 11 Cost-effectiveness scatterplot (N: 1000)

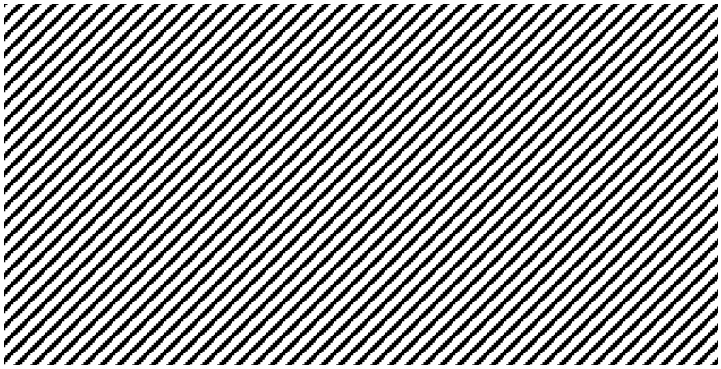
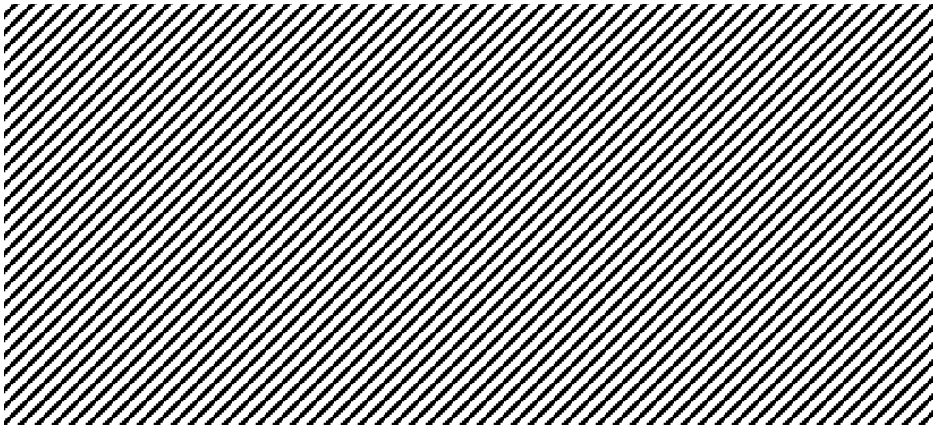


Figure 12 Cost-effectiveness acceptability curve (N:1000)



13. Budget impact analysis

Budget impact assumptions and results with all medicines costed at pharmacy purchase prices.

Number of patients (including assumptions of market share)

Table 49 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years	437	449	461	473	485
Prevalent patients expected to be treated by palopegteriparatide in case of approval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corresponding market share in case of approval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population	437	449	461	473	485
Recommendation					
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-recommendation					
Palopegteriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 50 Expected budget impact of recommending the medicine for the indication (Mill DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

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Appendix A. Main characteristics of studies included

Table 51 Main characteristic of studies included

Trial name: PaTHway study	NCT number: NCT04701203
Objective	To demonstrate the efficacy and safety of paloptegeriparatide versus placebo in terms of serum calcium (sCa), therapeutic doses of active vitamin D (i.e. calcitriol or alfacalcidol) and calcium after 26 weeks of treatment in adult patients with hypoparathyroidism
Publications – title, author, journal, year	• Khan AA, Rubin MR, Schwarz P, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. J Bone Miner Res. 2023;38(1):14-25. doi:10.1002/jbmr.4726
Study type and design	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, with an open-label extension phase, investigating the safety and efficacy of palopegteriparatide administered daily subcutaneously. Randomization was stratified according to the etiology of hypoparathyroidism (post-surgical or other).
Sample size (n)	A total sample of 82 patients was included
Main inclusion criteria	• Men and women aged ≥ 18 years • Patients with chronic post-surgical hypoparathyroidism or autoimmune, genetic or idiopathic hypoparathyroidism for at least 26 weeks. The diagnosis of hypoparathyroidism was established on the basis of a history of hypocalcemia in the presence of excessively low serum PTH concentrations (hypocalcemia was defined as a value below the reference range of normal in the analytical laboratory). A serum PTH concentration that was too low was defined as being equal to or below the median value of the normal reference interval in the laboratory concerned, while the concomitant serum calcium concentration was low. If specific laboratory results at the time of initial diagnosis were not available, a historical diagnosis affirming both was sufficient for inclusion. • Requirement of conventional thearpy doses (e.g. calcitriol, alfacalcidol, calcium) equal to or above a minimum threshold: a dose of calcitriol ≥ 0.5 µg/day, or alfacalcidol ≥ 1.0 µg/day and calcium (elemental) ≥ 800 mg/day (e.g. calcium citrate, calcium carbonate, etc.) for at least 12 weeks prior to selection . In addition, the dose of calcitriol, or alfacalcidol, or calcium had to be stable for at least 5 weeks prior to selection, • Optimization of conventional calcium and vitamin D treatment doses prior to randomization to achieve target serum levels of: o 25(OH) vitamin D concentration of 20-80 ng/mL (49-200 nmol/L) AND o Magnesium concentration within normal range, or just below normal range, i.e.: ≥ 1.3 mg/dL (0.53 mmol/L) AND o Albumin-adjusted or ionized serum calcium concentration within normal limits, or just below the lower limit of normal, i.e.:

Trial name: PaTHway study	NCT number: NCT04701203
	○ Serum calcium adjusted to albumin between 7.8- and 10.6 mg/dL (or 1.95-2.64 mmol/L) ○ Ionized serum calcium between 4.40 and 5.29 mg/dL (or 1.10-1.32 mmol/L) • The patient had a 24-hour urinary calcium excretion of ≥ 125 mg/24h (on a sample taken within 52 weeks prior to selection or during the selection period). • Body mass index (BMI) of 17 to 40 kg/m^2 at time of selection, • If age is ≤ 25 years, radiological evidence of epiphyseal closure on the basis of an X-ray of the non-dominant wrist and hand, • Thyroid-stimulating hormone (TSH) within normal laboratory limits during the 6 weeks prior to visit 1; in case of suppressive therapy for a history of thyroid cancer, TSH level had to be ≥ 0.2 mIU/L. • In the case of thyroid hormone replacement therapy, the dose had to have been stable for ≥5 weeks prior to selection. • eGFR ≥ 30 ml/min/1.73 m^2 at time of selection • Patient able to perform daily SC self-injections of treatment (or have a designated person perform the injections) using a pre-filled injection pen.
Main exclusion criteria	• Impaired reactivity to PTH (pseudohypoparathyroidism), characterized by resistance to PTH, with elevated PTH concentrations in the context of hypocalcemia, • Any disease likely to have affected calcium metabolism or phosphocalcic homeostasis or PTH concentrations other than hypoparathyroidism, such as active hyperthyroidism, gets disease of the bone, severe hypomagnesemia, type 1 diabetes or poorly controlled type 2 diabetes (HbA1c > 9%, a documented HbA1c result obtained within 12 weeks prior to screening is acceptable); chronic severe liver or kidney disease; Cushing's syndrome; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well-differentiated thyroid cancer or non-melanoma skin cancer); active hyperparathyroidism; parathyroid carcinoma within 5 years of screening; acromegaly; or multiple endocrine neoplasia types 1 and 2, • High-risk thyroid cancer within 2 years, requiring TSH suppression < 0.2 mIU/L, • Use of loop diuretics, phosphate binders (other than calcium supplements), digoxin, lithium, methotrexate, biotin > 30 µg/day or systemic corticosteroids (other than as part of replacement therapy), • Use of a thiazide diuretic within 4 weeks prior to the 24-hour urine sample scheduled for the week preceding visit 1, • Use of PTH-related drugs, including PTH(1-84), PTH(1-34) or other N-terminal fragments or analogues of PTH or PTH-related protein, within 4 weeks prior to screening, • Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (> 0.5 mg/day), strontium or cinacalcet hydrochloride, within 12 weeks prior to selection, • Use of osteoporosis treatments known to influence bone and calcium metabolism, i.e. bisphosphonates (oral or intravenous [IV]), denosumab, raloxifene or romosozumab in the two years prior to selection,

Trial name: PaTHway study	NCT number: NCT04701203
	• Non-hypocalcemic seizure disorder with a history of epileptic seizures in the 26 weeks preceding selection, Note: A history of epileptic seizures in the setting of hypocalcemia has not been excluded, • Increased risk of osteosarcoma, for example in cases of Paget's disease of the bone or unexplained elevation of alkaline phosphatase, hereditary disorders predisposing to osteo-sarcoma or a history of extensive external or implant radiotherapy to the skeleton
Intervention	Palopegteriparatide, 18µg, one subcutaneous injection per day (dose was then titrated progressively and individually to an optimal dose in 3µg/day increments, from 6 to 60µg/day)
Comparator(s)	Placebo; solution of excipients, one subcutaneous injection per day
Follow-up time	26 weeks, followed by a 156-week open-label extension phase.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint** Proportion of patients meeting the following 4 criteria at 26 weeks of treatment (ITT population): • Calcemia adjusted for albumin measured within 4 weeks prior to week 26 visit and at week 26 visit within normal range (8.3-10.6 mg/dL), Note: Except for the week 26 visit, albumin-adjusted serum calcium was considered "abnormal" if 2 consecutive results confirmed that serum calcium was outside the normal range in the 4 weeks preceding the week 26 visit. • Active vitamin D independence in the 4 weeks prior to the week 26 visit (i.e. any daily dose of active vitamin D equal to zero AND pro re nata utilization (PRN, as needed/rescued)) ≤ 7 days during the 4 weeks), • Independence from therapeutic doses of calcium in the 4 weeks prior to the week 26 visit (i.e. average daily dose of elemental calcium ≤ 600 mg AND use of PRN doses for ≤ 7 days during the 4 weeks). This dose of elemental calcium ≤ 600 mg/day in tablet, powder, liquid suspension or transdermal patch form was considered "complementary" to the recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism, • No increase in the dose of study treatment (in the palopegteriparatide arm or the placebo arm) in the 4 weeks prior to the Week 26 visit. Secondary endpoints Key secondary endpoints (secondary endpoints with protection from alpha risk inflation via a hierarchic sequence.): Change from inclusion at 26 weeks of treatment for the following endpoints: • HPES - Symptom - Physical domain score, • HPES - Symptom - Cognitive domain score, • HPES - Impact - Score in the area of physical functioning, • HPES - Impact - Score in the daily life domain, • Score of the Physical Function subscale of the 36-item Short Form Survey (SF-36). Secondary endpoints not evaluated in a hierarchical sequence are also included in the protocol: • Doses of calcium and active vitamin D

	• Daily burden of active vitamin D and calcium tablets (in the form of oral tablets, powder, liquid solutions, liquid suspensions or transdermal patches) • Serum phosphate • Serum calcium-phosphate product adjusted to albumin, including proportion of subjects with serum calcium-phosphate product adjusted to albumin ≤ 55 mg^2/dL^2, ≤ 52 mg^2/dL^2 and ≤ 44 mg^2/dL^2 • Serum calcium adjusted to albumin • Bone mineral density and trabecular bone score using dual-energy X-ray absorptiometry • Bone remodeling markers (serum P1NP and CTx) • Serum magnesium • EQ-5D • Overall clinical impression of severity • HPES: HPES impact domain scores (Psychological well-being and Social life and relationships) and HPES total scores on symptoms and impact • SF-36: SF-36 subscale scores (role limitations due to physical health problems, body pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health) and SF-36 component summary scores (physical component score [PCS] and mental component score [MCS]).
Method of analysis	Please see Appendix D
Subgroup analyses	NA
Other relevant information	NA

Appendix B. Efficacy results per study

Results of the primary endpoint and secondary endpoints of the PaTHway trial are presented in Table 52 below.

Table 52 Results of PaTHway (NCT04009291)

				Estimated effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value		
PaTHway								
Primary endpoint: Number of patients meeting the primary multi-component endpoint criteria at week 26	Palopegteriparatide	61	48 (78.7% CI: 66.3, 88.1)	47 (74.0 p.p.)	60.4; 87.6 p.p.	*P < 0.0001*	The Cochran-Mantel-Haenszel test controlling for aetiology of hypoparathyroidism (post surgical vs other) was used to compare the odds of meeting the primary endpoint in palopegteriparatide group to the odds in the placebo group	Khan A. et al., 2023 [4] EPAR assessment report[74]
	Placebo	21	1 (4.8% CI: 0.1, 23.8)					
Change from baseline to week 26 in HPES symptom – physical domain score	Palopegteriparatide	59	-21.01 (2.2)	-16.20 (5.02)	NA	*P =0.0038*	ANCOVA models with unequal variance were used to analyze the above key secondary endpoints after potential multiple imputation. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate. A 2-sided 95% confidence interval was calculated for the difference in least square means between the 2 treatment groups. Subjects with missing data for key secondary endpoints had the post-baseline data imputed using a multiple imputation model stratified by treatment	EPAR assessment report[74]
	Placebo	19	-4.81 (5.02)					
Change from baseline to week 26 in HPES symptom – Cognitive domain score	Palopegteriparatide	59	-20.49 (2.59)	-- 14.33 (4.67)	NA	*P =0.0055*		EPAR assessment report[74]
	Placebo	19	-6.16 (4.71)					
Change from baseline to week 26 in HPES impact – physical	Palopegteriparatide	59	-18.29 (2.65)	-- 17.28 (5.50)	NA	*P =0.0046*		EPAR assessment report[74]
	Placebo	19	-1.01 (5.49)					

Outcome	Study arm	N	Result (CI)	Estimated effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
functioning domain score							group, under the assumption of missing at random (MAR).	
Change from baseline to week 26 in HPES impact – daily life domain score	Palopegteriparatide	59	-17.65 (2.37)	-- 17.29 (5.68)	NA	*P =0.0061*		EPAR assessment report[74]
	Placebo	19	-0.36 (5.68)					
Change from baseline to week 26 in SF36 – physical functioning subscale score	Palopegteriparatide	59	5.29 (0.91)	5.16 (2.29)	NA	*P =0.0347*		EPAR assessment report[74]
	Placebo	19	0.12 (2.29)					
Change from baseline to week 26 in EQ-5D VAS (95%CI) LS mean diff between groups (95%CI)	Palopegteriparatide	59	BL: 70 (30;97) Change w 26: 8 (3;14)	8	(-1;17)	*P =0.0706*	Change from baseline is ANCOVA least square mean.	EPAR assessment report[74]
	Placebo	19	65 (8; 100) Change w 26: 0 (-9;9)					
Calcium dose (mg/day) (LS mean CFB palo vs pbo) w26	Palopegteriparatide	61	BL: 1748 (904) W26: 274 (1372)	-1501 (359)	NA	*P =0.0003*	Change from baseline in each of the endpoint by visit over 26 weeks was analysed using ANCOVA model with unequal variance including treatment assignment and aetiology of hypoparathyroidism as fixed factors and baseline value of the response variable as a covariate.	EPAR assessment report[74]
	Placebo	21	BL: 2105 (1382) W26: 1847 (1326)					
Active D vitamin D dose (mcg/day)	Palopegteriparatide	61	BL: 0.992 (0.7373) W26: 0	-0.620 (0.0917)	NA	*P < 0.0001*		EPAR assessment report[74]
	Placebo	21	BL: 0.940 (0.6220) W26: 0.618 (0.7330)					
Daily pill burden of active vit D and calc (#/day)	Palopegteriparatide	61	BL:6.69 (2.203) W26: 0.45 (1.661)	-5.08 (0.735)	NA	*P < 0.0001*		EPAR assessment report[74]
	Placebo	21	BL: 6.74 (2.990) W26: 5.42 (3.220)					

Outcome	Study arm	N	Result (CI)	Estimated effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
Serum phosphte (mmol/L)	Palopegteriparatide	61	BL: 1.361 (0.1918) W26: 1.229 (0.1846)	-0.073 (0.0536)	NA	*P =0.1861*		EPAR assessment report[74]
	Placebo	21	BL: 1.263 (0.2600) W26: 1.252 (0.2919)					
Albumin adjusted serum calcium (mmol/L)	Palopegteriparatide	61	BL: 2.200 (0.1722) W26: 02.236 (0.1675)	0.173 (0.0365)	NA	*P < 0.0001*		EPAR assessment report[74]
	Placebo	21	BL: 2.159 (0.1598) W26: 2.055 (0.1322)					
BMD by DXA (corrected Z scores)	Palopegteriparatide	61	BL: Lumbar spine: 1.5 (1.54) Total hip: 0.9 (1.25) Femoral neck: 0.8 (1.25) Sis 1/3 radius: 0.3 (1.01) W26: Lumbar spine: 0.7 (1.49) Total hip: 0.5 (1.28) Femoral neck: 0.4 (1.31) Sis 1/3 radius: 0.3 (1.05)	-0.9 (0.09) -0.5 (0.05) -0.6 (0.07) 0 (0.08)	NA	*P < 0.0001* *P < 0.0001* *P < 0.0001* *P= 0.7993*		EPAR assessment report[74]
	Placebo	21	BL: Lumbar spine: 2 (1.29) Total hip: 1.2 (0.73) Femoral neck: 1 (0.82) Sis 1/3 radius: 0.5 (0.93) W26: Lumbar spine: 1.8 (1.02) Total hip: 1.1 (0.71) Femoral neck: 1 (0.77) Sis 1/3 radius: 0.5 (0.92)					

Outcome	Study arm	N	Result (CI)	Estimated effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
Serum P1NP (ng/ml)	Palopegteriparatide	61	BL: 33.788 (19.4846) W26:120.450 (52.5390)	77.748 (5.8940)	NA	*P < 0.0001*		EPAR assessment report[74]
	Placebo	21	BL: 30.185 (10.3563) W26: 37.322 (24.4166)					
Serum CTx (ng/L)	Palopegteriparatide	61	BL: 227.5 (193.99) W26: 966.3 (445.07)	712 (52.8)	NA	*P < 0.0001*		EPAR assessment report[74]
	Placebo	21	BL: 168.6 (60.77) W26: 182.1 (98.13)					
24 hour urine calcium excretion (mg/day(	Palopegteriparatide	61	BL:391.95 (175.365) W26: 219.79 (122.663)	-89.81	NA	*P =0.0085*	Change from baseline in 24-hour urine calcium by visit over 26 weeks was analysed using ANCOVA model with unequal variance including treatment assignment and aetiology of hypoparathyroidism as fixed factors and baseline 24-hour urine calcium as a covariate. The percentage of subjects with normal 24-hour uCa excretion (or >=50% reduction from baseline) at Week 26 was summarised.	EPAR assessment report[74]
	Placebo	21	BL: 328.95 (140.042) W26: 292.47 (125.484)					
24 hour urine calcium excretion n (%)*	Palopegteriparatide	61	W26:37(60.7)	NA	NA	*P=0.0213*		EPAR assessment report[74]
	Placebo	21	W26:6 (28.6)					

*number of subjects with (n(%)) with normal 24 hour urine calcimum (>0250 mg/day)

Appendix C. Comparative analysis of efficacy

Table 53 Comparative analysis of studies comparing Palopegteriparatide to placebo for patients with hypoparathyroidism

				Estimated effect			Method used for quantitative synthesis	Results used in the health economic analysis
PaTHway Outcome	**Study arm**	**N**	**Result (%, CI)**	**Difference**	**95% CI**	***P* value**		
Primary endpoint: Number of patients meeting the primary multi-component endpoint criteria at week 26	Palopegteriparatide	61	48 (78.7% CI: 66.3, 88.1)	47 (74.0 p.p.)	60.4; 87.6 p.p.	*P < 0.0001*	The Cochran-Mantel-Haenszel test controlling for aetiology of hypoparathyroidism (post surgical vs other) was used to compare the odds of meeting the primary endpoint in palopegteriparatide group to the odds in the placebo group	No
	Placebo	21	1 (4.8% CI: 0.1, 23.8)					
Change from baseline to week 26 in HPES symptom – physical domain score	Palopegteriparatide	59	-21.01 (2.2)	-16.20 (5.02)	NA	*P =0.0038*	ANCOVA models with unequal variance were used to analyze the above key secondary endpoints after potential multiple imputation. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate. A 2-sided 95% confidence interval was calculated for the difference in least square means between the 2 treatment groups. Subjects with missing data for key secondary endpoints had the post-baseline data imputed using a multiple imputation	No
	Placebo	19	-4.81 (5.02)					
Change from baseline to week 26 in HPES symptom – Cognitive domain score	Palopegteriparatide	59	-20.49 (2.59)	--14.33 (4.67)	NA	*P =0.0055*		No
	Placebo	19	-6.16 (4.71)					

				Estimated effect			Method used for quantitative synthesis	Results used in the health economic analysis
PaTHway Outcome	**Study arm**	**N**	**Result (%, CI)**	**Difference**	**95% CI**	***P* value**		
Change from baseline to week 26 in HPES impact – physical functioning domain score	Palopegteriparatide	59	-18.29 (2.65)	--17.28 (5.50)	NA	*P =0.0046*	model stratified by treatment group, under the assumption of missing at random (MAR).	No
	Placebo	19	-1.01 (5.49)					
Change from baseline to week 26 in HPES impact – daily life domain score	Palopegteriparatide	59	-17.65 (2.37)	--17.29 (5.68)	NA	*P =0.0061*		NO
	Placebo	19	-0.36 (5.68)					
Change from baseline to week 26 in SF36 – physical functioning subscale score	Palopegteriparatide	59	5.29 (0.91)	5.16 (2.29)	NA	*P =0.0347*		No
	Placebo	19	0.12 (2.29)					
Change from baseline to week 26 in EQ-5D VAS (95%CI)	Palopegteriparatide	59	BL: 70 (30;97) Change w 26: 8 (3;14)	8	(-1;17)	*P =0.0706*		No, post-hoc analysis of EQ-5D-5L utility index was used in the model
	Placebo	19	65 (8; 100)					

				Estimated effect			Method used for quantitative synthesis	Results used in the health economic analysis
PaTHway Outcome	**Study arm**	**N**	**Result (%, CI)**	**Difference**	**95% CI**	***P* value**		
LS mean diff between groups (95%CI)			Change w 26: 0 (-9;9)					
Calcium dose (mg/day) (LS mean CFB palo vs pbo) w26	Palopegteriparatide	61	BL: 1748 (904) W26: 274 (1372)	-1501 (359)	NA	*P =0.0003*	Change from baseline in each of the endpoint by visit over 26 weeks was analysed using ANCOVA model with unequal variance including treatment assignment and aetiology of hypoparathyroidism as fixed factors and baseline value of the response variable as a covariate.	Yes
	Placebo	21	BL: 2105 (1382) W26: 1847 (1326)					
Active D vitamin D dose (mcg/day)	Palopegteriparatide	61	BL: 0.992 (0.7373) W26: 0	-0.620 (0.0917)	NA	*P < 0.0001*		Yes
	Placebo	21	BL: 0.940 (0.6220) W26: 0.618 (0.7330)					
Daily pill burden of active vit D and calc (#/day)	Palopegteriparatide	61	BL:6.69 (2.203) W26: 0.45 (1.661)	-5.08 (0.735)	NA	*P < 0.0001*		No
	Placebo	21	BL: 6.74 (2.990) W26: 5.42 (3.220)					

				Estimated effect			Method used for quantitative synthesis	Results used in the health economic analysis
PaTHway Outcome	**Study arm**	**N**	**Result (%, CI)**	**Difference**	**95% CI**	***P* value**		
Serum phosphte (mmol/L)	Palopegter iparatide	61	BL: 1.361 (0.1918) W26: 1.229 (0.1846)	-0.073 (0.0536)	NA	*P =0.1861*		No
	Placebo	21	BL: 1.263 (0.2600) W26: 1.252 (0.2919)					
Albumin adjusted serum calcium (mmol/L)	Palopegter iparatide	61	BL: 2.200 (0.1722) W26: 02.236 (0.1675)	0.173 (0.0365)	NA	*P < 0.0001*		No
	Placebo	21	BL: 2.159 (0.1598) W26: 2.055 (0.1322)					
BMD by DXA (corrected Z scores)	Palopegter iparatide	61	BL: Lumbar spine: 1.5 (1.54) Total hip: 0.9 (1.25) Femoral neck: 0.8 (1.25) Sis 1/3 radius: 0.3 (1.01) W26: Lumbar spine: 0.7 (1.49) Total hip: 0.5 (1.28)	 -0.9 (0.09) -0.5 (0.05) -0.6 (0.07) 0 (0.08)	NA	 *P < 0.0001* *P < 0.0001* *P < 0.0001* *P= 0.7993*		No

				Estimated effect			Method used for quantitative synthesis	Results used in the health economic analysis
PaTHway Outcome	**Study arm**	**N**	**Result (%, CI)**	**Difference**	**95% CI**	***P* value**		
			Femoral neck: 0.4 (1.31) Sis 1/3 radius: 0.3 (1.05)					
	Placebo	21	BL: Lumbar spine: 2 (1.29) Total hip: 1.2 (0.73) Femoral neck: 1 (0.82) Sis 1/3 radius: 0.5 (0.93) W26: Lumbar spine: 1.8 (1.02) Total hip: 1.1 (0.71) Femoral neck: 1 (0.77) Sis 1/3 radius: 0.5 (0.92)					
Serum P1NP (ng/ml)	Palopegteriparatide	61	BL: 33.788 (19.4846) W26:120.450 (52.5390)	77.748 (5.8940)	NA	*P < 0.0001*		
	Placebo	21	BL: 30.185 (10.3563)					

				Estimated effect			Method used for quantitative synthesis	Results used in the health economic analysis
PaTHway Outcome	**Study arm**	**N**	**Result (%, CI)**	**Difference**	**95% CI**	***P* value**		
			W26: 37.322 (24.4166)					
Serum CTx (ng/L)	Palopegteriparatide	61	BL: 227.5 (193.99) W26: 966.3 (445.07)	712 (52.8)	NA	*P < 0.0001*		
	Placebo	21	BL: 168.6 (60.77) W26: 182.1 (98.13)					
24 hour urine calcium excretion (mg/day(	Palopegteriparatide	61	BL:391.95 (175.365) W26: 219.79 (122.663)	-89.81	NA	*P =0.0085*	Change from baseline in 24-hour urine calcium by visit over 26 weeks was analysed using ANCOVA model with unequal variance including treatment assignment and aetiology of hypoparathyroidism as fixed factors and baseline 24-hour urine calcium as a covariate. The percentage of subjects with normal 24-hour uCa excretion (or >=50% reduction from baseline) at Week 26 was summarised.	
	Placebo	21	BL: 328.95 (140.042) W26: 292.47 (125.484)					
24 hour urine calcium excretion n (%)*	Palopegteriparatide	61	W26:37(60.7)	NA	NA	*P=0.0213*		
	Placebo	21	W26:6 (28.6)					

Appendix D. Efficacy outcome measure – method of investigation

PaTHway trial

For analyses during the blinded treatment period, the Cochran-Mantel-Haenszel (CMH) test controlling for the stratification factor of randomization (etiology of hypoparathyroidism: post-surgical vs. other) was used for the primary analysis and other categorical endpoints. Continuous efficacy endpoints were analyzed using the ANCOVA model with unequal variance and Satterthwaite approximation for degrees of freedom. In general, the continuous criterion of interest or change from inclusion was included in the model as a response variable. Treatment allocation and hypoparathyroidism etiology were introduced as fixed effects, and the baseline value of the variable of interest was introduced as a covariate, unless otherwise specified.

For the extension period, all judgment criteria were summarized descriptively, and no statistical tests were performed.

Analysis of primary endpoint:

As the primary analysis, the two-tailed MHC test controlling for etiology of hypoparathyroidism (post-surgical vs. other) was performed to test the following hypothesis for the primary efficacy endpoint with a risk alpha 0.05:

H0: ORPost = OROther =1,

where ORPost and OROther are the odds ratios (i.e. the probability of achieving the primary endpoint in the TransCon PTH group vs. the probability in the placebo group) in the post-surgery group and in the other groups, respectively. The common OR between the treatment group and the primary endpoint, taking into account the etiology of hypoparathyroidism, with 95% CI, is also shown.

In order to assess the robustness of the primary analysis, the following sensitivity analyses of the primary endpoint were performed on the ITT population (with the exception of sensitivity analysis 1). In all sensitivity analyses (with the exception of sensitivity analysis 1), patients with missing data on one or more of the sensitivity analysis endpoints were considered non-responders. The MHC test controlling for the etiology of hypoparathyroidism was performed for all sensitivity analyses (with the exception of sensitivity analysis 3).

Sensitivity analysis 1: primary endpoint analyzed for the completed study population, defined as patients in the ITT population who had completed 26 weeks of blinded treatment and had data on all components of the primary endpoint.

Sensitivity analysis 2: primary endpoint defined as the proportion of patients meeting the following 4 criteria after 26 weeks of blinded treatment:

- albumin-adjusted sCa, measured within 4 weeks prior to week 26 visit, within normal range (8.3-10.6 mg/dL)
- In the 4 weeks preceding week 26:
    - No active vitamin D intake AND PRN intake ≤ 7 days during these 4 weeks
    - No calcium intake and use of PRN doses for ≤ 7 days during these 4 weeks
    - No increase in study treatment dose

Sensitivity analysis 3: In sensitivity analysis 3, the two-tailed MHC test (Cochran-Mantel-Haenszel test) controlling for gender (Female vs. Male) was performed to test the primary endpoint.

Sensitivity analysis 4: primary endpoint defined as the proportion of patients meeting the following criteria after 26 weeks of blinded treatment:

- albumin-adjusted sCa, measured in the 4 weeks prior to the week 26 visit, in the range 7.5 to 10.6 mg/dL,
- Reduction of at least 50% in active vitamin D dose compared with the value at inclusion
- At least 50% reduction in elemental calcium dose compared with inclusion value

Sensitivity analysis 5: primary endpoint defined as the proportion of patients meeting the following criteria after 26 weeks of blinded treatment:

- albumin-adjusted sCa, measured in the 4 weeks prior to the week 26 visit, within the normal range (8.3-10.6 mg/dL),
- In the 4 weeks preceding week 26:
    - Active vitamin D independence in the 4 weeks prior to the week 26 visit (i.e. all daily doses of active vitamin D are zero AND there has been no PRN use in the 4 weeks),
    - Independence from therapeutic doses of calcium in the 4 weeks prior to the week 26 visit (i.e. mean daily dose of elemental calcium ≤600 mg AND no use of PRN during the 4 weeks),
    - No increase in study treatment dose in the 4 weeks prior to the Week 26 visit.

Analysis of the main secondary endpoints:

Unequal variance ANCOVA models were used to analyze the aforementioned primary secondary endpoints after potential multiple imputation. The change from inclusion of the variable of interest at week 26 was included in the model as response variables. The following null hypothesis was tested for each of the key secondary endpoints:

H0: $\pi PTH - \pi PBO = 0$,

where πPTH and πPBO were the mean changes from inclusion of the secondary endpoint for the Palopegteriparatide and placebo groups, respectively.

Treatment assignment and hypoparathyroidism etiology were introduced as fixed effects, and the baseline value of the variable of interest was introduced as a covariate. A two-sided 95% confidence interval was calculated for the difference in least-squares means between the two treatment groups. Estimates from the 100 adjusted ANCOVA models for each of the 100 imputed data sets were combined to provide an overall estimate of the difference between treatment groups with a corresponding confidence interval and p-value. The ANCOVA model was also repeated for patients with both baseline and post-baseline data (i.e. observed cases) without multiple imputation.

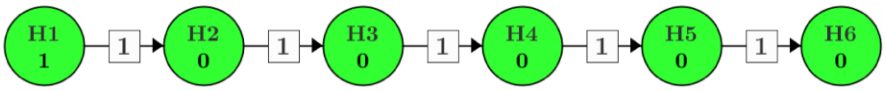
Multiplicity adjustment was applied to control the type I error rate for all key secondary endpoints.

Multiplicity adjustment:

The primary endpoint and the five key secondary endpoints were tested sequentially to control the overall significance level at 0.05. Considering that H1 represents the null

hypothesis of the primary endpoint; H2 to H6 represent the null hypotheses of key secondary endpoints 1 - 5, respectively, the order of testing is illustrated in Figure 3.

Figure 13. PaTHway study - Graphical illustration of sequential tests for primary and key secondary endpoints



Where a null hypothesis could not be rejected, statistical significance for the associated outcome was not reported, but test results were still reported. No adjustment was made for multiple tests/comparisons in other secondary and exploratory endpoints.

Analysis of other secondary endpoints:

In the analysis of the blinded treatment period, all continuous endpoints were analyzed using an ANCOVA model with unequal variance. Categorical variables were analyzed using the MHC test, taking into account the etiology of hypoparathyroidism.

In the open-label extension (OLE) analyses, all other secondary endpoints were summarized by scheduled visit.

Appendix E. Extrapolation

All relevant information on extrapolation of treatment effect and transition probabilities was presented in section 8.

E.1 Extrapolation of [effect measure 1]

E.1.1 Data input

E.1.2 Model

E.1.3 Proportional hazards

E.1.4 Evaluation of statistical fit (AIC and BIC)

E.1.5 Evaluation of visual fit

E.1.6 Evaluation of hazard functions

E.1.7 Validation and discussion of extrapolated curves

E.1.8 Adjustment of background mortality

E.1.9 Adjustment for treatment switching/cross-over

E.1.10 Waning effect

E.1.11 Cure-point

Appendix F. Serious adverse events

Table 54 Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Blinded Period

System Organ Class Preferred Term	palopegteriparatide (n=61)	Placebo (n=21)	Total (n=82)
Subjects with at Least One Serious Treatment-Emergent Adverse Event	5 (8.2)	3 (14.3)	8 (9.8)
Gastrointestinal disorders	2 (3.3)	0	2 (2.4)
Colitis	1 (1.6)	0	1 (1.2)
Rectal haemorrhage	1 (1.6)	0	1 (1.2)
Metabolism and nutrition disorders	2 (3.3)	0	2 (2.4)
Hypercalcaemia	1 (1.6)	0	1 (1.2)
Hypocalcaemia	1 (1.6)	0	1 (1.2)
Cardiac disorders	1 (1.6)	0	1 (1.2)
Cardiac arrest	1 (1.6)	0	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps	0	1 (4.8)	1 (1.2)
Invasive breast carcinoma	0	1 (4.8)	1 (1.2)
Psychiatric disorders	0	1 (4.8)	1 (1.2)
Bipolar disorder	0	1 (4.8)	1 (1.2)
Reproductive system and breast disorders	0	1 (4.8)	1 (1.2)
Endometrial disorder	0	1 (4.8)	1 (1.2)

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event;

MedDRA version 24.1. Percentages were calculated based on the number of subjects in the Safety Analysis Population.

TEAEs occurring prior to the first dose of open-label treatment are included. Sorted in descending order of frequency based on the “total” column.

Appendix G. Health-related quality of life

Quality of life instruments

The EQ-5D is a generic Quality of life (QoL) instrument used to describe and value health according to societal preference and is recommended for use by many HTA bodies.[82] It encompasses multiple versions, notably the EQ-5D-5L and the EQ-5D-3L, which differ in the number of response levels per QoL dimension. Both systems comprise five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L categorizes health states into three levels (no problems, some/Moderate problems, and extreme problems), whereas the EQ-5D-5L uses five levels (no problems, slight problems, Moderate problems, severe problems, and extreme problems). The augmentation of levels in the 5L version aims to improve detecting minor changes and reduce ceiling effects observed in the 3L version. This was particularly notable in general population surveys and certain patient cohort.

Cross-walking and utility analysis

To support the population of the economic model, Adelphi Values PROVE™ have supported in analyzing trial data to generate utility values from the PaTHway clinical trial.

Statistical software

The utility analysis was performed in R-project software using standard R programming packages that can be found in the Comprehensive R Archive Network library. Additionally, the *eq5d* package was used to map EQ-5D-5L questionnaire scores onto the relevant utility index. The packages used were kept to those that were essential for the analysis and these have been well validated and documented.

Datasets used for the analysis

The analyses were performed for the ITT population as well as for a subgroup of patients with moderate to severe HPES score at baseline.

EQ-5D value sets

EQ-5D-3L UK utility index scores. NICE does not recommend using the EQ-5D-5L value set for England published by Devlin et al., 2018, but instead the EQ-5D-3L value set developed by the EuroQol Group. The EQ-5D-5L data collected during the PaTHway clinical trial was therefore mapped to the EQ-5D-3L descriptive system to calculate utility values using the descriptive patient characteristics as required. For the analysis using the

UK utility index, the 3L value set was used based on the NICE DSU crosswalk. For Denmark the Jensen et al. (2021)[83] value set was applied.

EQ-5D-3L baseline analyses and change from baseline

To understand the observed utility values and the change from baseline, first descriptive statistics were calculated to show the sample size, mean, median, standard error, standard deviation, minimum and maximum. The change from baseline was then calculated for the patients who completed the questionnaire at the baseline and time point of assessment. The change from baseline was assessed by an analysis of covariance (ANCOVA) model to assess the change from baseline in EQ-5D and the difference between the treatment and control arm. The methods used for the ANCOVA model were aligned with those used for the trial analysis. Separate ANCOVA analysis were conducted for the change from baseline to week 10, week 20 and week 26. The ANCOVA analysis report the difference in least square means. These timepoints aligned with the EQ-5D collection in the clinical trial, and therefore had suitable sample sizes for analysis.

The analysis examined the ITT population and a subgroup of patients who were HPES health state Moderate/Severe at baseline.

Results

Intention to treat (ITT)

Table 55 provides the ED-5D-5L values using the Danish value set and the ANCOVA results for the change from baseline to week 10 for the ITT population. Table 56 shows the observed values along with the ANOCOVA change from baseline to week 20, while Table 57 shows the change from baseline to week 26.

The change from baseline is assessed for patients, building on the baseline assessment. The tables also report the comparison between the treatment and control group in least squares mean and the associated p-value.

The results show that treatment improved EQ-5D-5L at Week 26 from baseline and was statistically significant compared to the control group. The change from baseline was assessed for patients who completed the EQ-5D-5L at week 26.

Table 55. Change from Baseline to Visit 6 (Week 10) ITT patients – EQ-5D-5L Denmark value set

	Treatment group	Control group
Baseline		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Observed		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ANCOVA model		
N	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
95% CI for LS Mean	[redacted]	[redacted]
Difference in LS Means (SE)	[redacted]	
95% CI for Difference in LS Means	[redacted]	
P-value (Treatment vs Control)	[redacted]	

Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EQ-5D-5L: European quality of life 5 dimensions 5 level version; ITT: Intent to treat; LS: Least squares; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error.

Table 56. Change from Baseline to Visit 9 (Week 20) ITT patients - EQ-5D-5L Denmark value set

	Treatment group	Control group
Baseline		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Observed		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ANCOVA model		
N	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
95% CI for LS Mean	[redacted]	[redacted]
Difference in LS Means (SE)	[redacted]	
95% CI for Difference in LS Means	[redacted]	
P-value (Treatment vs Control)	[redacted]	

Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EQ-5D-5L: European quality of life 5 dimensions 5 level version; ITT: Intent to treat; LS: Least squares; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error.

Table 57. Change from Baseline to Visit 10 (Week 26) ITT patients - EQ-5D-5L Denmark value set

	Treatment group	Control group
Baseline		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Observed		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ANCOVA model		
N	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
95% CI for LS Mean	[redacted]	[redacted]
Difference in LS Means (SE)	[redacted]	
95% CI for Difference in LS Means	[redacted]	
P-value (Treatment vs Control)	[redacted]	

Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EQ-5D-5L: European quality of life 5 dimensions 5 level version; ITT: Intent to treat; LS: Least squares; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error.

Subgroup: Moderate/Severe HPES at baseline

To understand the quality of life for the patients with HPES of moderate/severe at baseline, a subgroup analysis was conducted to assess the impact. Table 58 provides the ED-5D-5L values using the Danish value set and the ANCOVA results for the change from baseline to week 10 for the ITT population. Table 59 shows the observed values along with the ANOCOVA change from baseline to week 20, while Table 60 shows the change from baseline to week 26 for the patients with baseline moderate/severe HPES.

The results show that treatment improved EQ-5D-5L at Week 26 from baseline and was statistically significant compared to the control group. This is consistent with the ITT population.

Table 58. Change from Baseline to Visit 6 (Week 10) for moderate/severe HPES at baseline – EQ-5D-5L Denmark value set

	Treatment group	Control group
Baseline		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Observed		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ANCOVA model		
N	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
95% CI for LS Mean	[redacted]	[redacted]
Difference in LS Means (SE)	[redacted]	
95% CI for Difference in LS Means	[redacted]	
P-value (Treatment vs Control)	[redacted]	

Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EQ-5D-5L: European quality of life 5 dimensions 5 level version; ITT: Intent to treat; LS: Least squares; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error.

Table 59. Change from Baseline at Visit 9 (Week 20) for moderate/severe HPES at baseline – EQ-5D-5L Denmark value set

	Treatment group	Control group
Baseline		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Observed		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ANCOVA model		
N	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
95% CI for LS Mean	[redacted]	[redacted]
Difference in LS Means (SE)	[redacted]	
95% CI for Difference in LS Means	[redacted]	
P-value (Treatment vs Control)	[redacted]	

Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EQ-5D-5L: European quality of life 5 dimensions 5 level version; ITT: Intent to treat; LS: Least squares; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error.

Table 60. Change from Baseline at Visit 10 (Week 26) for moderate/severe HPES at baseline – EQ-5D-5L Denmark value set

	Treatment group	Control group
Baseline		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Observed		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD, SE	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ANCOVA model		
N	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
95% CI for LS Mean	[redacted]	[redacted]
Difference in LS Means (SE)	[redacted]	
95% CI for Difference in LS Means	[redacted]	
P-value (Treatment vs Control)	[redacted]	

Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EQ-5D-5L: European quality of life 5 dimensions 5 level version; ITT: Intent to treat; LS: Least squares; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error.

Appendix H. Probabilistic sensitivity analyses

The inputs used to perform the probabilistic sensitivity analysis are presented in the table below.

Table 61. Overview of parameters in the PSA

Parameter	Point estimate	Lower confidence interval	Upper confidence interval	Distribution
[redacted]				

Parameter	Point estimate	Lower confidence interval	Upper confidence interval	Distribution
[redacted]				

Parameter	Point estimate	Lower confidence interval	Upper confidence interval	Distribution
[redacted]				

Parameter	Point estimate	Lower confidence interval	Upper confidence interval	Distribution
[redacted]				

Parameter	Point estimate	Lower confidence interval	Upper confidence interval	Distribution
[redacted]				

Parameter	Point estimate	Lower confidence interval	Upper confidence interval	Distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix I. Literature searches for the clinical assessment

N/A. All clinical comparative data is sourced from a single RCT

Appendix J. Literature searches for health-related quality of life

N/A

Appendix K. Literature searches for input to the health economic model

N/A

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